Burden and determinants of cardiovascular health and outcomes in patients with cancer

Thesis submitted for the degree of Doctor of Philosophy

University of East Anglia

Dr CHAN Shi Kai Jeffrey

Year of submission: 2025

Word count: 81,047

To my dearest wife Dawnie

Declaration

I confirm that the work in this thesis is my own apart from where referenced or acknowledged. All published work presented in this thesis have been reproduced with permission from the publisher where required.

Abstract

Introduction: Cardiovascular diseases in patient with cancer present an increasing health problem, the burden and determinants of which remains to be better understood.

Methods and results: First, using data of up to 37,882 individuals from the United States' National Health Interview Survey, two cross-sectional studies demonstrated associations for social determinants of health and psychological distress with cardiovascular health in cancer survivors, and a prospective cohort study demonstrated independent associations between social determinants of health and cardiovascular mortality in these individuals. Then, using a cohort of up to 13,537 patients with prostate cancer receiving androgen deprivation therapy (ADT), five retrospective cohort studies were performed to quantify their cardiovascular burden and explore determinants of cardiovascular outcomes. Key findings included: 1) major adverse cardiovascular events (MACE) rose in incidence with patients having worse cardiometabolic profile over time despite declining mortality rates, 2) the number of major cardiac comorbidities may be more prognostic of cardiovascular outcomes than their types, 3) ADT worsened visit-to-visit HbA1c variability which was prognostic of MACE, and 4) gonadotropin-releasing hormone antagonists may have similar short-term risk but higher long-term risk of MACE compared to agonists. Lastly, using a cohort of up to 4324 patients with cancer receiving immune checkpoint inhibitors (ICI), a retrospective cohort study was performed to quantify their burden of MACE and cardiovascular hospitalizations, a self-controlled case series demonstrated transient short-term elevations in the risk of myocardial infarction following ICI use, and a retrospective cohort study demonstrated poor implementation of guideline-recommended pre-ICI initiation cardiometabolic workup, despite some improvements over time which did not improve cardiovascular outcomes.

Conclusions: Psychosocial factors, patient factors such as comorbidities, and cancer factors such as cancer therapies are all important determinants of cardiovascular outcomes in patients with cancer. Large gaps persist in these aspects of the cardio-oncology literature which remain to be explored.

Abstract word count: 299

Table of contents

List of tables

List of figures

List of supplementary tables

List of supplementary figures

Acknowledgements

I would like to thank my supervisors Prof Vassilios Vassiliou and Dr Gareth Matthews for their continual support and advice throughout the duration of this doctoral programme.

Importantly, I would like to thank Prof Gary Tse, Prof Anthony Chi Fai Ng, and Prof Tong Liu for their invaluable support, advice, and tutelage when I initially carried out and published the studies included in this thesis. These studies – and thus this thesis – would not have been possible without them, and I will forever be grateful for their time and support in spite of their incredibly busy schedules.

Just as importantly, I would like to thank Ms Yan Hiu Athena Lee for her collaboration and assistance in many parts of chapters 5-12, and Dr Danish Iltaf Satti for similar involvements in chapters 2-5. I would also like to thank Dr Edward Christopher Dee for introducing me to the National Health Interview Survey and helping me understand it. Additionally, I must thank Dr Dee, alongside Dr Kenrick Ng, for providing much needed oncological input in chapters 5-12. I am grateful for the support in data access and processing offered by other team members of mine, especially Dr Oscar Hou In Chou, Mr Teddy Lee, Mr Steven Leung, and Dr Kang Liu.

Furthermore, I must thank my dearest friends Thompson, Vanessa and Raymond for their generous and unwavering support even when I was at my lowest. They helped me get through some of the toughest moments in my life thus far, and the completion of this thesis is in no small part thanks to their support and friendship.

I am also grateful to my family for supporting me throughout this doctoral programme.

Lastly, words cannot adequately express my gratitude to my most amazing wife and the love of my life, Dawnie. She has been my greatest supporter, my rock, and the reason that I had the strength to complete the included studies and this thesis. I went through periods of self-doubt and mood swings throughout the course of these studies – her love and care kept me sane and powered me to keep striving. She remains the reason that I keep working hard every day and waking up every morning feeling blessed. I cannot thank her enough and I am forever grateful for her love, care, and company – with that, I dedicate this thesis to her.

1. Chapter 1: General introduction

This introduction is based on a published narrative review, with further expansion and elaboration where appropriate:(1) **Chan JSK**, Chan RNC, Lee YHA, Satti DI, Dee EC, Ng K, Achim A, Ng CF, Liu T, Matthews GDK, Tse G, Vassiliou VS. Cardiovascular health of patients with cancer: challenges abound. *Trends Cardiovasc Med*. 2025; 35(1): 24-31. doi: 10.1016/j.tcm.2024.04.004

1.1. Epidemiology of cardiovascular conditions in patients with cancer

Cancer has been one of the most common causes of mortality and morbidity globally. In 2019, an estimated 10 million deaths and 250 million disability-adjusted life years were attributable to cancer.(2) The same year saw an estimated 23.6 million new cases of cancer, constituting a 26.3% increase compared to 2010, and is expected to continue rising in the future.(2) Concurrently, improving cancer therapeutics, amongst other factors, have led to consistently declining mortality rates amongst patients with cancer, with an estimated 33% reduction in 2019 compared to 1991.(3)

This combination of increasing cancer incidence and declining cancer-related mortality rates will result in an ever-growing number of cancer survivors, who will have increased risks of incident cardiovascular diseases and cardiovascular mortality when compared to the general population. This was demonstrated by a Canadian study of 4,519,243 adults, which found that patients with cancer had a 33% increase in the risk of cardiovascular mortality, a 44% increase in the risk of incident stroke, a 62% increase in the risk of incident heart failure, and a 243% increase in the risk of incident pulmonary embolism.(4) These findings were mostly replicated by a contemporary study of 12,414 individuals from the Atherosclerosis Risk In Communities study,(5) as well as another study of 1.1 million Taiwanese patients.(6) Similarly, large-scale studies using data from the Surveillance, Epidemiology, and End Results program of the United States demonstrated that patients with cancer had significantly increased risks of fatal heart disease and cardiovascular mortality.(7,8) Importantly, there is evidence that cardiovascular diseases and cardiovascular risk factors are undertreated in patients with cancer,(9,10) and a study by Agarwal and colleagues found that cardiovascular burden increased in American patients with cancer between 2003 and 2014.(11) Overall, these findings and the temporal trends in cancer epidemiology suggest that cardiovascular diseases in patients with cancer will become an ever-more important clinical issue.

Concordantly, cardio-oncology, a subspecialty at the intersection between cardiology and oncology, has received increasing attention in recent years. Since 2010, the number of cardio-oncology publications in peer-reviewed journals has grown exponentially, exceeding 260 publications in 2021, and accruing over 5000 relevant citations.(12) The significance of cardio-oncology as both a clinical and research field of interest was further consolidated by the cardio-oncology guidelines published in 2022 by the European Society of Cardiology (ESC),(13) which represented the first cardio-oncology guideline published by a major cardiovascular society.

Despite the established association between cancer and cardiovascular risk, quantification of cardiovascular disease burden in patients with different types of cancer is still incomplete. The risk factors and therapies differ for different cancers, the respectively associated cardiovascular burden may be different, and an accurate and personalized approach to prognostication is important when communicating with patients. Additionally, there are substantial ethnic differences in cardiovascular burden.(14–16) Some large-scale studies of Caucasian-predominant cohorts have quantified the cardiovascular burden in patients with cancer in general,(4,8,17,18) and some have stratified for the type/site of cancer.(4,19–22) However, findings from Caucasian-predominant cohorts may not be translatable to other ethnicities. Recent years have also seen more such studies using data from non-Caucasian cohorts,(21,22) although they remain relatively uncommon – a common phenomenon in cardio-oncology research.(12,23) Further to such ethnic underrepresentation, there is substantial heterogeneity in the definition of cardiovascular outcomes between studies. Notably, many use time-fixed point estimates (e.g. incidence rates) as summary statistics. For the lay person, these may be more difficult to understand than time-specific estimates (e.g. five-year risk). These also assume a constant incidence rate, which has been shown to be untrue.(4) Overall, ethnically diverse studies quantifying the cardiovascular burden in patients with various cancer types/sites, usage of more clinically relevant estimates, and a more uniform definition of cardiovascular outcomes remain warranted.

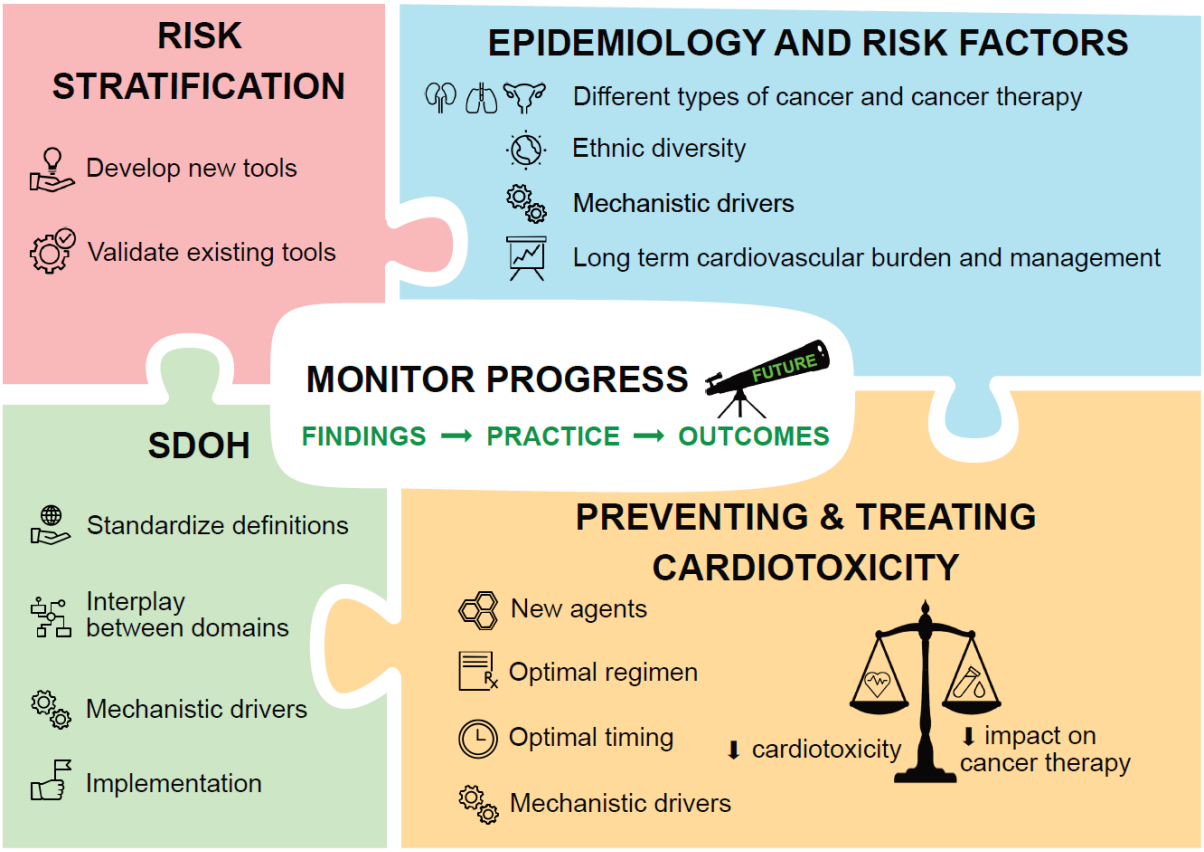
1.2. Determinants of cardiovascular health and outcomes in patients with cancer

Numerous factors may impact cardiovascular health in cancer survivors. In general, these factors can be classified as cancer factors, patient factors, and social factors. Cancer factors include cancer characteristics and, most prominently, cancer therapies. Patient factors are personal characteristics including genetics, anthropometric and biological measurements, and medical comorbidities. Social factors refer to social determinants of health (SDOH). These factors affect cardiovascular health in cancer survivors in complex manners with numerous gaps in understanding, as highlighted in the following sections, as well as in Table 1.1 and Figure 1.1.

Table 1.1 Critical gaps in the cardio-oncology literature.

Domain	Key areas for research
Epidemiology	• Cardiovascular burden in non-Caucasian patients with cancer • Long-term cardiovascular burden in patients with cancer • Cardiovascular burden in patients with different types/sites of cancers • Standardizing the definition of cardiovascular outcome in cardio-oncology studies • Use of estimates that are clinically easy to interpret and communicate
Cardiovascular risk factors	• Interplay between cardiovascular risk factors • Long-term management of cardiovascular risk factors in patients with cancer • Mechanisms underlying the increased cardiovascular risk in patients with cancer
Cancer therapy-related cardiotoxicity	
Epidemiology	• Burden in non-Caucasian patients with cancer receiving specific cancer therapies • Long-term burden specific to different cancer therapies
Mechanisms	• Mechanisms underlying cancer therapy-related cardiotoxicity • Potential targets for preventing / ameliorating cancer therapy-related cardiotoxicity
Risk stratification	• Development and validation of cardiovascular risk stratification tools specific to cancer therapies • Development and validation of more sensitive and/or specific biomarkers for cancer therapy-related cardiotoxicity • Assessment of the performance of cardiovascular risk stratification tools developed for the general population when used on patients with cancer
Prevention and management	• The efficacy of different chemoprevention or treatment for cardiotoxicities related to different cancer therapies • Optimal regimen of cardiovascular medications as chemoprevention or treatment • Optimal timing of cardiovascular medications as chemoprevention or treatment
Social determinants of health	• Standardizing the definition and quantification of social determinants of health, with special attention paid to the interplay and overlap between different potential domains • Delineating the drivers underlying the associations between social determinants of health and cardiovascular health in patients with cancer • Devising policies to translate research findings into patient care
Monitoring progress	• Temporal trends in clinical practice and adherence with guidelines • Whether changes in guidelines and/or clinical practice influenced patient outcomes • Using standardised quality indicators

Figure 1.1 Graphical summary of the gaps in evidence for the main areas of research in cardio-oncology. SDOH, social determinants of health.



1.2.1. Patient factors: shared biological risk factors between cancer and cardiovascular diseases

The reasons underlying the elevated cardiovascular risks in patients with cancer are complex and incompletely understood. Aside from the adverse cardiovascular effects of cancer therapies,(24,25) the main underlying factors likely include shared risk factors, and heightened inflammation and oxidative stress in cancer.(26) In particular, obesity, physical inactivity, diabetes mellitus, smoking, alcoholism, and poor diet, all of which are well-established cardiovascular risk factors, have been associated with elevated risks of cancer. A meta-analysis of 98 studies demonstrated strong associations between obesity and cancer in both male and female patients,(27) while a study of 1.46 million white adults demonstrated significant associations between obesity and cancer-related mortality.(28) Similarly, a meta-analysis of 71 prospective cohort studies demonstrated a strong, inverse, non-linear dose-response relationship between the amount of physical activity and cancer mortality.(29) A meta-analysis of 151 cohorts including over 32 million individuals found strong associations between type 2 diabetes mellitus and multiple cancer types, although the association for some cancers may have been attributable to confounders.(30) Additionally, smoking has long been recognized as a strong risk factor for multiple cancers, particularly respiratory cancers,(31) and has been identified as the risk factor to which the highest number of cancer deaths were attributable in 2019.(32) High alcohol intake has been similarly demonstrated to associate with elevated risks of multiple cancer types, as seen in a meta-analysis of 572 studies including 486,538 cancer

cases.(33) Finally, poor diet has been shown to account for 80,110 new cases of cancer in the United States in 2015, with colorectal cancer having the highest number and proportion of diet-related cases, and with low consumption of whole grain / dairy products, and high consumption of processed meats being the most important dietary factors.(34) The mechanisms underlying these associations are complex and incompletely understood, with inflammation, oxidative stress and insulin resistance being some of the key mechanistic drivers.(26) Nonetheless, a detailed discussion of these mechanisms is beyond the scope of this introduction and has been covered in specialized review articles.(26,35,36)

These risk factors are interlinked, and the effects of each risk factor are difficult to isolate. Although it is obvious that optimization of cardiovascular risk factors can lower cardiovascular risk, the multifactorial nature of cardiovascular diseases in patients with cancer means that the efficacy and optimal strategy of controlling these risk factors and managing cardiovascular conditions may not be the same in these patients. Although the 2022 ESC cardio-oncology guidelines detailed the long-term follow-up of cancer survivors, the majority of recommendations were only based on expert consensus or low-quality observational studies.(13) Further high-quality research of the long-term cardiovascular care of patients with cancer is required.

1.2.2. Disease factors: cancer therapy-related cardiotoxicity

Adverse cardiovascular effects of cancer therapies are an important contributor to cardiovascular diseases in patients with cancer.(37) A large number of studies have demonstrated clear evidence for cardiotoxicities due to anthracyclines,(38) ErB2/HER2 inhibitors,(39) androgen deprivation therapy (ADT),(40,41) immune checkpoint inhibitors (ICIs),(42,43) epidermal growth factor receptor inhibitors,(44) vascular endothelial growth factor (VEGF) signaling pathway inhibitors,(45) and radiotherapy.(46) Specifically, whilst heart failure and ischaemic heart disease are well-recognized cardiotoxic effects of cancer therapies, studies have suggested that arrhythmias, such as atrial fibrillation and ventricular tachyarrhythmias, may be important consequences and even prognosticators of cancer therapy-related cardiotoxicity.(37,47,48) Furthermore, pulmonary hypertension may be another overlooked cardiotoxic effect of cancer therapies, with diagnosis being difficult due to its non-specific clinical presentation.(49,50) Nevertheless, a detailed review of the evidence underlying associations between different cancer therapies and cardiotoxicities is outside the scope of this introductions and has been covered in great details by the above-cited reviews.(38–46,51) The pathophysiological mechanisms of such cardiotoxicities are complex and incompletely understood, but mostly relate to inhibition of DNA transcription and protein synthesis (e.g. alkylating agents, HER2 inhibitors, anthracyclines), oxidative stress and reactive oxygen species (e.g. anthracyclines), microtubular disassembly disruption (e.g. taxanes), immune activation causing autoimmune responses (e.g. ICIs), blockade of sex hormone pathways (e.g. ADT), and/or fibrosis of the myocardium or other cardiac structure (e.g. radiotherapy).(24,40,46,52) Moreover, some studies have shown that premorbid cardiometabolic conditions, including hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation / flutter, and high body-mass index, are risk factors for adverse cardiovascular events related to cancer therapies, such as anthracyclines,(53) VEGF inhibitors,(54) and HER2

inhibitors.(55) It is also noteworthy that there may be significant differences in cardiovascular risks associated with different cancer therapeutic agents in the same class, such as enzalutamide and abiraterone which are both androgen receptor signaling inhibitors used in ADT.(56)

1.2.2.1. Epidemiology, risk factors, and risk stratification

Cancer therapies appropriately prioritize cancer-specific efficacy, to ensure longer survival from cancer. The concern about cardiotoxicity was thus only explored and studied after these therapies have been widely adopted and enabled patients to live sufficiently long for cardiovascular effects to be noticeable. There are many gaps in the understanding of cancer therapy-related cardiotoxicity, which will likely remain the case due to rapid and continual advances in cancer therapy. For instance, the predisposing and prognostic factors of cancer therapy-related cardiotoxicity are incompletely understood. These gaps in evidence are present not only due to the novelty of some cancer treatments, but also because certain life-threatening cardiotoxic effects, such as myocarditis related to ICIs, are extremely uncommon.(57) Cancer therapy-related cardiotoxicity burden, especially long-term burden, in non-Caucasian patients is also only increasingly studied in recent years,(58–61) These gaps in understanding meant that developing cardiovascular risk tools specific for patients with cancer is difficult. Additionally, the inherently different treatment and natural history of different cancers may necessitate separate risk models for different cancers or even cancer therapies, which may require frequent updating and recalibration owing to the rapid advancement of cancer therapeutics.

The presence of traditional cardiovascular risk factors is generally accepted to be associated with higher probability of cancer therapy-related cardiotoxicity. This is because patients with cardiovascular risk factors – who are generally more prone to have established or subclinical cardiovascular disease – may be considered to have reduced cardiac functional reserve and thus can tolerate less cardiac insults before cancer therapy-related cardiotoxicity becomes clinically manifest (62). Nonetheless, a wide array of pathophysiological mechanisms underlying cancer therapy-related cardiotoxicity from different cancer therapies, which necessarily implies varying extents of associations between cardiovascular risk factors and the risk of cancer therapy-related cardiotoxicity.

The empirical literature for cancer therapy-related cardiotoxicity is dominated by studies of patients treated with anthracyclines or trastuzumab, with risk factors such as hypertension, diabetes, and dyslipidemia having been consistently observed to be associated with cardiotoxicity (63,64). Nonetheless, thematically similar observations have been made in patients receiving other cancer therapies. For instance, hypertension has been shown to be a predictor of cancer therapy-related cardiotoxicity related to vascular endothelial growth factor inhibitors (65), and diabetes has been associated with the risk of cancer therapy-related cardiotoxicity related to ICIs.(66,67) Meanwhile, richer evidence exists for longer-term cardiovascular health, with multiple cohort studies having observed strong associations for premorbid hypertension, diabetes, and coronary artery disease with long-term cardiovascular events among cancer survivors (68–70).

The complexity of cardiovascular risk stratification in patients receiving cancer therapies and the paucity of specific cardiovascular risk stratification tools were evident from the 2022 ESC cardio-oncology guidelines, which recommended the Heart Failure Association – International Cardio-Oncology Society (HFA-ICOS) risk assessment tool for patients on a limited range of cancer therapies (e.g. anthracyclines), and a cautious use of the SCORE2 / SCORE2-OP cardiovascular risk scores in others (e.g. ADT).(13,71) However, the evidence underlying the HFA-ICOS risk assessment tool was weak, with the guideline recommendations most supported by low-quality observational studies or expert consensus.(71) Furthermore, this tool only offered qualitative cardiovascular risk assessment for some cancer therapies, which is not ideal for clinicians who are obliged to clearly communicate the risks of cancer therapies to patients. The qualitative nature also meant that the tool could not consider interactions between different comorbidities. Meanwhile, the SCORE2 and SCORE2-OP risk scores were originally developed for use in the general population, and has not been thoroughly validated in patients with cancer, particularly non-Caucasian ones. Similar issues exist for most other common cardiovascular risk scores such as QRISK3 and JBS3. Whilst recent years have seen attempts to develop cardiovascular risk scores for patients with breast cancer,(72) acute myeloid leukaemia,(73) prostate cancer,(74) or diffuse large B-cell lymphoma treated with anthracyclines,(75) these scores generally lacked thorough external validation and have not seen widespread clinical use, with the 2022 ESC guidelines opting for the more general HFA-ICOS risk assessment tool instead. Similar studies have remained scarce, and much more effort is urgently required to address the unmet need for risk stratification tools in patients with cancer.

1.2.2.2. Prevention and management

Compared to cardiovascular risk stratification, there has been somewhat more interest in the prevention and management of cancer therapy-related cardiotoxicity. Given the impact of cardiovascular risk factors in oncologic patients receiving cancer therapies, it is imperative that clinicians seek to continuously optimize them before, during and after cancer therapy. Optimization of cardiovascular risk factors remains important after the completion of cancer therapy as multiple classes of cancer therapies, such as ADT and ICIs, are known to be associated with varyingly elevated risks of developing cardiovascular risk factors such as diabetes and dyslipidaemia. This may be especially important in survivors of childhood cancer (68,76). The 2022 ESC guidelines on cardio-oncology recommended lifestyle modifications including smoking cessation, restriction of alcohol consumption to no more than 100 g per week, and adequate physical exercise (13). Whilst specific evidence on the efficacy of such changes on the risk of cancer therapy-related cardiotoxicity is scarce, substantially more evidence exists for longer-term cardiovascular benefits. In particular, a large cohort study has shown that patients with cancer who abandoned smoking after being diagnosed with cancer had an estimated 36% lower risk of incident cardiovascular diseases than those who continued (77). Meanwhile, high levels of alcohol consumption have been observed to be associated with drastically higher risk of incident cardiovascular diseases in long-term colorectal cancer survivors (78). As well, healthier diet has been shown to be associated with lower risk of cardiovascular disease in cancer survivors (79).

Pharmacologically, one of the best examples is dexrazoxane, which has been shown in a meta-analysis of randomized controlled trials (RCTs) to reduce the risk of clinical heart failure by 78% amongst adults with cancer receiving anthracyclines.(80) Similarly, another meta-analysis of RCTs has shown that liposomal-encapsulated doxorubicin reduces the risk of clinical heart failure by 80%.(81) As such, both dexrazoxane and liposomal anthracyclines were recommended by the 2022 ESC cardio-oncology guidelines for use in patients with high or very high risk of cancer therapy-related cardiotoxicity who are indicated for anthracycline chemotherapy.(13) More recently, statins have been explored for the same purpose. Although the PREVENT (Preventing Anthracycline Cardiovascular Toxicity with Statins) trial, the first randomized controlled trial testing statin's efficacy in patients receiving anthracyclines, showed no significant effect on absolute change in left ventricular ejection fraction (LVEF),(82) the subsequent STOP-CA (Statins to Prevent the Cardiotoxicity of Anthracyclines) trial randomized patients with lymphoma due to receive anthracycline chemotherapy and showed that 40 mg/day atorvastatin reduced the incidence of significant declines in LVEF (10% or greater to a final LVEF of <55%) compared to placebo over a 12-month period.(83) Subsequent meta-analyses confirmed that statin significantly reduced the incidence of cardiotoxicity, whilst high levels of heterogeneity, likely due to inter-study differences in follow-up durations and baseline cardiovascular risk, precluded meaningful conclusions to be drawn for changes in left ventricular ejection fraction.(84,85) The 2022 ESC cardio-oncology guidelines recommended statins for adult lymphoma patients with cancer at high or very high risk of cancer therapy-related cardiotoxicity.

Besides statins, other common cardiovascular medications have also demonstrated efficacy in preventing cancer therapy-related cardiotoxicity. As early as 2006, a RCT has shown that early treatment with enalapril reduced the development of late cardiotoxicity in patients with cancer initiated on high-dose chemotherapy (86). The PRADA (Prevention of cardiac dysfunction during adjuvant breast cancer therapy) trial also demonstrated that candesartan had protective effects against early decline in global LV function in patients with early breast cancer treated with adjuvant anthracyclines (87). Another RCT showed that both lisinopril and carvedilol reduced the occurrence of cardiotoxicity in patients with HER2-positive breast cancer treated with trastuzumab (88). Meta-analytically, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and beta-blockers have been shown to increase LVEF regardless of whether they were given alone or in conjunction (89). The 2022 ESC cardio-oncology guidelines advised the use of ACEI/ARB and beta-blockers for adults with cancer at high or very high risk of cancer therapy-related cardiotoxicity who are scheduled to receive cancer therapies causing heart failure, particularly anthracyclines and/or anti-HER2 therapies. Meanwhile, observational studies have suggested that other agents may have similar effects, such as sodium-glucose cotransporter-2 inhibitors and metformin.(90,91) However, a pairwise meta-analysis and a network meta-analysis failed to find heart failure therapies to be efficacious in preventing HER2 inhibitor-related cardiotoxicity.(92,93) Further studies including rigorous RCTs remain required before these treatments may be formally recommended.

On the other hand, the 2022 ESC cardio-oncology guidelines provided relatively detailed guidance on the cardiovascular surveillance for patients with cancer while receiving cancer

therapies, as well as the management of cancer therapy-related cardiotoxicity.(13) For the latter, there was a recurring theme of multidisciplinary team care, initiation of workup and treatments according to the presenting clinical syndrome (e.g. heart failure, or acute coronary syndrome) similar to those in patients without cancer, and interrupting cancer therapy with the potential for re-initiation in non-severe cases after resolution of the acute cardiotoxicity.(13) These recommendations were centered around the critical cardio-oncology concept of 'permissive cardiotoxicity', where cardiotoxicity is to be proactively minimized with minimal impact on the overall cancer treatment.(94)

Nonetheless, as was the case for many other areas, the recommendations made by 2022 ESC cardio-oncology guidelines, in terms of the prevention and management of cancer therapy-related cardiotoxicity, were heavily reliant on low-quality observational studies and/or expert consensus. Further to the abovementioned PREVENT and STOP-CA trials, there have been an increasing number of cardiovascular-focused trials either comparing cancer therapeutic agents or testing cardioprotective strategies. For instance, the PRONOUNCE trial compared degarelix (a gonadotropin-releasing hormone antagonist) against leuprolide (a gonadotropin-releasing hormone agonist), both commonly used for the treatment of prostate cancer, in terms of the risk of major adverse cardiovascular events,(95) a question which several observational studies had attempted to answer but arrived at contradicting conclusions.(96,97) Unfortunately, patient recruitment for PRONOUNCE was impacted by the COVID-19 pandemic, and the trial was ended prematurely, resulting in underpowered analyses which found no significant differences between the two agents.(95) There are also a number of ongoing randomized controlled trials being conducted in diverse populations. For instance, the ongoing Norwegian PRADAII trial will assess the efficacy of sacubitril/valsartan, which had shown promising results in pre-clinical and observational studies,(98) in preventing cardiotoxicity in patients with breast cancer receiving adjuvant epirubicin with/without trastuzumab/pertuzumab (NCT03760588).(99) Another example is an Egyptian trial which will assess the efficacy of rosuvastatin in preventing cardiotoxicity in patients with breast cancer receiving both doxorubicin and trastuzumab (NCT05338723). Also ongoing is another Taiwanese trial which will assess the efficacy of initiating sacubitril/valsartan as preventive therapy versus rescue therapy in patients with breast cancer receiving trastuzumab (NCT05892146). The multinational, European RESILIENCE trial will assess the efficacy of remote ischaemic conditioning, which had not shown significant benefits in smaller trials of low-risk patients,(100,101) in patients with lymphoma and high cardiovascular risks receiving anthracyclines (NCT05223413). These trials and other emerging epidemiological and observational studies will hopefully give much-needed insights into the prevention and treatment of cancer therapy-related cardiotoxicity, not only pertaining to the efficacy of individual agents, but also the optimal regimen and timing of such agents.

1.2.3. Social factors: social determinants of health

SDOH, broadly referring to socioeconomic factors that may affect health, have been increasingly recognized as a determinant of cardiovascular health. Whilst there is no universal consensus on its definition, the United States' governmental Healthy People 2030 initiative has grouped SDOH into five main components, i.e. economic stability, education access and quality,

healthcare access and quality, neighborhood and built environment, and social and community context (102). Some have also considered additional factors, such as systemic discrimination, as components of SDOH (103). A large-scale prospective cohort study of 182,375 participants from 20 countries demonstrated significant associations between low education levels and higher risk of major adverse cardiovascular events,(104) with similar findings in another large cohort study of 303,036 participants from Asia or Australasia.(105) A cohort study of participants from United States and Finland also demonstrated associations between low income and increased risks of sudden cardiac death, non-sudden cardiac death, and non-fatal myocardial infarction,(106) the significance of which likely remains stable with age.(107) Similar associations have been demonstrated in patients with cancer. A study of 81,418 Canadian patients with cancer showed that a rural residence, low education level, and low income were all associated with elevated risk of incident cardiovascular diseases.(108) Similarly, another study of 1,139,767 American women with breast or gynaecological cancers found associations between rural residence and higher risk of cardiovascular mortality, which was likely driven by behavioural risk factors (e.g. smoking) and poorer access to healthcare.(109) Unlike in the general population where the association between income and cardiovascular risk appeared to be mostly applicable to older persons,(107) such associations were observed in adolescent and young adult cancer survivors too, as evident from an analysis of data from the United States' nationally representative National Health Interview Survey (NHIS).(110)

Notwithstanding the above, most studies have only explored selected aspects of SDOH, and few have explored links between SDOH and cardiovascular health in patients with cancer comprehensively. This is difficult due to the inter-correlated nature of multiple domains of SDOH, the lack of a universal and objective definition of SDOH, and the broadness of SDOH, which means very few studies collected sufficient data to explore SDOH comprehensively.(111) Additionally, different components of SDOH are inter-related, likely with bidirectional relationships in many instances, and it is difficult, if not impossible, to disentangle their influences on cardiovascular health (103). This means that comprehensive, composite "poly-social" risk scores are difficult to construct. Moreover, the drivers of SDOH's association with cardiovascular health in patients with cancer are unclear. Some studies in the general population have found access to healthcare as a driver.(109) Others have suggested neighbourhood environment, specifically pollution as a likely driver.(112) Overall, further research into the definition, quantification, modelling, and drivers of SDOH's association with cardiovascular health in patients with cancer is warranted.

1.3. Monitoring progress

Whilst progress is continually being made in cardio-oncology, it is important to stay critical and assess whether such progress has translated into differences in practice and patient outcomes. Unfortunately, these studies of temporal trends are exceedingly rare. A nationwide, American study demonstrated evolving cardiovascular needs amongst patients with cancer.(113) Another study using the same database showed reducing rates of cardiovascular mortality, particularly in males and patients living in rural areas.(114) More studies like these are needed to monitor the progress that we, as a field, are making.

1.4. Aims of this thesis

This thesis is based on eleven published works, each constituting one chapter (chapters 2-12). These chapters explored the importance of different cancer factors, patient factors, or social factors in terms of cardiovascular health and/or outcomes in cancer survivors / patients with cancer. Chapters 2-4 aimed to make use of nationally representative survey data from the United States of America to explore the associations between SDOH, cardiovascular health and related outcomes in cancer survivors. Chapters 5-9 aimed to make use of population-based data from Hong Kong to explore the burden, trends, and prognostic determinants of cardiovascular events amongst patients with prostate cancer receiving ADT. Chapters 10-12 aimed to make use of similar data from Hong Kong to explore the cardiovascular burden and trends in pre-therapeutic workup amongst patients with cancer receiving ICIs. Aside from administrative reasons such as the availability of appropriate collaborators and data sources, ADT and ICIs were chosen for this thesis for different reasons. ADT was chosen as long-term Asian data on the cardiovascular burden in patients receiving ADT was scarce. Since it has been in use for a long time for the treatment of prostate cancer, long-term follow-up data is available for a large number of patients in Hong Kong, allowing for good statistical power and exploration of temporal trends which contributes to bridging the aforementioned gap in literature. On the other hand, although ICIs are well known to cause severe immune-mediated cardiotoxicity, most prominently myocarditis, their atherosclerotic effects were less explored. Asian and longer-term follow-up data on the cardiovascular burden of patients receiving ICIs was also lacking. In both cases, findings from Caucasian cohorts may not be directly generalizable to Asian patients due to important ethnic differences in the epidemiology and risk of cardiovascular diseases.(115) Overall, this thesis had the overarching aim of exploring the burden, trends, and/or determinants of cardiovascular health and outcomes in patients with cancer.

2. Chapter 2: Associations between social determinants of health and cardiovascular health of US adult cancer survivors

This chapter is based on the following publication: **Chan JSK***, Satti DI*, Dee EC, Lee YHA, Wai AKC, Dani SS, Virani SS, Shapiro MD, Sharma G, Liu T, Tse G. Associations between social determinants of health and cardiovascular health of US adult cancer survivors. *JACC CardioOnc.* 2023; 6(3): 439-450. doi: 10.1016/j.jaccao.2023.07.010 * co-first authors

2.1. Introduction

Recent advances in cancer care have led to significantly improved cancer survival rates, resulting in a growing population of cancer survivors.(116) In 2022, there were an estimated 18.1 million cancer survivors in the United States (US), i.e., ~5% of the population.(117) Compared to the general population, cancer survivors have increased risks of cardiovascular diseases (CVD) and cardiovascular mortality, resulting from overlapping risk factors underlying cancer and CVD (17,18,118,119) and cancer therapy-related cardiotoxicity.(8,120–122) Therefore, cardiovascular care for these patients is increasingly important.

The increased CVD burden among cancer survivors may not be entirely attributable to traditional cardiovascular risk factors.(8) Studies have highlighted associations of socioeconomic status with CVD risk factors and mortality in the general population.(104,105,123) Therefore, it is plausible that social determinants of health (SDOH) — encompassing socioeconomic, environmental, and psychosocial factors that influence health — are also associated with CVD in cancer survivors. However, despite efforts to address SDOH-related cardiovascular health (CVH) disparities,(124) the relationship between SDOH and CVH among cancer survivors remains underexplored. This knowledge gap is particularly relevant as cancer affects both SDOH(125) and CVH,(126) meaning that associations between CVH and SDOH observed in other populations may not be directly extrapolated to cancer survivors. Hence, this study aimed to investigate the association between SDOH and CVH among cancer survivors.

2.2. Methods

2.2.1. Data source

The National Health Interview Survey (NHIS) is an annual household survey conducted by the National Center for Health Statistics/Centers for Disease Control and Prevention, collecting health data for non-institutionalized civilian adults.(127) Utilizing multistage probability sampling, the NHIS generates representative estimates for the non-institutionalized US population. (127) The NHIS uses sampling weights that account for the complex survey design, including stratification, clustering, and oversampling of certain population groups. These weights are calculated to ensure that the estimates derived from the survey data accurately reflect the characteristics of the non-institutionalized U.S. population.(128) Harmonized data were obtained through the Integrated Public Use Microdata Series (IPUMS) Health Survey

database.(129) Since all data used were de-identified and publicly available, it was exempt from review by an institutional review board.

2.2.2. Study population

We analyzed NHIS data from 2013 to 2017 as only these iterations of the NHIS contained all variables required in the ascertainment of cardiovascular health (CVH) score and SDOH score (detailed below). We included adults (aged ≥18 years) reporting a diagnosis of cancer, defined as patients who responded "*Yes*" when asked if they had ever been told "*by a doctor or other health professional that [they] had cancer or a malignancy of any kind.*" Those reporting a diagnosis of non-melanoma skin cancer were excluded, consistent with other cancer survivorship studies.(130,131) Those with missing data for any domain of SDOH or CVH, or any of the pre-specified covariates (sex, age, race, sexual orientation, and the presence of any known cardiac condition) were also excluded.

2.2.3. Ascertainment of Cardiovascular Health

The primary outcome was CVH, quantified by American Heart Association's Life's Essential Eight model.(132) As the NHIS does not include detailed dietary data, the score comprised seven binary domains / risk factors (hypertension, diabetes mellitus, hypercholesterolemia, current smoking, physical activity, inappropriate sleep, and obesity). Current smoking status was self-reported. Obesity was defined as body mass index ≥30 kg/m^2. Insufficient physical activity was defined as not engaging in ≥75 min/week of vigorous exercise, ≥150 min/week of moderate intensity exercise or combination, or a total combination of ≥150 minutes per week of moderate intensity/vigorous exercise. Inappropriate sleep duration was defined as <6 hours or >10 hours of sleep on average per night. Each of the seven CVH domains was coded as 0 (absence of a risk factor) or 1 (presence of a risk factor), with a maximum composite CVH score of 7. A higher composite score indicated worse CVH. This score has been published previously.(133)

2.2.4. Ascertainment of the social determinants of health

We developed a comprehensive SDOH framework based on the six domains defined by the Kaiser Family Foundation: economic stability, neighborhood, community and social context, food poverty, education, and access to healthcare.(134) Using NHIS data, we identified 38 individual components across these domains (**Supplemental Table 2.1**). Each component was classified as favorable or unfavorable, with a value of 0 assigned to the former and 1 to the latter with a maximum score of 38. To calculate an aggregate SDOH score, we added the scores for individual components. Consequently, a higher aggregate SDOH score indicated worse deprivation. The aggregate SDOH score was used to divide the study population into quartiles, with the 1st quartile representing the least deprived (lowest SDOH scores) and the 4th quartile representing the most deprived (highest SDOH scores). This score has been published previously.(133,135)

2.2.5. Statistical analyses

Survey-specific statistics including sampling weights (divided by the number of survey years included, as per NHIS recommendations) and stratification by the survey year were used to obtain estimates representative of the US population. Continuous variables were described as weighted mean ± weighted standard deviation. Multivariable Poisson regression was used to test the relationships between the SDOH score (in quartiles) and CVH, with the first quartile as reference, and with risk ratio (RR; 'risk' refers to the risk of having a worse CVH score) and the corresponding 95% confidence interval (CI) as summary statistics. Regressions were adjusted for pre-specified covariates which were part of the self-reported NHIS data: sex, age, race, sexual orientation, and the presence of any known cardiac condition (self-reported history of any heart condition or disease). A five-knot restricted cubic spline was used to assess the linearity of the association between the SDOH score (as a continuous variable) and the CVH score, with knots placed at 5^{th}, 27.5^{th}, 50^{th}, 72.5^{th}, and 95^{th} percentiles as recommended by Harrell.(136)

To further understand whether any of the domains of SDOH had particularly strong associations with CVH and vice versa, multivariable Poisson regression was used to explore these relationships. Individual domains of the SDOH score containing ≥3 sub-items were analyzed as both a continuous and categorical variable. Wherever the data distribution allowed, these variables were analyzed as quartiles. Fewer categories were used wherever meaningful quartiles could not be generated. Multivariable logistic regression (with odds ratio (OR) and the corresponding 95% CI as summary statistics) or Poisson regression was used as appropriate.

Four pre-specified subgroup analyses were performed to further delineate the relationship between SDOH score (as quartiles) and CVH score, stratifying for age (18-45 years vs. 46-64 years vs. ≥65 years), sex (male vs. female), race (White vs. non-White), and cancer sites (breast, prostate, lung, colon/rectum, and skin [melanoma], which were the five most common sites for incident cancer in the US).(3)

Three pre-specified sensitivity analyses were performed. First, although the American Heart Association's composite CVH score combined different domains with equal weighting, it is unclear whether each domain has equal prognostic values. Thus, each unit-increment in CVH score may not be prognostically equal. Therefore, a sensitivity analysis was performed for the CVH score using ordinal logistic regression instead, with OR and the corresponding 95% CI as summary statistics. Second, to further remove and thus clarify the effects that known cardiac conditions may have on the observed associations, a sensitivity analysis was performed in which only patients without any known cardiac condition were analyzed.

The third sensitivity analysis explored the relationship between SDOH (in quartiles) and varying definitions of CVH by using multivariable Poisson regression. As the definition of CVH is still evolving, testing different potential definitions may better reflect the robustness of the observed associations. In this analysis, excessive alcohol use was added as a CVH

component, defined as >14 drinks/week [for men] or >7 drinks/week [for women] in the past year.(137)

Finally, as worse CVH might have been due to better detection by higher rates of cardiometabolic workup, a post-hoc exploratory analysis was performed to explore the association between the SDOH score (in quartiles) and a self-reported history of having had blood pressure, fasting blood glucose, and cholesterol checked within the past year. Multivariable logistic regression was used for this analysis.

All p-values were two-sided, with $p<0.05$ considered statistically significant. As participants with missing values were excluded, the study population had no missing data. All analyses were performed using version 16.1 (StataCorp LLC, College Station, Texas, US).

2.3. Results

Of the 16,586 subjects with known cancer in NHIS 2013-2017, 8254 were analyzed after applying the exclusion criteria (**Figure 2.1**), representing a weighted population of 10,887,989 persons. The distribution of the SDOH score is visualized in **Supplementary Figure 2.1,** with a weighted mean score of 5.3±4.2. Subjects in the first quartile of the SDOH score had a score of 0-2, the second quartile had a score of 3-4, the third quartile had a score of 5-7, and the fourth quartile had a score of 8-28. The per-component distribution of the SDOH score is detailed in **Supplementary Table 2.2**. The distribution of the CVH score is visualized in **Supplementary Figure 2.2**, with a weighted mean score of 2.9±1.5. Characteristics of the included subjects are summarized in **Table 2.1**. Characteristics of subjects were also tabulated against the included subjects in **Supplementary Tables 2.3** and **2.4**. The included and excluded subjects were generally comparable, except for older age, more commonly male, had higher rates of hypercholesterolemia, and less commonly had low family income.

Figure 2.1 Study flowchart

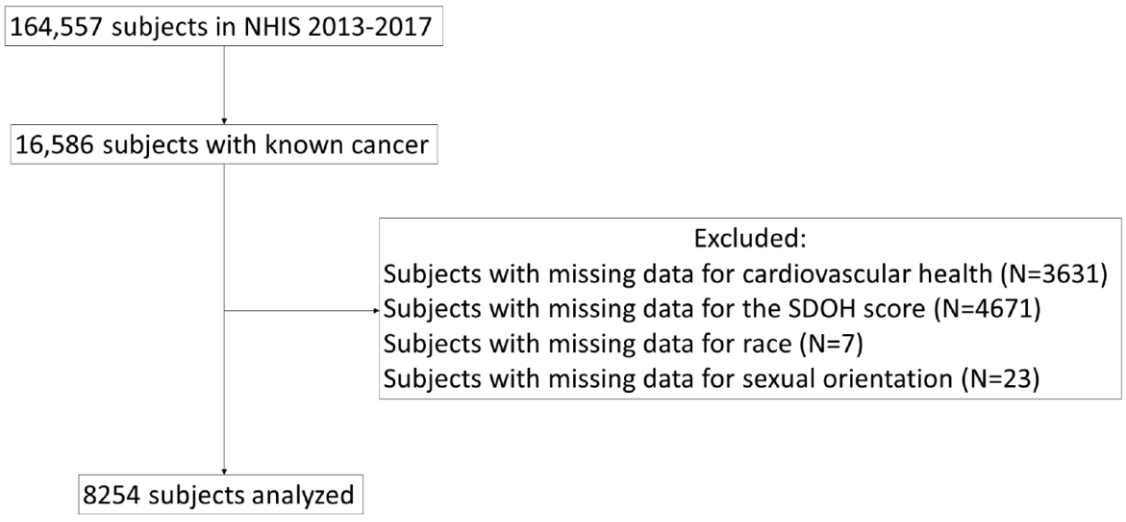


Table 2.1 Demographics and components of cardiovascular health in the included subjects

	Overall	SDOH			
		Quartile 1	Quartile 2	Quartile 3	Quartile 4
Sample size	8254	2493	2010	1801	1950
Weighted sample size	10,887,989	3,233,506	2,619,067	2,433,199	2,602,216
Demographics					
Age in years, N (%)					
18-45	581 (7.0)	53 (2.1)	76 (3.8)	156 (8.7)	296 (15.2)
46-64	2524 (30.6)	478 (19.2)	508 (25.3)	607 (3.7)	931 (47.7)
65 or above	5149 (62.4)	1962 (78.7)	1426 (71.0)	1038 (57.6)	723 (37.1)
Male, N (%)	3755 (45.5)	1343 (53.9)	934 (46.5)	772 (42.9)	706 (36.2)
Race, N (%)					
White	7405 (89.7)	2299 (92.2)	1842 (91.6)	1604 (89.1)	1660 (85.1)
Black / African American	526 (6.4)	122 (4.9)	101 (5.0)	117 (6.5)	186 (9.5)
American Indian / Alaskan native	39 (0.5)	8 (0.3)	3 (0.2)	13 (0.7)	15 (0.8)
Asian	154 (1.9)	41 (1.6)	34 (1.7)	40 (2.2)	39 (2.0)
Multiple race	130 (1.6)	23 (0.9)	30 (1.5)	27 (1.5)	50 (2.6)
Heterosexual, N (%)	7995 (96.9)	42 (1.7)	55 (2.7)	54 (3.0)	108 (5.5)
Type of cancer (not mutually exclusive)					
Breast, N (%)	1502 (18.2)	438 (17.6)	364 (18.1)	337 (18.7)	365 (18.7)
Prostate, N (%)	1094 (13.3)	442 (17.7)	287 (14.3)	210 (11.7)	155 (8.0)
Lung, N (%)	274 (3.3)	78 (3.1)	59 (2.9)	61 (3.4)	76 (3.9)
Colorectal, N (%)	531 (6.4)	166 (6.7)	122 (6.1)	107 (5.9)	136 (7.0)
Skin (melanoma), N (%)	646 (7.8)	219 (8.8)	164 (8.2)	136 (7.6)	127 (6.5)
Other types, N (%)	2687 (32.6)	622 (25.0)	588 (29.3)	628 (64.9)	849 (43.5)
Unknown, N (%)	2097 (25.4)	718 (28.0)	553 (27.5)	448 (24.9)	378 (19.4)
Cardiovascular health domains					
Hypertension, N (%)	4883 (59.2)	1530 (61.4)	1182 (58.8)	1065 (59.1)	1106 (56.7)
Diabetes mellitus, N (%)	1955 (23.7)	502 (20.1)	474 (23.6)	447 (24.8)	532 (27.3)
Hypercholesterolemia, N (%)	4411 (53.4)	1394 (55.9)	1099 (54.7)	944 (52.4)	974 (50.0)
Smoking, N (%)	4313 (52.3)	1236 (49.6)	1017 (50.6)	943 (52.4)	1117 (27.3)

Physical inactivity, N (%)	5204 (63.1)	1498 (60.1)	1188 (59.1)	1153 (64.0)	1365 (70.0)
Inadequate sleep, N (%)	1239 (15.0)	236 (9.5)	252 (12.5)	278 (15.4)	473 (24.3)
Obesity, N (%)	2702 (32.7)	687 (27.6)	577 (28.7)	636 (35.3)	802 (41.1)
Excessive alcohol use, N (%)	458 (5.6)	126 (7.9)	117 (9.0)	97 (8.9)	118 (10.0)

SDOH, social determinants of health. Percentages are unweighted.

2.3.1. Association between social determinants of health and cardiovascular health

The highest (fourth) quartile of the SDOH score was independently associated with a higher risk of having worse CVH (RR 1.30, 95% CI 1.25-1.35, p<0.001, **Table 2.2**). The relationship between the SDOH score and CVH (**Figure 2.2A**) was grossly linear.

Table 2.2 Associations between the social determinants of health (SDOH) score and Cardiovascular Health (CVH) score

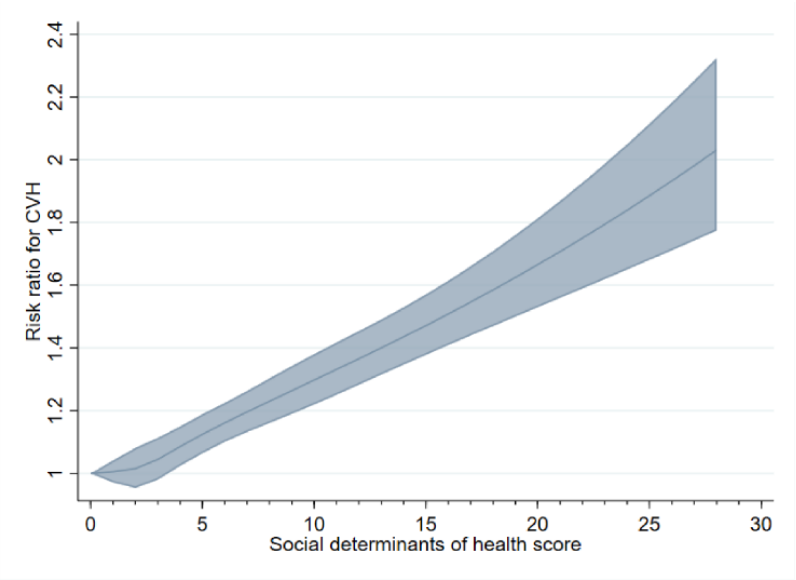
		Primary outcome (CVH score)[1]
SDOH Score Risk Ratio (95% CI) P-value	Quartile 1	1 (reference)
	Quartile 2	1.04 (1.00-1.08) 0.085
	Quartile 3	1.13 (1.09-1.18) <0.001
	Quartile 4	1.30 (1.25-1.35) <0.001

CVH, Cardiovascular Health. Adjusted risk ratios and the corresponding 95% confidence intervals are displayed.

[1] Adjusted for sex, age, race, sexual orientation, and the presence of any known cardiac condition.

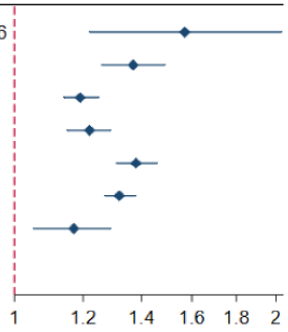
Figure 2.2 Summary of key results. **(A)** A five-knot restricted cubic spline shows a direct and grossly linear relationship between the social determinants of health (SDOH) score and the primary outcome (Cardiovascular Health; CVH). **(B)** Subgroup analyses for the primary outcome show particularly strong SDOH-CVH associations in younger or female cancer survivors. Adjusted risk ratios and confidence intervals (CI) from multivariable Poisson regression are displayed.

A



B

Subgroup	Sample size	Weighted population	Risk ratio with 95% CI for the 4th quartile of SDOH score	p-value	p-value for interaction
Age 18-45	581	901913	1.57 [1.22, 2.03]	<0.001	Age 18-45 vs 46-64: 0.696
Age 46-64	2524	3798639	1.37 [1.26, 1.49]	<0.001	Age 18-45 vs ≥65: 0.026
Age ≥65	5149	6187436	1.19 [1.14, 1.25]	<0.001	Age 46-64 vs ≥65: 0.003
Male	3755	5245061	1.22 [1.15, 1.29]	<0.001	0.001
Female	4499	5642928	1.38 [1.31, 1.46]	<0.001	
White	7405	9870601	1.32 [1.27, 1.38]	<0.001	0.051
Non-White	849	1017388	1.17 [1.05, 1.29]	0.004	

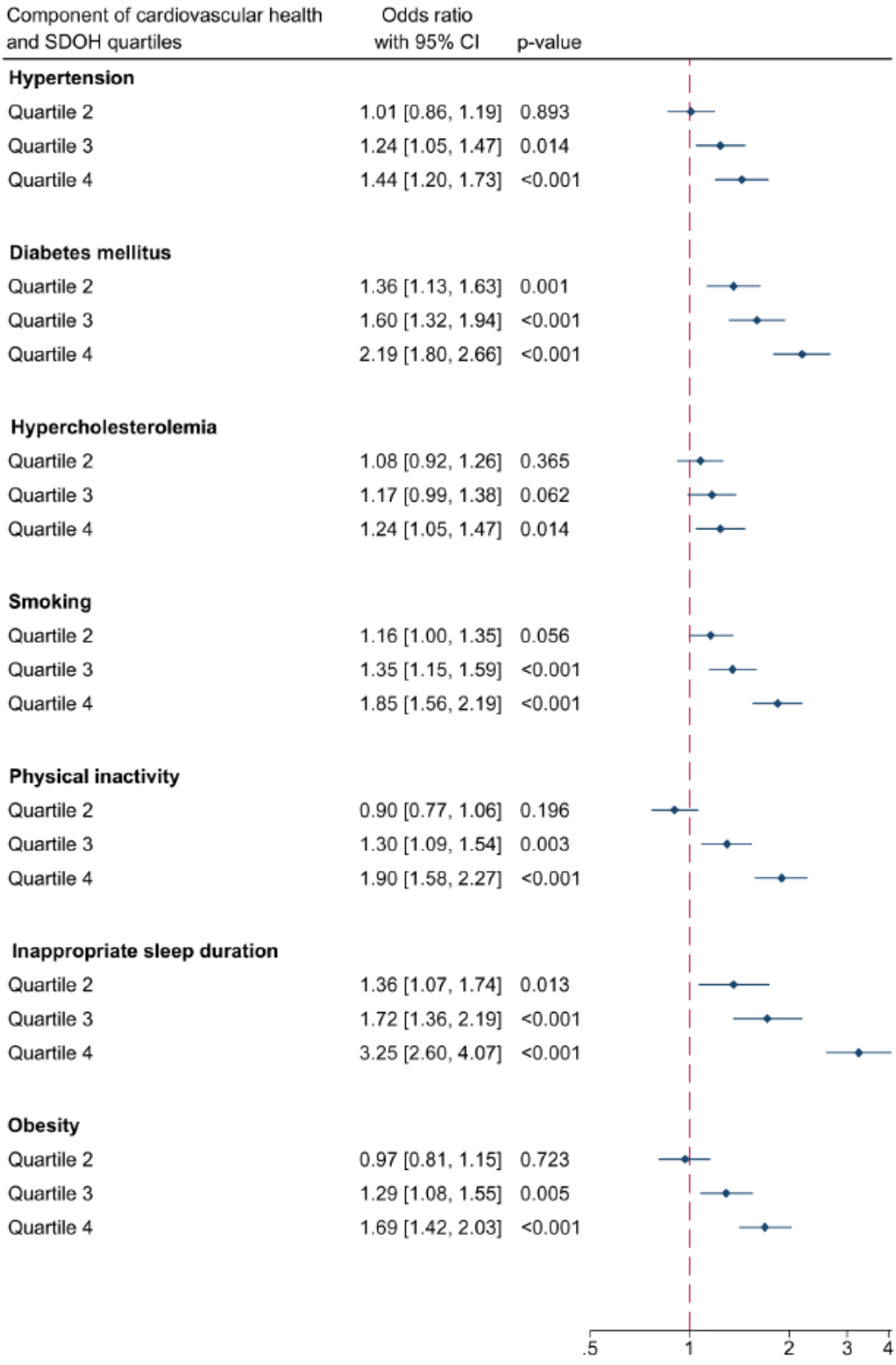


Except for the education domain, higher values in all other domains of the SDOH score were independently associated with worse CVH (**Table 2.3**), with the strongest association observed for food insecurity (RR 1.38, 95% CI 1.31-1.45, p<0.001). Meanwhile, independent associations were noted between the highest quartile of the SDOH score and all components of CVH (**Figure 2.3**), with the strongest association observed for inappropriate sleep duration (OR 3.25, 95% CI 2.60-4.07, p<0.001).

Table 2.3 Associations between individual domains of the social determinants of health (SDOH) score and cardiovascular health

Domain of the SDOH score	Number of domains	Primary outcome (CVH score)[1] Adjusted risk ratio [95% CI]	p value
Economic stability	13		
As a continuous variable		1.04 [1.03-1.04]	<0.001
As quartiles			
Q1		1 (reference)	
Q2		1.03 [0.99-1.07]	0.14
Q3		1.11 [1.06-1.15]	<0.001
Q4		1.28 [1.23-1.33]	<0.001
Neighbourhood, physical environment, and social cohesion	5		
As a continuous variable		1.06 [1.05-1.07]	<0.001
As terciles[2]			
T1		1 (reference)	
T2		1.06 [1.03-1.10]	0.001
T3		1.20 [1.16-1.24]	<0.001
Community and social context	1	1.29 [1.2-1.37]	<0.001
Food	1	1.38 [1.31-1.45]	<0.001
Education	7		
As a continuous variable		0.99 [0.98-1.01]	0.48
≤1 domain[2]		1 (reference)	
≥2 domains[2]		0.99 [0.96-1.02]	0.39
Healthcare system	11		
As a continuous variable		1.05 [1.03-1.06]	<0.001
No domain[2]		1 (reference)	
Any domain[2]		1.07 [1.03-1.11]	<0.001

Figure 2.3 Associations for the components of cardiovascular health. This forest plot shows significant associations between the social determinants of health (SDOH) score and all components of the cardiovascular health score. Adjusted odds ratios and 95% confidence intervals from multivariable logistic regression are displayed.



2.3.2. Subgroup analyses

After stratifying for age, sex, and race, the SDOH score remained independently associated with CVH (**Figure 2.2B** and **Supplementary Table 2.5**). The associations were significantly stronger in participants who were younger (age 18-45 vs. ≥65: $p_{interaction}$=0.026; age 46-64 vs. ≥65: $p_{interaction}$=0.003). No statistically significant interaction between the SDOH score and race was observed ($p_{interaction}$=0.051).

Stratification for cancer sites showed largely consistent results, with significant associations for CVH observed for all five specified cancer sites (**Supplementary Table 2.5**).

2.3.3. Sensitivity analyses

Results from sensitivity analyses were consistent with the main analyses (**Supplementary Table 2.6**). Ordinal logistic regression demonstrated a robust and independent relationship between the highest quartile of the SDOH score and higher CVH score (OR 2.57, 95% CI 2.21-2.98, p<0.001). Meanwhile, a similar association was observed for CVH among those without any known cardiac condition (RR 1.34, 95% CI 1.27-1.40, p<0.001). Adding excessive alcohol use to CVH as a component of cardiovascular health (RR 1.33, 95% CI 1.27-1.40, p<0.001) also resulted in consistently strong associations with the SDOH score.

2.3.4. Exploratory analyses

Post-hoc exploratory analyses (**Supplementary Table 2.7**) found no significant association between the SDOH score and self-reported history of having had blood pressure (OR for the highest quartile of SDOH: 0.89, 95% CI 0.50-1.58, p=0.70), fasting blood glucose (OR for the highest quartile of SDOH: 1.07, 95% CI 0.89-1.28, p=0.47), or blood cholesterol (OR for the highest quartile of SDOH: 0.94, 95% CI 0.70-1.26, p=0.69) checked within the past year.

2.4. Discussion

Using nationally representative US data, we demonstrated a strong and robust relationship between disadvantaged SDOH profile and suboptimal CVH among cancer survivors, which was particularly prominent among women and younger participants (**Figure 2.4** / **Central Illustration)**. To our knowledge, this is the first study to investigate this association among cancer survivors directly.

2.4.1. Comparison with Previous Literature

Unfavorable SDOH profiles have been associated with higher prevalence of CVD and cancer-related mortality in the general population.(104,133,138,139) Previous studies demonstrated that various domains of SDOH influence CVH in complex and variable ways. For example, Makhlouf and colleagues found that neighborhood walkability and the green space availability

were associated with better CVH in the US.(140) Similarly, in another cross-sectional survey, food insecurity was associated with suboptimal CVH.(141) Housing insecurity has also been identified to be associated with CVH in the general population.(142)

While all these SDOH domains are important, only specific facets of SDOH have been investigated for their relationships with CVH in cancer survivors. For instance, Batra and colleagues found that rural residence, low income, and low education were associated with higher risks of developing CVD in cancer survivors.(108) These were confirmed by Berkman and colleagues who found that an annual household income <USD50,000 was associated with increased the odds of CVD in young adult cancer survivors,(110) and Appiah and colleagues who showed that breast and gynecologic cancer survivors residing in rural areas had higher risks of cardiovascular mortality.(109)

However, SDOH extend beyond these few specific factors, and as individual domains of SDOH are likely associated with CVH in complex and intersectional ways, studying them in isolation is inadequate. Instead, an aggregate SDOH risk score may better identify and improve care for socially disadvantaged individuals.(143)Hence, we used a well-established and published aggregate SDOH score, ensuring reliability, robustness, and objectivity. Similar issues may exist for CVH quantification which is evolving. Therefore, we referenced the American Heart Association's Life's Essential 8 model, an evidence-based framework created in 2022 to define and quantify CVH.(132) Although the original model involved more detailed measurements and included diet, the CVH score used in this study had been published previously and shown to be a robust measurement of CVH.(133,135)The use of this CVH score thus ensured robustness of our findings. This was further reinforced by sensitivity analyses, in one of which excessive alcohol use was added to the CVH score in recognition of CVH as an evolving concept.

Importantly, we found that the association between SDOH and CVH was particularly strong among females or young individuals, congruent with previous research on associations between social vulnerability and mortality due to comorbid cancer and CVD.(144) The worse CVH associated with disadvantaged SDOH may have contributed to such observations for mortality, further emphasizing the need to prioritize interventions that address social and economic disadvantage in female and young cancer survivors.

2.4.2. Underlying Mechanisms

The association between SDOH and CVH is likely multifactorial. However, our exploratory analyses suggested that differences in rates of cardiometabolic workup within the past year were unlikely to be the driving factor behind this association. We speculate that the adverse association between socioeconomic disadvantage and mental health may be one of the potential mediators.(145,146) We previously showed that psychological distress is associated with worse CVH in adult cancer survivors.(147) Others have also hypothesized that psychological factors mediate associations between social/physical environments and CVD(148,149) which may be

positive (e.g., social support improving health behaviors among racial/ethnic minority groups by reducing depressive symptoms)(150,151) or negative (e.g., poorly built environments increasing the risk of CVD via an increased likelihood of mental disorders causing chronic life stress).(152,153) Nevertheless, other mediating mechanisms likely also exist. Further studies are required to delineate the drivers of our observations.

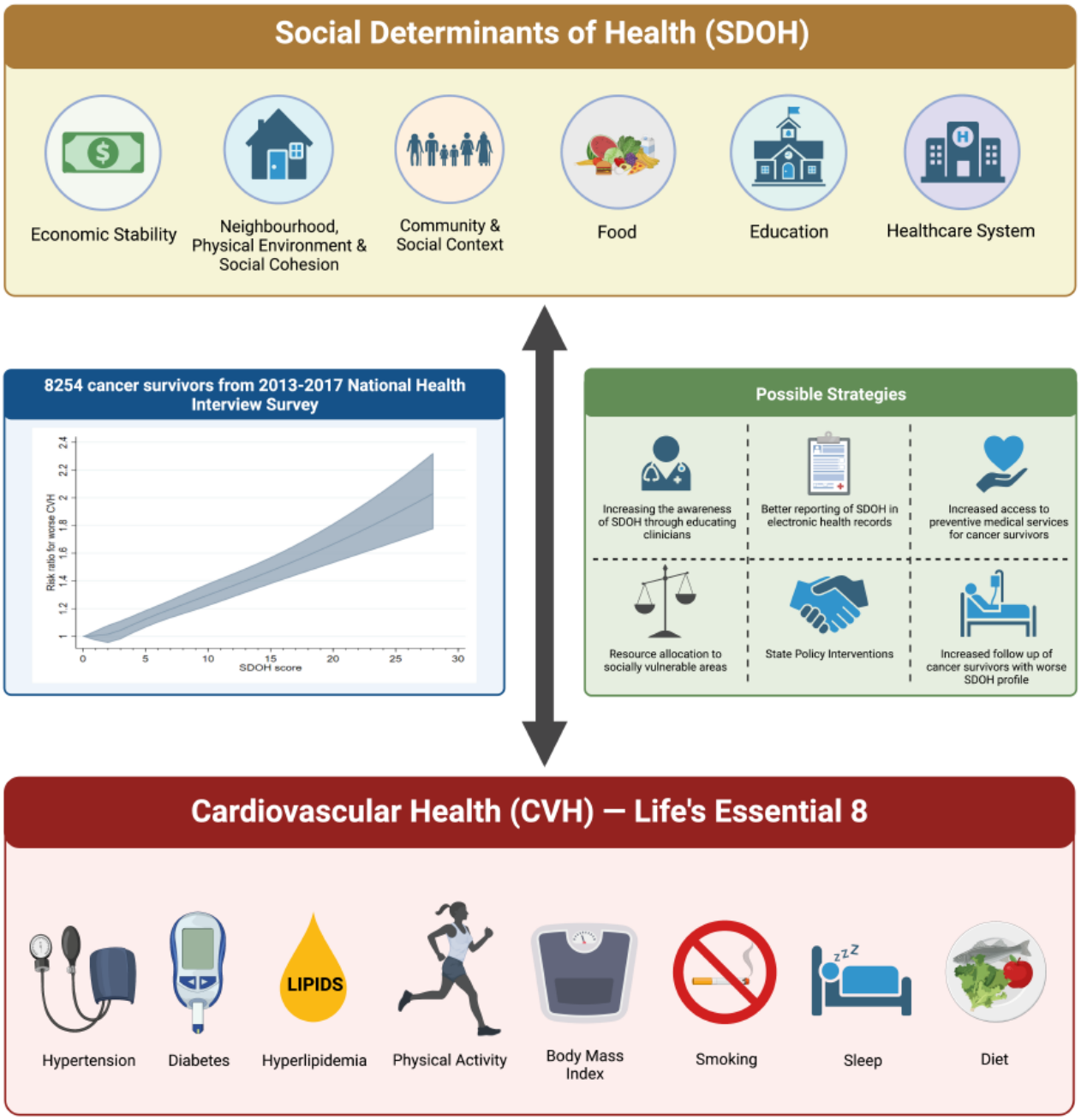
2.4.3. Clinical and Policy Implications

Our findings have substantial clinical and public health implications, as they underscore the pivotal roles of social, economic, and environmental conditions in determining the CVH of cancer survivors, particularly younger individuals, and women. Our results demonstrated substantial social disparity in CVH among cancer survivors, highlighting the need for comprehensive interventions at various levels to minimize social disparity and ultimately optimize cardiovascular outcomes in this population.

At the clinical level, clinicians must be educated about the strong links between SDOH and CVH in cancer survivors so that those with poor SDOH profiles can be flagged and targeted for specific interventions (**Figure 2.4)**. This process may also benefit from better reporting of patients' SDOH within electronic health records, facilitating SDOH profiling and risk stratification, and enabling more in-depth research into this area.

At the healthcare system and policy level, investments in healthcare infrastructure may need to be increased in socially vulnerable areas to ensure equitable access to quality healthcare. State policies may also need to be recalibrated to enhance cancer survivors' access to preventive medicine services, such as ensuring continued follow-up care for those with disadvantaged SDOH profiles. Given the interconnected nature of these factors and their cascading downstream effects on health outcomes, national efforts are needed to reduce social disparities in CVH among cancer survivors, likely within broader programs such as the Centers for Medicare and Medicaid Services (CMS) initiative(154): focusing on addressing SDOH for Medicare and Medicaid beneficiaries, the CMS initiative aims to support healthcare providers in identifying and addressing SDOH factors by screening patients for SDOH risks, providing referrals to community resources, and integrating SDOH interventions into care plans. It also aims to standardize data collection and analysis related to SDOH, as well as collaborations with community organizations and other stakeholders to address SDOH more broadly. Similar programs are needed to target cancer survivors and optimize their CVH.

Figure 2.4. Social determinants of health and cardiovascular health of cancer survivors. The Central Illustration highlights the significant associations observed between various social determinants of health (SDOH) factors and the cardiovascular health (CVH) of cancer survivors. It provides a visual summary of the key findings, emphasizing the impact of SDOH on CVH outcomes. The figure underscores the importance of considering SDOH factors in promoting cardiovascular well-being among cancer survivors and highlights potential areas for targeted interventions and support.



2.4.4. Strengths and Limitations

We utilized a nationally representative US database, ensuring the generalizability of our findings within the US, with potential generalizability to other developed countries. In addition, the robustness of our analyses was reinforced by multiple sensitivity analyses which consistently yielded similar observations. Finally, the use of well-established and published measurement tools of SDOH and CVH ensured objectivity and reliability.

However, our study is not devoid of limitations. First, as all NHIS data are self-reported, they are subject to misreporting, under-reporting, and recall bias. Specifically, any history of cancer diagnosis and all components of CVH were self-reported without cross-checking with physicians or against medical records. However, participants who reported a history of cancer were subsequently asked for the cancer type, thereby partly mitigating the risk of misreporting.

Second, as detailed dietary data are available in the NHIS, we were unable to include dietary variables in our assessment of *Life's Essential Eight*. This was partially mitigated in our sensitivity analyses, where excessive alcohol use was used as a surrogate for poor dietary habits within the cardiovascular health component, with consistent results.

Third, the cross-sectional design of NHIS precludes any establishment of causality. While existing evidence predominantly supports the role of SDOH as a predictor of CVH (with the posited direction of the association being from unfavorable SDOH to worse CVH and not otherwise),(155) it remains possible that worse CVH leads to more unfavorable SDOH via increased medical expenditure, reduced exercise/socialization, or other mechanisms. Future research should explore the potential and implications of reverse causation in the SDOH-CVH-cancer context. Residual confounding was also possible.

Additionally, although we explored differences in the association between SDOH and CVH between races/ethnicities, very few of the analyzed cancer survivors were non-White, which was not unexpected as NHIS is representative of the US where the population is predominantly White. The small sample sizes limited the statistical power of the interaction analysis and barred further stratification of non-White cancer survivors into detailed races/ethnicities. Therefore, with substantially different point estimates, minimally overlapping 95% CIs, and borderline statistical significance, inter-racial differences in the said association could not be definitively excluded. Overall, the demographics of the sampled individuals in NHIS meant that our findings might not be directly generalizable to countries with substantially different racial/ethnic compositions. Larger international studies are needed to corroborate our findings across cancer survivors of different races/ethnicities.

Finally, we acknowledge that the subjects included in our analysis differed in certain aspects from those who were excluded, which may impact generalizability and representativeness of

our findings. Large prospective studies with minimal data missingness remain required to verify our findings.

2.5. Conclusions

Among cancer survivors in the United States, an unfavorable SDOH profile was independently associated with worse CVH, especially in young and female subjects. This highlights the need for a comprehensive approach to healthcare for cancer survivors that considers the broader socioeconomic and environmental factors associated with their CVH.

3. Chapter 3: Association between psychological distress and cardiovascular health amongst cancer survivors in the United States: findings from nationally representative data

This chapter is based on the following publication: **Chan JSK**, Satti DI, Dee EC, Sharma G, Virani SS, Liu T, Tse G. Association between psychological distress and cardiovascular health amongst cancer survivors in the United States: findings from nationally representative data. *Eur J Prev Cardiol.* 2023; 30(16): e74-e77. doi: 10.1093/eurjpc/zwad162

3.1. Introduction

Cancer is associated with increased long-term cardiovascular risks(4) and psychological distress.(156) Whilst psychological distress has been linked to elevated cardiovascular risks,(157) the strong correlation between cancer and cardiovascular diseases may modify the cardiovascular effects of psychological distress. It is thus unclear if these associations hold true for cancer survivors. Investigations in this area are needed as the number of cancer survivors increases.(158) We therefore investigated the relationship between psychological distress and cardiovascular health amongst cancer survivors.

3.2. Methods

3.2.1. Study design and source of data

This cross-sectional study used data from the National Health Interview Survey (NHIS), a publicly available dataset collected via annual in-person interviews conducted by the National Center for Health Statistics/Centers for Disease Control and Prevention. The NHIS utilizes multistage probability sampling, stratification, clustering, and over-sampling to provide health data representative of the non-institutionalized population of the United States. Harmonised data were obtained from the Integrated Public Use Microdata Series (IPUMS).(159) As all the data are deidentified and publicly available, this study was exempt from ethics approval.

3.2.2. Inclusion and exclusion criteria

Subjects aged ≥18 years old sampled between 2013-2017 were included. Patients with missing data for the outcome or any of the independent variables were excluded, as were those with non-melanotic skin cancer as the only cancer diagnosis, consistent with prior studies.(160) Cancer survivorship was ascertained by responses to the question, “Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?” (IPUMS NHIS variable *cancerev*).

3.2.3. Ascertainment of outcomes and exposure

Measurement of the outcome, cardiovascular health, was based on the American Heart Association’s *Life’s Essential Eight*.(132) As the NHIS has no dietary data, the cardiovascular

health score included seven one-point domains (hypertension [ascertained from the IPUMS NHIS variable *hypertenev*], diabetes mellitus [ascertained from the IPUMS NHIS variables *diabeticev*, *insulin*, and *diapills*], dyslipidaemia [ascertained from the IPUMS NHIS variables *cholhighyr*, *cholhighev*, and *cholmednow*], physical inactivity [defined as <75 hours/week of vigorous exercise or <150 hours/week of moderate exercise; ascertained from the IPUMS NHIS variables *mod10dmin*, *mod10fwk*, *vif10dmin*, and *vig10fwk*], inappropriate sleep duration [defined as <6 or ≥10 hours of sleep per night; ascertained from the IPUMS NHIS variable *hrsleep*], smoking [ascertained from the IPUMS NHIS variable *smokestatus2*], and obesity [defined as body-mass index ≥30 kg/m^2; ascertained from the IPUMS NHIS variable *bmicalc*]), with higher scores indicating poorer cardiovascular health. This score has been published before.(133)

Psychological distress was measured by the six-item Kessler scale (K6), a validated screening tool for psychological distress. It consists of six five-point (0-4) Likert questions about emotional state, with possible total scores of 0-24.(161) K6 was binarized, with scores≥13 representing severe psychological distress (SPD), consistent with previous studies.(161) K6 was ascertained from the IPUMS NHIS variables *asad*, *anervous*, *arestless*, *ahopeless*, *aeffort*, and *aworthless*. All data were self-reported as per the NHIS' nature.

3.2.4. Statistical analysis and covariate ascertainment

Survey-specific statistics with sampling weights (divided by the included number of years as per the NHIS' recommendations) and stratification for survey year were used to generate nationally representative estimates. Multivariable Poisson regression adjusting for pre-specified covariates (the presence of any known cardiac condition [ascertained from the IPUMS NHIS variables *cheartdiev*, *heartattev*, *heartconev*, and *angipecev*], family income [ascertained from the IPUMS NHIS variable *poverty*], education level [ascertained from the IPUMS NHIS variable *educ*], race [ascertained from the IPUMS NHIS variable *racenew*], sex [ascertained from the IPUMS NHIS variable *sex*], sexual orientation [ascertained from the IPUMS NHIS variable *sexorien*], insurance coverage [ascertained from the IPUMS NHIS variable *hinotcov*], and age [ascertained from the IPUMS NHIS variable *age*]) was used to investigate the relationship between SPD and the cardiovascular health score, with risk ratios (representing the comparative risk of having worse cardiovascular health) and 95% confidence intervals as summary statistics. A three-knot restricted cubic spline with K6 as a continuous variable was used to explore the linearity of this relationship, using Harrell's recommended knot positions.(136) Multivariable logistic regression adjusting for pre-specified covariates was used to explore relationships between SPD and each component of the cardiovascular health score amongst cancer survivors, with odds ratios and 95% confidence intervals as summary statistics.

Pre-specified subgroup analyses were performed amongst cancer survivors, with stratifications for known cardiac condition(s) (with vs without), age (18-45 years old vs 46-64 years old vs ≥65 years old), sex (male vs female), race (white vs non-white), income (family income <200%

vs ≥200% of the poverty threshold), and cancer site (breast, prostate, colon/rectum, skin [melanotic], and lung).

Two *post hoc* exploratory analyses were done. First, the relationship between SPD and the presence of known cardiovascular diseases was explored using multivariable logistic regression with similar covariate adjustments as described above; odds ratios and 95% confidence intervals were used as summary statistics. Second, as the pre-specified subgroup analyses identified significant interactions for age groups and sex with K6, similar subgroup analyses and testing for interactions were performed amongst participants without any reported history of cancer.

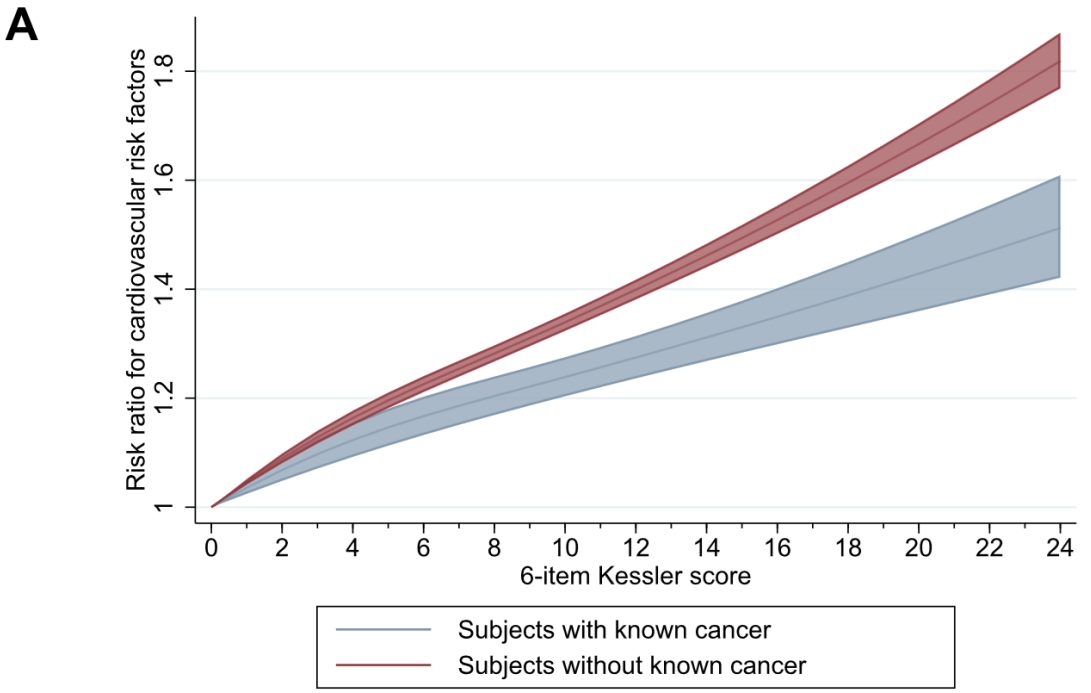
Two-sided $p<0.05$ were considered statistically significant. All analyses were performed using Stata v16.1 (StataCorp LLC, USA).

3.3. Results

Of the 164,557 subjects in 2013-2017 NHIS, 138,001 (representing a weighted population of 203,223,831) were analysed after applying all exclusion criteria, of whom 13,485 (9.8%; representing a weighted population of 17,648,471) were cancer survivors; 13,354 had data for the age of cancer diagnosis, of whom 2.7% were diagnosed by 14 years old, 30.8% between 14-45, 41.8% between 46-64, and 24.7% at ≥65 years old. The weighted mean cardiovascular health score was 2.8±1.6 for cancer survivors and 2.0±1.4 for those without known cancer. Their respective weighted prevalence of SPD were 3.8% [95% CI: 3.5%-4.3%] and 3.2% [3.0%-3.3%].

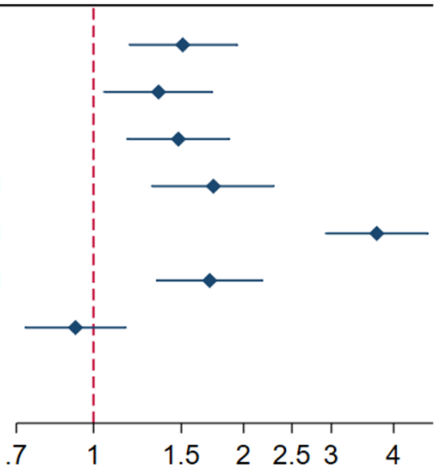
SPD was independently associated with worse cardiovascular health both in cancer survivors (adjusted RR 1.24 [1.19-1.29], $p<0.001$) and those without known cancer (adjusted RR 1.41 [1.39-1.44], $p<0.001$), but the former association was significantly weaker ($p_{interaction}=0.001$; **Figure 3.1A**). The relationship between psychological distress and cardiovascular health was grossly linear, regardless of cancer history (**Figure 3.1A**). Amongst cancer survivors, SPD was independently associated with all components of the cardiovascular health score except obesity (**Figure 3.1B**), with the strongest association observed for inappropriate sleep duration (adjusted OR 3.70 [2.93-4.68], $p<0.001$). Exploratory analysis showed a strong relationship between SPD and known cardiovascular disease amongst cancer survivors (odds ratio 2.95 [2.30-3.78], $p<0.001$).

Figure 3.1 Graphical summary of results. **(A)** Restricted cubic spline showing the relationship between the six-item Kessler score and cardiovascular health, stratified by whether the subjects had known cancer. Risk ratio and 95% confidence intervals are shown, with risk ratio>1 representing an association with more cardiovascular risk factors (i.e. worse cardiovascular health). **(B)** Forest plot showing the associations between severe psychological distress and individual components of the cardiovascular health score amongst cancer survivors. Adjusted odds ratios and 95% confidence intervals (CIs) are shown.



B

Components of the cardiovascular health score	Odds ratio with 95% CI	p-value
Hypertension	1.51 [1.18, 1.94]	0.001
Diabetes mellitus	1.35 [1.05, 1.73]	0.017
Dyslipidaemia	1.48 [1.17, 1.87]	0.001
Physical inactivity	1.74 [1.31, 2.30]	<0.001
Sleep deprivation	3.70 [2.93, 4.68]	<0.001
Smoking	1.71 [1.34, 2.18]	<0.001
Obesity	0.92 [0.73, 1.16]	0.491



Subgroup analyses demonstrated that amongst cancer survivors, the association between SPD and cardiovascular health was significantly stronger in those who were younger ($p_{interaction}<0.05$; **Figure 3.2**) or female ($p_{interaction}=0.014$), but did not differ significantly by family income ($p_{interaction}=0.992$), race ($p_{interaction}=0.147$), or the presence of known cardiac conditions ($p_{interaction}=0.187$). The association remained significant in those with cancer of the breast (N=2445; adjusted RR 1.34 [1.21-1.49], p<0.001), prostate (N=1642; adjusted RR 1.23 [1.08-1.38], p=0.001), colon/rectum (N=873; adjusted RR 1.20 [1.06-1.35], p=0.004), and skin (melanotic; N=1024; adjusted RR 1.46 [1.20-1.77], p<0.001), but not that of the lung (N=430; adjusted RR 1.08 [0.90-1.29], p=0.417). Exploratory subgroup analyses in participants without known cancer showed similar interactions for age groups, but not for sex (**Table 3.1**).

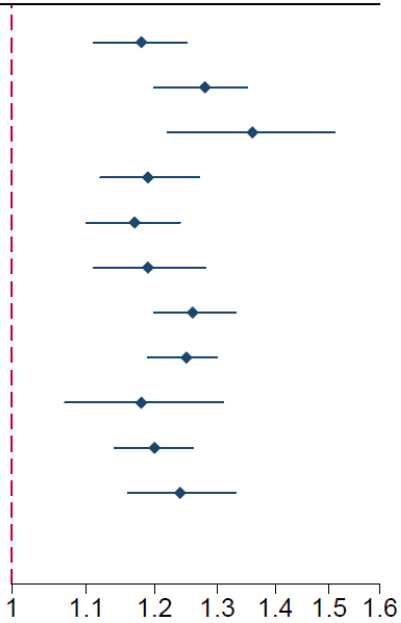
Table 3.1 Results of the post hoc exploratory subgroup analyses amongst participants without known cancer.

Subgroup		Adjusted RR [95% CI]	$p_{interaction}$
Age, years old	18-45	1.48 [1.43, 1.54], p<0.001	All pairwise $p_{interaction}<0.001$
	46-64	1.33 [1.29, 1.36], p<0.001	
	≥65	1.24 [1.20, 1.29], p<0.001	
Sex	Male	1.44 [1.39, 1.49], p<0.001	0.901
	Female	1.40 [1.36, 1.43], p<0.001	

CI, confidence interval. RR, risk ratio.

Figure 3.2 Forest plot showing the results of pre-specified subgroup analyses amongst cancer survivors. Adjusted risk ratios and 95% confidence intervals (CIs) are shown.

Subgroup	Sample size	Weighted population	Risk ratio with 95% CI	p-value	p-value for interaction
With known cardiac condition(s)	3700	4539067	1.18 [1.11, 1.25]	<0.001	0.187
Without any known cardiac condition	9785	13109404	1.28 [1.20, 1.35]	<0.001	
Age 18-45	1322	193058	1.36 [1.22, 1.51]	<0.001	Age 18-45 vs 46-64: 0.010
Age 46-64	4393	6487668	1.19 [1.12, 1.27]	<0.001	Age 18-45 vs ≥65: <0.001
Age ≥65	7770	9167745	1.17 [1.10, 1.24]	<0.001	Age 46-64 vs ≥65: 0.043
Male	5786	8045962	1.19 [1.11, 1.28]	<0.001	0.014
Female	7699	9602509	1.26 [1.20, 1.33]	<0.001	
White	11932	15864972	1.25 [1.19, 1.30]	<0.001	0.147
Non-White	1553	1783499	1.18 [1.07, 1.31]	0.001	
Family income <200% of poverty threshold	3878	4035440	1.20 [1.14, 1.26]	<0.001	0.992
Family income ≥200% of poverty threshold	9607	13613031	1.24 [1.16, 1.33]	<0.001	



3.4. Discussion

This is the first study investigating the association between psychological distress and cardiovascular health amongst cancer survivors. The significant association between SPD and cardiovascular health was consistent with findings in other populations.(157) The association being weaker in cancer survivors was likely due to the adverse cardiovascular effects of cancer and cancer therapies diminishing the relative influence of psychological distress. Importantly, younger individuals were particularly vulnerable to this association, likely because ageing has more dominant effects on cardiovascular health in older individuals. Female cancer survivors were also more vulnerable to the captioned association, as observed elsewhere as well.(157) The underlying mechanisms are less clear, probably including social factors such as sexism,(157) and biological factors such as lower vaso-reactivity, greater stress-induced reduction in endothelial function in females, and female-specific cardiovascular risk factors (e.g. hormone-related).(162)

Clinically, our findings highlighted the importance of a holistic and multidisciplinary approach to the care of cancer survivors, specifically being attentive to their psychological well-being and involving mental health professionals in a timely manner, and especially for younger or female patients. Our findings also provided insights for policymakers about patients who may benefit the most from quality improvement programs. Using data from a national survey, our findings were representative and widely applicable. Nonetheless, the self-reported nature meant that recall bias and misclassification of variables were possible, and residual/unobserved confounders could exist. Additionally, the cross-sectional nature of the NHIS prevented establishment of causality. Reverse causality is also possible, as poorer cardiovascular health may cause SPD.

3.5. Conclusion

SPD was associated with worse cardiovascular health amongst cancer survivors, especially younger or female patients, although the association was weaker than that in non-cancer subjects.

4. Chapter 4: Associations between social determinants of health and cardiovascular and cancer mortality in cancer survivors: a prospective cohort study

This chapter is based on the following publication: **Chan JSK**, Satti DI, Ching YLA, Lee Q, Dee EC, Ng K, Chou OHI, Liu T, Tse G, Lai A. Associations between social determinants of health and cardiovascular and cancer mortality in cancer survivors: a prospective cohort study. *Eur J Prev Cardiol*. 2024. doi: 10.1093/eurjpc/zwae318 [Online ahead of print]

4.1. Introduction

Cardiovascular diseases and cancer are both common causes of death and disability worldwide – in 2021, cardiovascular diseases were accountable for 19.4 million deaths and 428 million disability-adjusted life years lost, while cancer was accountable for 9.9 million deaths and 253 million disability-adjusted life years lost.(163,164) Despite rising incidences of both cardiovascular diseases and cancer, cancer mortality rates have been declining due to advancing treatments and earlier detection, with an estimated 33% reduction in 2019 compared to 1991.(3) Such combinations in epidemiological trends have led to an increasing number of cancer survivors, who have been shown to have higher cardiovascular risks than individuals without cancer.(8,126) Thus, cardiovascular diseases in cancer survivors have become a growing and ever-more important clinical issue.

Amongst numerous factors that affect cardiovascular health, social determinants of health (SDOH) have been increasingly recognized to substantially influence cardiovascular health in both the general population and cancer survivors.(1,165) This was reinforced recently by a nationwide cross-sectional study of cancer survivors which found strong associations between SDOH and cardiovascular health.(166) However, evidence pertaining to the influence of such associations on mortality was less clear. Previous studies have shown associations between SDOH and cardiovascular/cancer mortality in the general population,(167,168) but these associations have rarely been studied using representative, individual-level data amongst cancer survivors – given their cancer history and elevated cardiovascular risk, relevant associations observed in the general population may not be directly generalizable to them. Additionally, few studies have explored SDOH comprehensively using composite metrics, with many only focusing on selected areas of SDOH. Therefore, we explored associations between SDOH and cause-specific mortality in cancer survivors using nationally representative data, specifically focusing on cardiovascular mortality as the primary outcome of interest and with SDOH quantified using a published composite score. Individuals without cancer were also studied to explore whether these associations varied with cancer survivorship.

4.2. Methods

4.2.1. Study design and source of data

Data from the National Health Interview Survey (NHIS) were used for this prospective cohort study. The NHIS, an annual health and sociodemographic survey of the United States' non-institutionalized population linked to the National Death Index (NDI), uses multistage

probability sampling to generate nationally representative estimates. Details of NHIS and data access have been described elsewhere.(159,166) All data underlying this study are publicly available.(159) Therefore, this study is exempt from ethics review. This study and manuscript were compliant with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

4.2.2. Inclusion and exclusion criteria

Participants in NHIS 2013-2017 with mortality follow-up data were included – only these years/iterations contained variables necessary for quantifying SDOH. Those with missing SDOH or covariate data were excluded.

4.2.3. Follow-up and outcomes

All subjects were followed up from questionnaire administration to the end of 2019 or death, whichever occurred earlier, as detailed elsewhere.(169) The primary outcome was cardiovascular mortality. The secondary outcomes were cancer mortality and all-cause mortality. All outcomes were ascertained through the NDI using death certificate information.(169) There is thus no identifiable loss to follow-up.

4.2.4. Data collected and ascertainment

Cancer survivorship was self-reported(166). Per convention, only individuals with cancers other than non-melanotic skin cancer were classified as cancer survivors.(166) SDOH was quantified using a self-reported 38-point score which has been published previously, with higher scores indicating worse deprivation.(166)

Covariates, including demographics (age, race, and sex) and comorbidities / risk factors (hypertension, diabetes mellitus, hypercholesterolemia, active smoking, obesity, chronic obstructive pulmonary disease or emphysema, stroke, weekly moderate/vigorous exercise duration, weekly number of alcoholic drinks, and cardiac and liver conditions), were ascertained from self-reported data as previously detailed.(166)

4.2.5. Statistical analysis

Survey-specific statistics with sampling weights (divided by 5 as five years' sample subjects were included, as per recommendations by the NHIS) were used via Stata's *svy* set of commands to produce nationally representative estimates. Due to the survey nature of the data, continuous variables were summarized as means and 95% confidence intervals (CIs), while categorical variable were summarized as proportions and 95% CIs. As individuals with missing data were excluded, there were no missing data amongst the analysed individuals in this study.

Due to right-skewing, the composite SDOH score was analysed as standardized continuous variables after log-transformation (i.e. ln[SDOH+1]; abbreviated as 'SDOH' hereafter). As non-cardiovascular-non-cancer mortality ('other-cause mortality') constituted a competing event for cardiovascular and cancer mortality, a cause-specific approach was adopted, modelling associations between SDOH and risks of each outcome and other-cause mortality using Cox regression. Schoefield residual-based tests showed no violation of the proportional hazard assumption (**Supplementary Table 4.1 and Supplementary Figures 4.1-4.6**). Kaplan-Meier cumulative incidence curves (i.e. 1-KM) were used to visualize the cumulative incidence of each outcome and other-cause mortality, with grouping by quartiles of the SDOH score. SDOH was quantitatively analysed as a continuous variable instead of quartiles because pairwise comparisons of individual quartiles, which are necessarily much smaller in their respective sample sizes with much fewer events than that in the overall cohort, against the lowest quartile (conventionally used as the reference group) would have led to substantially lower statistical power with additional degrees of freedom. These rendered quartile-based analysis infeasible given the already-low event rates. To account for potential non-linearity in associations, three-knot restricted cubic splines (with knots placed at the 10^{th}, 50^{th}, and 90^{th} percentiles, as recommended by Harrell(136)) were fitted and plotted to visualize the association between SDOH and the risk of each outcome across the observed range of SDOH. Adjusted hazard ratios (aHRs) and 95% CIs were used as summary statistics, representing estimates per standard deviation-increase in the SDOH score.

As the main analysis, associations in cancer survivors and individuals without cancer were modelled separately. Two multivariable models were pre-specified for each outcome based on clinical knowledge: model 1 was adjusted for demographics, while model 2 was adjusted for demographics, comorbidities, and risk factors. This allowed exploration of whether associations between the SDOH score and the outcomes, if any, were explained by comorbidities and risk factors, which had been shown to be associated with SDOH.(166)

As the main analysis found statistically significant associations between the SDOH score and cardiovascular and cancer mortality in cancer survivors with full multivariable adjustments (i.e. model 2 as above-described), a *post hoc*, exploratory analysis was performed to explore potential associations between the composite score of each domain of the SDOH score (i.e. economic stability [0-13 points], neighbourhood, physical environment, and social cohesion [NPESC; 0-5 points], psychological distress [binary], food insecurity [binary], education [0-7 points], and healthcare system [0-11 points]; higher points / category indicated worse deprivation in the respective domain) and the risk of cardiovascular and cancer mortality, respectively, amongst cancer survivors. Similar to the above, multivariable Cox regressions (model 2) were used. In view of the *post hoc* nature of this analysis, p-values were not reported, and only the aHRs and 95% CIs were reported. For non-binary-score domains, the aHRs represented estimates per point-increase in each domain's score.

P-values were two-sided and, to avoid excessive reliance on p-values and potential issues with multiple hypothesis testing, were only reported for the main analysis of the primary outcome,

with $p<0.05$ considered statistically significant. All analyses were performed using Stata v16.1 (StataCorp LLC, College Station, Texas, USA).

4.3. Results

A total of 37,882 individuals were analysed (**Figure 4.1**), representing a population of 57,696,771 persons after applying sampling weights. These included 4179 cancer survivors (representing a population of 5,762,493 persons after applying sampling weights) and 33,703 individuals without cancer (representing a population of 51,934,278 persons after applying sampling weights). Their characteristics were summarized in **Table 4.1**.

Amongst cancer survivors, 9.9% [95% CI: 8.8%-11.0%] died over a mean follow-up of 4.6 years, with cardiovascular mortality occurring in 2.2%, cancer mortality occurring in 4.6%, and other-cause mortality occurring in 3.0%. Amongst individuals without cancer, 2.4% died over a mean follow-up of 4.8 years, with cardiovascular mortality occurring in 0.7%, cancer mortality occurring in 0.5%, and other-cause mortality occurring in 1.1%.

Figure 4.1 Flow diagram of study participants. Weighted N refers to the population represented by the respective sample cohort after applying sampling weights. NHIS, National Health Interview Survey. SDOH, social determinants of health.

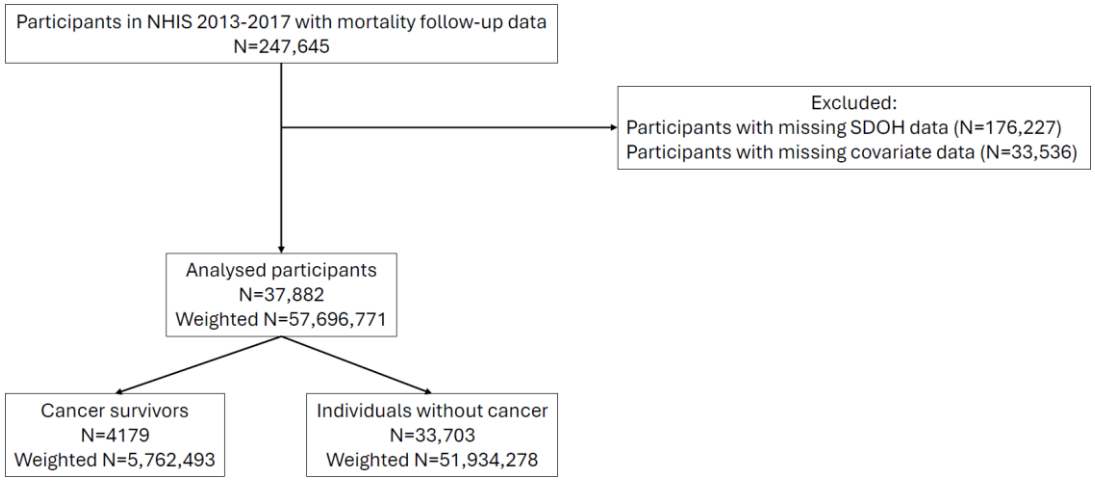


Table 4.1 Summary of the characteristics of analysed individuals. Continuous variables were summarized as means and 95% confidence intervals (CIs). Categorical variables were summarized as proportions and 95% CIs.

	Individuals without cancer	Cancer survivors
Sample size	33,703	4179
Weighted sample size	51,934,278	5,762,493
Demographic and comorbid characteristics, mean [95% CI] or proportion (%) [95% CI (%)]		
Age, years old		
18-25	9.4 [8.8-9.9]	0.8 [0.4-1.3]
26-35	16.6 [16.1-17.2]	2.9 [2.3-3.6]
36-45	17.4 [16.9-17.9]	6.2 [5.3-7.3]
46-55	20.5 [19.9-21.1]	14.7 [13.2-16.3]
56-65	19.9 [19.3-20.5]	24.1 [22.4-25.9]
66-75	11.5 [11.1-12.0]	30.6 [28.8-32.3]
≥76	4.7 [4.4-5.0]	20.8 [19.3-22.3]
Male	48.8 [48.1-49.5]	49.6 [47.6-51.6]
Race		
White	85.4 [84.7-86.1]	92.2 [91.1-93.2]
Black / African American	9.2 [8.7-9.7]	5.7 [4.9-6.7]
American Indian / Alaskan native	0.8 [0.7-1.0]	0.5 [0.3-0.7]
Chinese	0.9 [0.7-1.0]	0.2 [0.1-0.7]
Filippino	1.1 [0.9-1.3]	0.4 [0.3-0.8]
Asian Indian	0.9 [0.7-1.1]	0.1 [0.0-0.2]
Other Asians	1.3 [1.1-1.5]	0.5 [0.3-0.8]
Other / multiple races	0.4 [0.4-0.5]	0.3 [0.2-0.6]
Hypertension	38.4 [37.7-39.1]	53.9 [51.8-56.0]
Diabetes mellitus	12.8 [12.3-13.2]	20.4 [18.8-22.1]
Taking insulin or diabetic pills	9.7 [9.4-10.1]	15.0 [13.7-16.5]
Hypercholesterolemia	36.1 [35.4-36.8]	51.6 [49.6-53.7]
Active smoking	42.4 [41.6-43.2]	55.0 [52.9-57.1]
Obesity	32.9 [32.2-33.6]	31.3 [29.4-33.1]

	Individuals without cancer	Cancer survivors
Cardiac condition	12.5 [12.0-12.9]	25.8 [24.1-27.5]
Liver condition	2.2 [2.0-2.4]	4.4 [3.7-5.3]
Chronic obstructive pulmonary disease or emphysema	3.3 [3.0-3.5]	8.5 [7.5-9.7]
Stroke	2.3 [2.1-2.5]	5.2 [4.4-6.2]
Weekly moderate/vigorous exercise duration, minutes	262 [256-268]	238 [220-256]
Weekly number of alcoholic drink(s)	4.7 [4.4-4.9]	4.8 [4.4-5.2]
Composite social determinants of health score	6.0 [5.9-6.1]	5.3 [5.2-5.5]
Log-transformed composite social determinants of health score	1.75 [1.74-1.76]	1.62 [1.59-1.65]
Specific cancer sites / types		
Breast	N/A	20.6 [18.9-22.3] [1]
Prostate	N/A	17.9 [16.5-19.5] [2]
Lung and bronchus	N/A	3.5 [2.8-4.3]
Colorectal	N/A	6.7 [5.7-7.8]
Skin (melanomatous)	N/A	11.0 [9.9-12.2]
Bladder	N/A	3.7 [3.0-4.5]
Lymphoma	N/A	3.1 [2.5-3.9]
Uterus	N/A	3.3 [2.7-4.0] [3]
Pancreas	N/A	0.4 [0.3-0.8]
Leukaemia	N/A	1.9 [1.4-2.5]
Others	N/A	32.4 [30.5-34.3]
Domains of the composite social determinants of health score, mean domain score [95% CI] or proportion (%) [95% CI (%)]		
Economic stability		
Never / previously employed	3.0 [2.7-3.2]	1.6 [1.2-2.2]
No paid sick leave	37.1 [36.4-37.9]	36.9 [34.9-38.9]
Low family income	18.1 [17.5-18.8]	16.4 [15.1-17.8]
Difficulty paying medical bills	12.9 [12.3-13.4]	11.9 [10.7-13.3]
Unable to pay medical bills	6.2 [5.8-6.5]	5.3 [4.5-6.2]
Cost-related medication non-adherence	8.7 [8.3-9.1]	8.9 [7.9-10.1]
Foregone / delayed medical care due to cost	9.2 [8.8-9.6]	7.4 [6.5-8.5]

	Individuals without cancer	Cancer survivors
Worried about money for retirement	47.5 [46.7-48.2]	37.9 [36.0-39.9]
Worried about medical costs of illness / accident	41.8 [41.0-42.6]	33.8 [32.0-35.7]
Worried about maintaining standard of living	37.4 [36.7-38.1]	33.5 [31.7-35.4]
Worried about medical costs of normal healthcare	25.3 [24.6-26.0]	21.8 [20.1-23.5]
Worried about paying monthly bills	24.3 [23.6-25.0]	21.8 [20.2-23.5]
Worried about paying rent / mortgage / housing costs	18.6 [18.0-19.2]	15.9 [14.5-17.5]
Neighborhood, physical environment, and social cohesion		
Housing was rental / from other arrangement	27.2 [26.4-28.0]	16.7 [15.4-18.2]
People in neighborhood did not help each other	14.4 [13.9-14.9]	11.7 [10.5-13.0]
There were not people that can be counted on in neighborhood	14.6 [14.1-15.2]	10.9 [9.7-12.1]
People neighborhood could not be trusted	33.6 [32.8-34.3]	31.0 [29.3-32.8]
Neighborhood was not close-knit	12.9 [12.3-13.4]	9.5 [8.3-10.7]
Psychological distress	3.3 [3.0-3.6]	3.3 [2.7-4.1]
Food insecurity	6.5 [6.1-6.8]	5.9 [5.0-6.8]
Education		
Could not speak English language well / at all	1.7 [1.5-1.9]	1.3 [0.9-1.8]
Did not look up health information on internet in the past 12 months	64.7 [63.9-65.4]	59.3 [57.3-61.3]
Did not fill a prescription on the internet in the past 12 months	16.4 [15.8-17.0]	17.3 [15.8-18.9]
Did not schedule medical appointment on the internet in the past 12 months	17.2 [16.5-18.0]	15.3 [13.8-16.9]
Did not communicate with healthcare provider by email in the past 12 months	19.0 [18.3-19.8]	21.0 [19.4-22.7]
Did not use chat groups to learn about health topics in the past 12 months	4.7 [4.4-5.0]	5.4 [4.5-6.5]
Less than high school education	25.9 [25.2-26.7]	27.5 [25.8-29.2]
Healthcare system		

	Individuals without cancer	Cancer survivors
Uninsured	5.3 [5.0-5.7]	2.5 [1.9-3.1]
No usual source of care	6.2 [5.8-6.5]	2.9 [2.4-3.7]
Trouble finding a doctor / healthcare provider	3.0 [2.8-3.3]	3.7 [3.0-4.6]
Not accepted by doctor's office as new patient	2.8 [2.6-3.1]	3.5 [2.8-4.3]
Insurance not accepted by doctor's office	3.8 [3.6-4.2]	4.3 [3.6-5.2]
Delayed medical care due to not being able to get through on the phone	3.1 [2.8-3.4]	3.2 [2.6-3.9]
Delayed medical care due to not being able to get an appointment soon enough	7.9 [7.5-8.4]	8.5 [7.4-9.7]
Delayed medical care due to waiting too long at the doctor's office	4.2 [3.9-4.5]	5.4 [4.6-6.4]
Delayed medical care due to the doctor's office not being open when there was time to visit	3.7 [3.4-4.0]	3.0 [2.4-3.8]
Delayed medical care due to a lack of transportation	1.5 [1.3-1.6]	2.1 [1.6-2.7]
Dissatisfied with the quality of care / no healthcare in the past year	6.6 [6.2-6.9]	5.1 [4.3-6.1]

4.3.1. Associations between SDOH and mortality in cancer survivors

Amongst cancer survivors, worse SDOH was associated with higher cardiovascular (aHR 1.57 [1.21-2.04], p=0.001), cancer (aHR 1.26 [1.06-1.50]), and all-cause (aHR 1.25 [95% CI: 1.10-1.42]) mortality when adjusted for demographics. On further adjustment for comorbidities and risk factors, point estimates were attenuated, but the corresponding 95% CIs did not include 1 (1.31 [1.02-1.68]; 1.20 [1.01-1.42]; and aHR 1.16 [1.02-1.31], respectively; **Figure 4.2** and **Figure 4.3**). Restricted cubic splines showed largely linear relationships (**Supplementary Figures 4.7-4.9**). No meaningful associations were found between SDOH and the competing event, i.e. other-cause mortality.

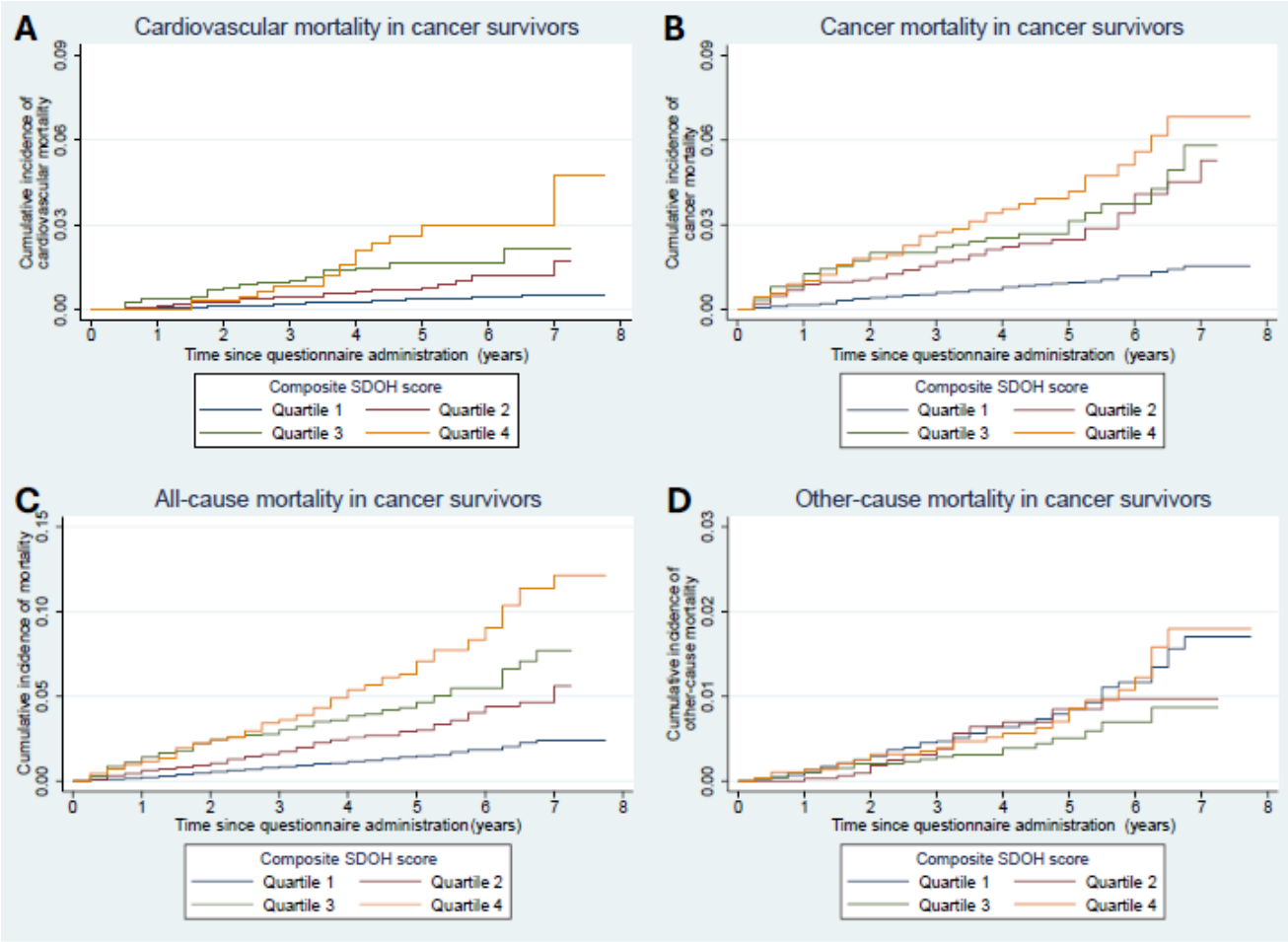
4.3.2. Associations between SDOH and mortality in individuals without cancer

Amongst individuals without cancer, worse SDOH was associated with higher cardiovascular (aHR 1.28 [1.08-1.51], p=0.004) and all-cause (aHR 1.24 [1.14-1.35]) mortality only when adjusted for demographics, but not when further adjusted for comorbidities and risk factors (aHR 1.09 [0.93-1.28], p=0.281; and aHR 1.08 [0.99-1.18], respectively; **Figure 4.4**). No meaningful associations between SDOH and cancer mortality were found regardless of the multivariable model used (model 1: aHR 1.02 [0.87-1.19]; model 2: aHR 0.91 [0.78-1.06]; **Figure 4.4**). Restricted cubic splines showed largely linear relationships for cardiovascular and cancer mortality (**Supplementary Figures 4.10-4.11**). Although the relationship for all-cause mortality displayed a slight J-shape in individuals with lower composite SDOH score, the relationship was linear in the rest of the analysed individuals (**Supplementary Figure 4.12**). Worse SDOH was associated with the competing event (other-cause mortality) in both multivariable models.

4.3.3. Post hoc analysis of the components of the SDOH score in cancer survivors

Post hoc, exploratory analysis was performed for cardiovascular, cancer, and all-cause mortality in cancer survivors (**Figure 4.5**). Psychological distress was associated with higher risks of all three outcomes. Meanwhile, worse economic stability and NPESC were both associated with higher risks of cardiovascular and all-cause mortality, but not cancer mortality. Furthermore, food insecurity was associated with higher risk of cardiovascular mortality, but not cancer nor all-cause mortality. Neither education nor healthcare system were associated with the risk of any of the three outcomes.

Figure 4.2 Kaplan-Meier cumulative incidence curves of cardiovascular (A), cancer (B), all-cause (C), and other-cause (D) mortality in cancer survivors. Associations between the log-transformed composite social determinants of health score and each outcome were visualized in forest plots (**E**). All summary statistics presented were adjusted hazard ratios (aHR) with 95% confidence intervals. Comorbidities and risk factors in model 2 included hypertension, diabetes mellitus, dyslipidaemia, active smoking, weekly number of alcoholic drinks, cardiac condition(s), chronic obstructive pulmonary disease or emphysema, liver disease, stroke, obesity, and weekly exercise duration.



E

	Adjusted hazard ratio with 95% CI	p-value
Cardiovascular mortality		
Model 1 (adjusted for age, race, and sex)	1.57 [1.21-2.04]	0.001
Model 2 (adjusted for age, race, sex, comorbidities, and risk factors)	1.31 [1.02-1.68]	0.037
Cancer mortality		
Model 1 (adjusted for age, race, and sex)	1.26 [1.06-1.50]	
Model 2 (adjusted for age, race, sex, comorbidities, and risk factors)	1.20 [1.01-1.42]	
All-cause mortality		
Model 1 (adjusted for age, race, and sex)	1.25 [1.10-1.42]	
Model 2 (adjusted for age, race, sex, comorbidities, and risk factors)	1.16 [1.02-1.31]	
Other-cause mortality		
Model 1 (adjusted for age, race, and sex)	1.06 [0.80-1.39]	
Model 2 (adjusted for age, race, sex, comorbidities, and risk factors)	1.00 [0.76-1.30]	

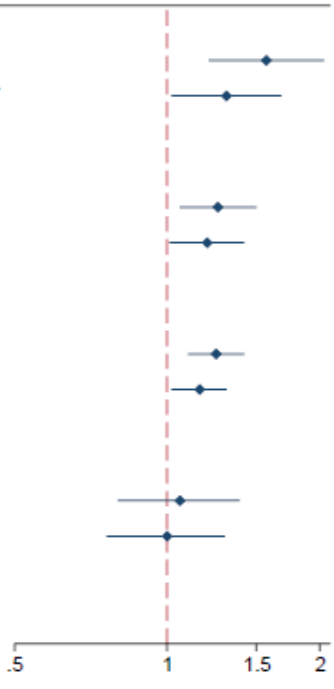


Figure 4.3 Graphical abstract. Summary of the study aim, methods, and key results. All estimates shown were adjusted hazard ratios (aHR; with 95% confidence intervals) for the associations between the log-transformed composite social determinants of health score and the respective risks of cardiovascular, cancer, all-cause, and other-cause mortality, adjusted for age, race, sex, comorbidities, and risk factors.

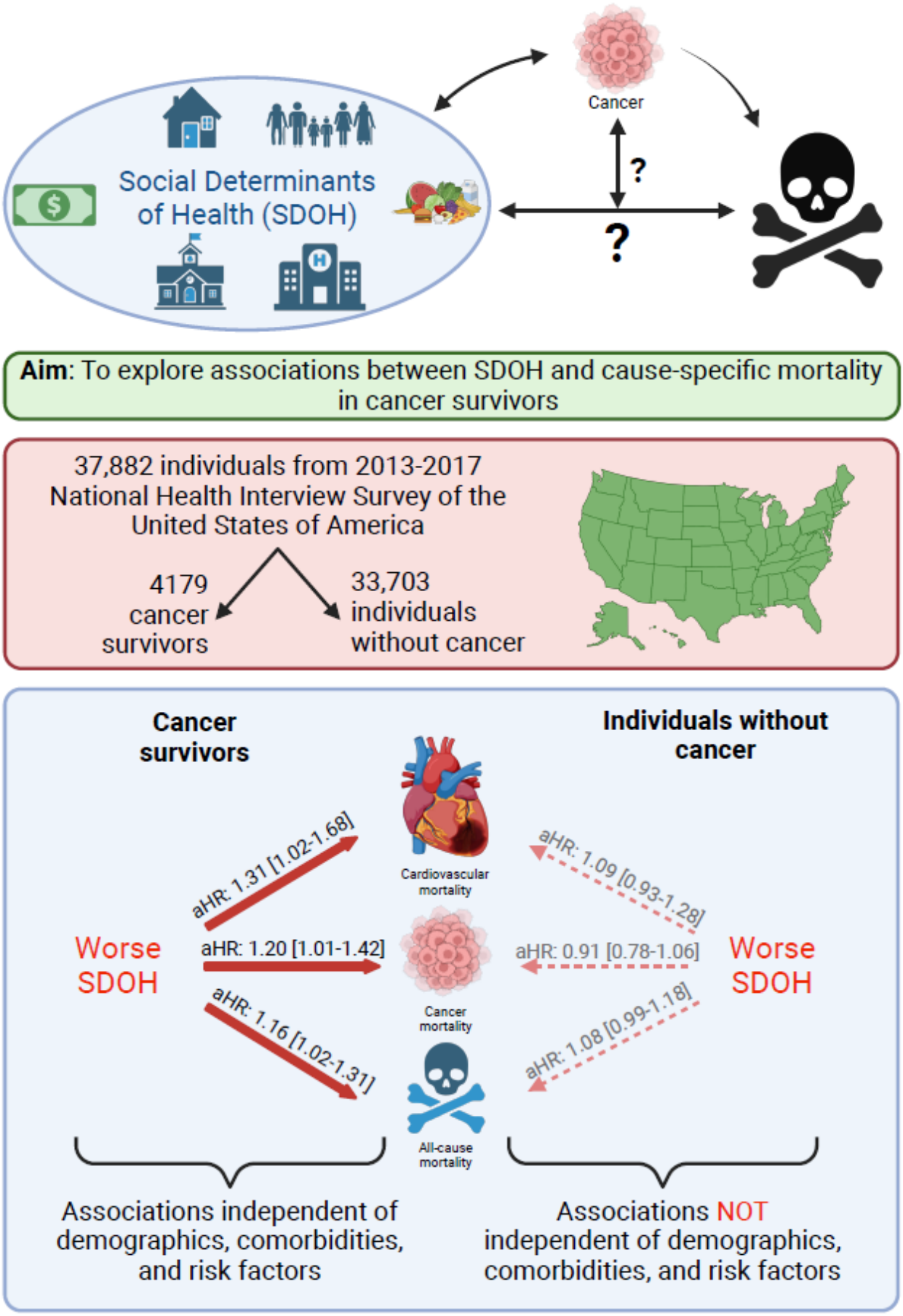
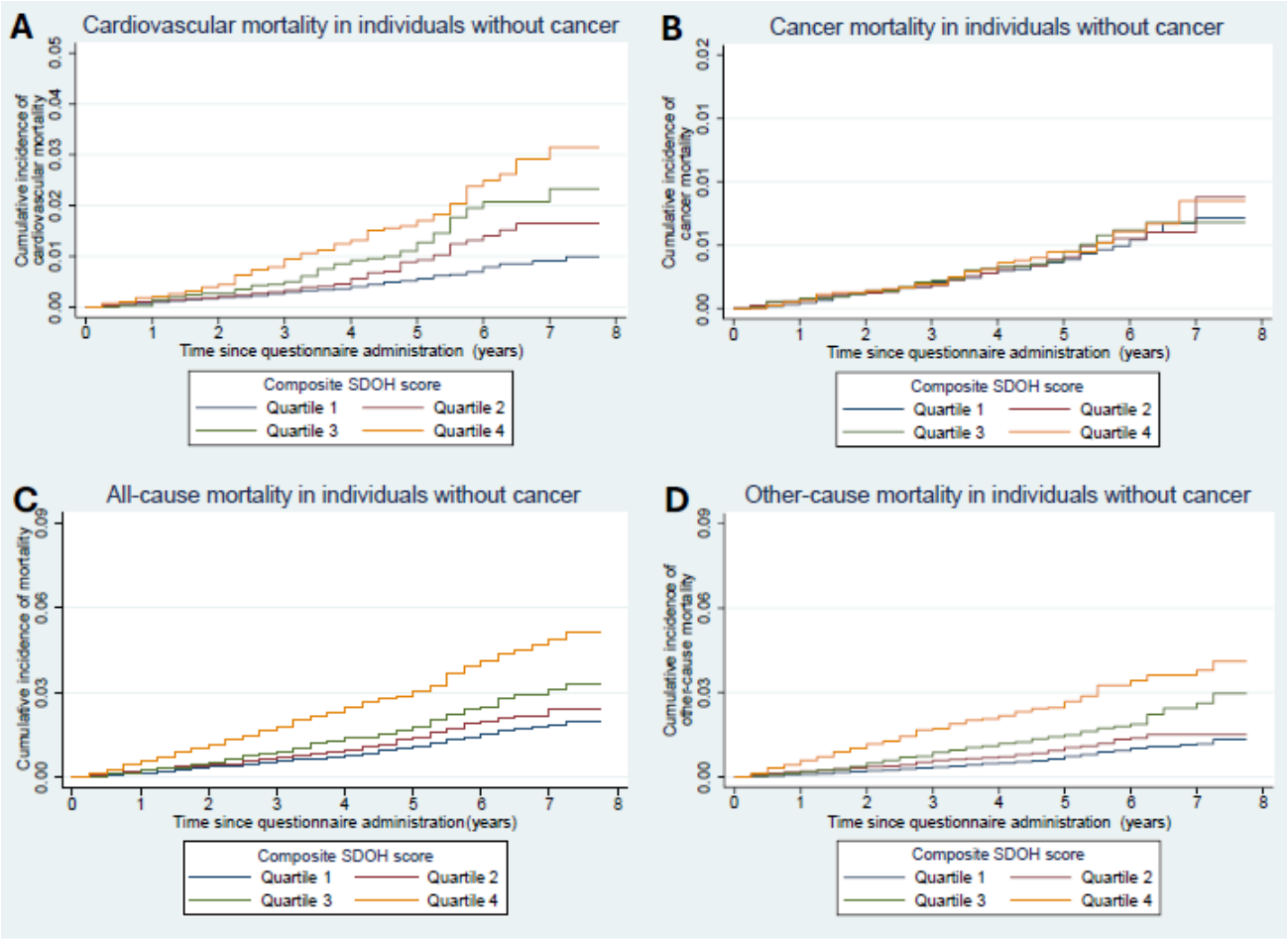


Figure 4.4 Kaplan-Meier cumulative incidence curves of cardiovascular (A), cancer (B), all-cause (C), and other-cause (D) mortality in individuals without cancer. Associations between the log-transformed composite social determinants of health score and each outcome were visualized in forest plots (**E**). All summary statistics presented were adjusted hazard ratios (aHR) with 95% confidence intervals. Comorbidities and risk factors in model 2 included hypertension, diabetes mellitus, dyslipidaemia, active smoking, weekly number of alcoholic drinks, cardiac condition(s), chronic obstructive pulmonary disease or emphysema, liver disease, stroke, obesity, and weekly exercise duration.



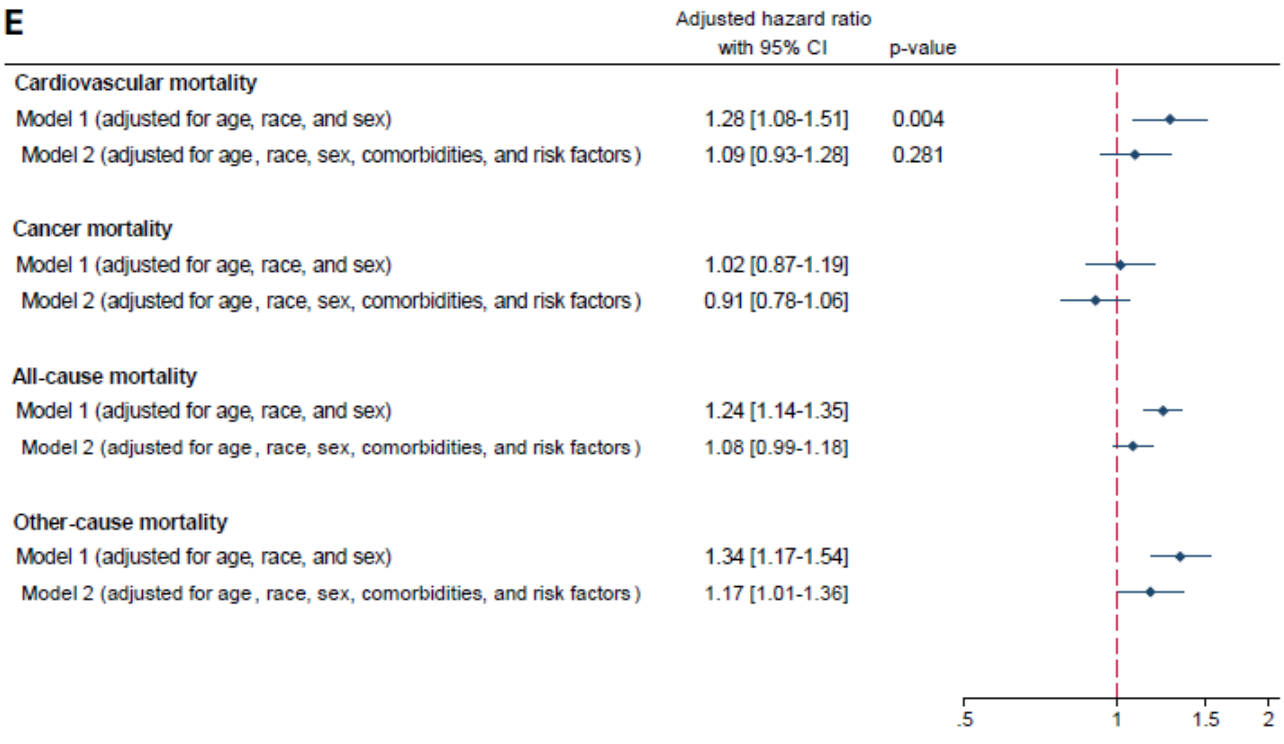
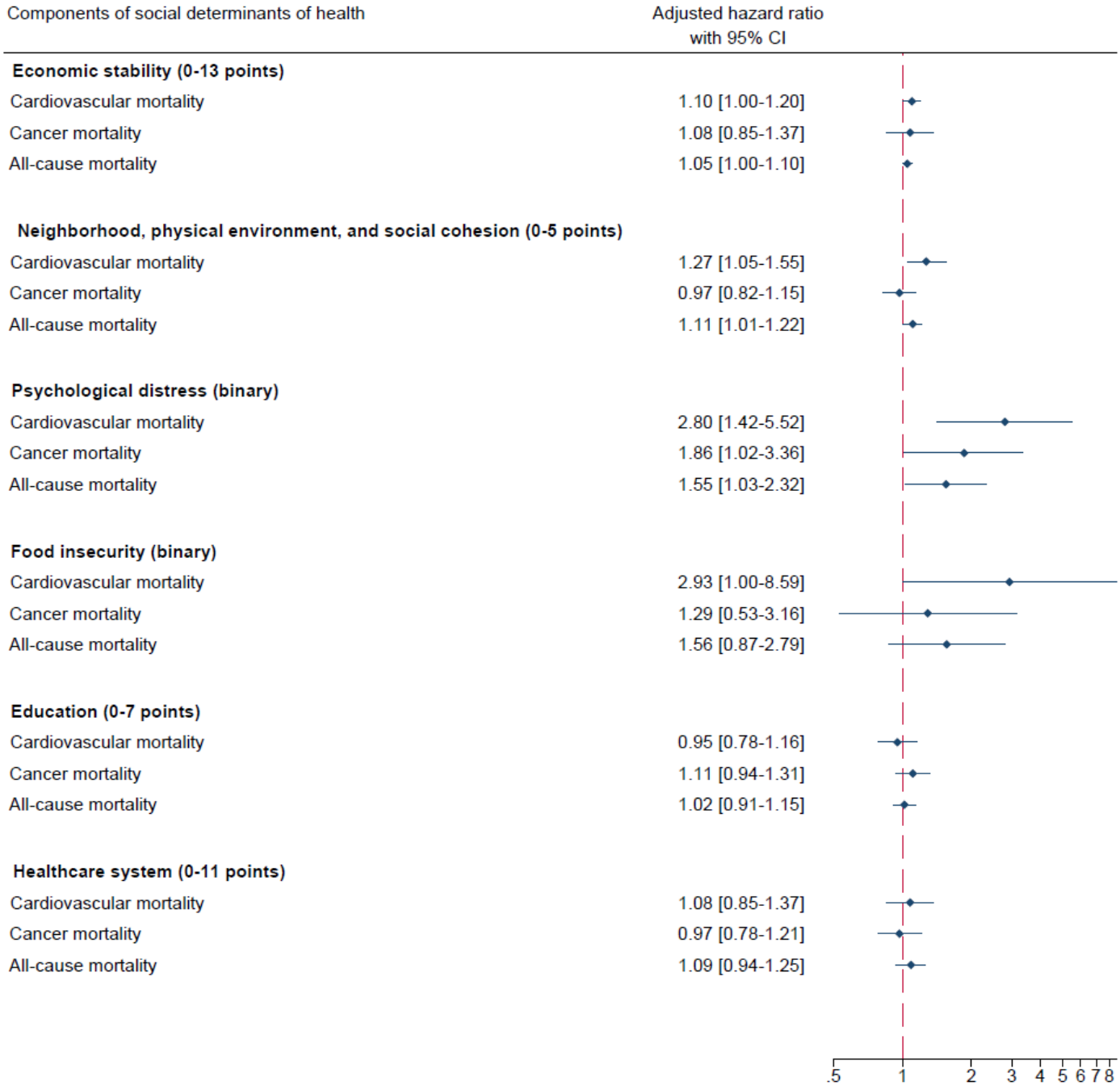


Figure 4.5 Forest plot summarizing the relationship between individual components of the composite social determinants of health score and the risk of cardiovascular, cancer, and all-cause mortality amongst cancer survivors. All summary statistics presented were adjusted hazard ratios (aHR) with 95% confidence intervals, with adjustment for age, sex, race, hypertension, diabetes mellitus, dyslipidaemia, active smoking, weekly number of alcoholic drinks, cardiac condition(s), chronic obstructive pulmonary disease or emphysema, liver disease, stroke, obesity, and weekly exercise duration.



4.4. Discussion

In this hypothesis-generating prospective cohort study using data representative of the non-institutionalized US population, associations between worse SDOH and cardiovascular, cancer, and all-cause mortality were observed amongst cancer survivors, which were independent of demographics, comorbidities, and risk factors. Although similar associations were observed amongst individuals without cancer for cardiovascular and all-cause mortality, they were not independent of and thus potentially explained by comorbidities and risk factors. Further exploratory analysis identified economic stability, NPESC, and psychological distress as domains of SDOH which were independently prognostic, albeit to different extents.

4.4.1. Comparison with existing literature, implications, and actionable targets

This is one of the first studies specifically investigating associations between SDOH and cardiovascular/cancer mortality in cancer survivors. Our findings suggested that in cancer survivors, SDOH have strong influences on cardiovascular/cancer mortality which is beyond what is explainable by comorbidities and risk factors. Contrastingly, in individuals without cancer, much of the association between SDOH and cardiovascular mortality may be 'explained away' and may therefore be driven by comorbidities and risk factors. Overall, these findings were congruent with the existing literature.(167,168) Particularly, the observations in individuals without cancer were not surprising, given the consistent association between worse SDOH and more comorbidities and risk factors which is likely bidirectional in nature,(166,170) and the strong and well-established mechanistic links between comorbidities / risk factors and cardiovascular conditions. Whilst these findings suggested that the relative importance of SDOH in cancer survivors may have been greater than that in individuals without cancer, they should not be seen as suggesting that SDOH are wholly unimportant for individuals without cancer, given the hypothesis-generating nature of this study, and that SDOH is known to be associated with cardiovascular morbidities – which are arguably not less important than mortality, particularly from the patients' perspective.

Our *post hoc*, exploratory analysis highlighted psychological distress as a particularly important and prognostic domain of SDOH in cancer survivors, with independent associations with all-cause, cardiovascular, and cancer mortality. Previous studies had found psychological distress and suboptimal mental health to be associated with increased cardiovascular risk both in the general population(171,172) and in patients with pre-existing cardiovascular conditions(173,174). A previous study by our team also found associations between psychological distress and cardiovascular health in cancer survivors(147). Although some of these studies suggested that such associations were largely mediated by behavioural risk factors, causal pathophysiological factors have been identified as well, such as autonomic activation, elevated cortisol levels, and endothelial dysfunction.(175,176) Whilst the exact nature of such association still requires further delineation, studies have shown that rapid psychological distress screening can identify individuals at elevated cardiovascular risk, and that psychological / mental health therapies are associated with significant reductions in cardiovascular risk in both the general population and those with coronary artery disease or heart failure.(177,178) Although relatively little is known about the cardiovascular implications

of psychological distress in cancer survivors, findings from this study – which is one of the first to report such associations in cancer survivors – highlight psychological distress as an actionable target for cardiovascular outcome improvement in cancer survivors. Further investigations confirming our observations and optimizing screening and management of psychological distress in cancer survivors are warranted.

We also observed that psychological distress was associated with higher risk of cancer-mortality in cancer survivors. This was consistent with the literature, with studies having found consistent links between psychological distress and higher risks of cancer mortality in patients with cancer.(179,180) Interestingly, a recent study has demonstrated that distressed patients with non-small-cell lung cancer had significantly shorter median progression-free survival compared with their non-distressed counterparts, with the association potentially driven by elevated cortisol levels in the former.(181) This suggested that a biological link may be at play, although the association is most likely multifactorial in nature, involving other socioeconomic factors as well. Regardless, there is evidence that mental health treatment is associated with reduced mortality in cancer survivors,(182) again highlighting psychological distress as a potentially actionable target for improving cancer survivors' outcomes.

In addition to psychological distress, worse economic stability and NPESC were both observed to be associated with higher risks of all-cause and cardiovascular mortality in cancer survivors. Previous studies of had shown similar associations with all-cause mortality,(183,184) but exploration of cardiovascular mortality has been rare. Our findings extended these associations to cardiovascular mortality and thus highlighted a window of opportunity for cardiovascular outcome improvement. Interestingly, economic stability and NPESC were associated with cardiovascular mortality, but not cancer mortality. Speculatively speaking, this may be because in cancer survivors, the risk of cancer mortality is more dependent on cancer therapy and cancer-specific healthcare, which are commonly prioritized over cardiovascular / cardio-oncology care – as the oncological issue is often more obvious – and thus is less susceptible than cardiovascular mortality to effects from social or financial vulnerability. This was partly supported by our observation that food insecurity was also associated with cardiovascular mortality but not cancer mortality – the effects of food insecurity are strongly mediated by nutritional and anthropometric factors, which are well-established cardiovascular risk factors but lack strong pathophysiological pathways affecting cancer. Overall, these findings suggested that disparity in access to cardio-oncology services may be an important actionable target for cardiovascular outcome improvement in cancer survivors.(185)

4.4.2. Gaps in evidence

Whilst our findings – which were hypothesis-generating in nature – highlighted several key areas of focus, further studies remain required to confirm these findings, as well as exploring the underlying drivers for better mechanistic understanding and identification of more specific / lower-level actionable targets.

Meanwhile, whether the observed SDOH-mortality associations differ by race/ethnicity warrants further research.(1,23) This was not possible in the current study due to the low rates of cardiovascular and cancer mortality preventing subgroup analyses with meaningful statistical power. Nevertheless, others had shown that socioeconomic deprivation may have significantly different effects on cardiovascular and cancer outcomes depending on race/ethnicity.(186) These effects and SDOH-race/ethnicity interactions may also vary geographically due to differences in racial/ethnic distributions and other sociocultural factors.

Furthermore, the aforementioned potential importance of access to cardio-oncology services may not only be related to socioeconomic barriers in access, but also physicians' awareness of cardio-oncology considerations in cancer survivors. Studies have demonstrated that, despite drastic increases in the volume of cardio-oncology research and evidently increasing cardiovascular burden amongst cancer survivors,(11,12,122) healthcare professionals' knowledge of cardio-oncology and adherence with guideline-recommended practices have remained poor.(187,188) Raising awareness of cardio-oncology amongst healthcare professionals and aligning practice with guidelines may be important steps in improving cardiovascular outcomes in cancer survivors.

In addition, further studies of the interactions between different domains of SDOH are warranted. Various domains of SDOH are often interrelated. For instance, financial difficulties have been associated with psychological distress.(160) This contributes to the difficulty of quantifying SDOH in general. Whilst the current study made use of a well-published composite SDOH score, the simple, additive nature of the score may not be optimal in capturing the health implications of SDOH. Further studies refining tools for quantifying SDOH with consideration of these complex interactions are warranted.

4.4.3. Limitations

Notwithstanding this study's nationally representative nature, it was limited by NHIS' self-reported nature which predisposes to information and recall bias, and the lack of individual data adjudication potentially predisposing to mortality data miscoding. Amongst cancer survivors, there was also no information on the status of cancer (active, remitted, recurred, second primary, etcetera) or the cancer therapy which have been or were being used, both of which has significant impact on cardiovascular risks.(1) Despite having accounted for a large number of potential confounders, the existence of residual confounding and unobserved confounders cannot be ruled out, which is a limitation inherent to observational studies in general. Also, a large proportion of individuals were excluded due to missing data, potentially introducing selection bias which may have influenced the findings. Additionally, low event rates precluded subgroup/exploratory analyses, and the observational nature precluded causal inferences. Furthermore, although the composite SDOH score used in this study has been used in other research studies, it was designed for the American population, and so our findings may not be directly generalizable to populations in other countries/regions. Lastly, despite the prognostic nature of this study, we could not use the Fine and Gray subdistribution model to account for competing risks. This was solely due to software limitations, as neither Stata nor R

had readily available packages for Fine-Gray competing risk regression that could account for complex survey designs. We have therefore handled the competing risk scenario with a cause-specific approach, with all competing events modelled and described separately. This approach has been used by other teams in numerous prior studies, including researchers at the authoritative National Center for Health Statistics of the United States.(189–191) Overall, given these limitations, our findings are hypothesis-generating in nature, and further confirmatory/mechanistic studies are necessary.

4.5. Conclusions

SDOH were independently associated with all-cause, cardiovascular and cancer mortality amongst cancer survivors but not amongst individuals without cancer. Different domains of SDOH may have different prognostic importance, with psychological distress, economic stability, NPESC, and food insecurity possibly being particularly prognostic domains of SDOH. Further studies are required to confirm these hypothesis-generating findings and explore underlying mechanisms.

5. Chapter 5: Temporal trends in cardiovascular burden among patients with prostate cancer receiving androgen deprivation therapy: a population-based cohort study

This chapter is based on the following publication: **Chan JSK**, Satti DI, Lee YHA, Hui JMH, Dee EC, Ng K, Liu K, Tse G, Ng CF. Temporal trends in cardiovascular burden among patients with prostate cancer receiving androgen deprivation therapy: a population-based cohort study. *Br J Cancer.* 2023; 128: 2253-2260. doi: 10.1038/s41416-023-02271-5

5.1. Introduction

With an estimated 1.4 million new cases and over 375,000 deaths, prostate cancer (PCa) was the third most common cancer globally in 2020 (192). Androgen deprivation therapy (ADT), which involves the use of pharmacological agents or surgery to suppress the levels of testosterone, is one of the key components of PCa therapy (193,194). Though proven efficacious for PCa treatment, research in recent decades, starting with the groundbreaking work by Keating and colleagues (195), has demonstrated an increasingly established link between ADT and adverse cardiovascular effects, including increased risks of cardiovascular mortality, non-fatal cardiovascular diseases, myocardial infarction, and stroke (40). Given the rising prevalence of PCa globally and cardiovascular diseases being the leading cause of non-cancer death among PCa patients (196–198), ADT-related adverse cardiovascular effects have become increasingly important.

Nonetheless, there is a paucity of studies characterizing the magnitude of cardiovascular burden amongst patients with PCa receiving ADT, despite the large number of studies having compared ADT to non-ADT treatments or between specific types of ADT (40). Furthermore, it is unclear whether the cardiovascular burden of these patients has evolved over time. It would have been reasonable to hypothesize that the significant progress made in our understanding of ADT-related adverse cardiovascular effects has significantly influenced the cardiovascular outcome of these patients. As such, this study aimed to describe the cardiovascular burden amongst patients with PCa receiving ADT and explore the temporal trends in such burden over the past decades.

5.2. Methods

This retrospective cohort study was performed in accordance with the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline, and was approved by the Joint Chinese University of Hong Kong– New Territories East Cluster Clinical Research Ethics Committee. The requirement for patient consent has been waived due to the use of deidentified data. All underlying data is available on reasonable request to the corresponding authors.

5.2.1. Source of data

Data were obtained from the Clinical Data Analysis and Reporting System (CDARS), a population-based, administrative electronic medical records database of all patients attending public healthcare institutions in Hong Kong which serve an estimated 90% of the population (199). Diagnoses were recorded by *International Classification of Diseases, Ninth revision* (ICD-9) codes regardless of the time of data entry, as CDARS has not implemented ICD-10 codes to date. Mortality data were obtained from the linked Hong Kong Death Registry, a governmental database containing the death record of all Hong Kong citizens, in which the cause of death is recorded using ICD-9 or ICD-10 codes. CDARS and the Hong Kong Death Registry have been used extensively in previous studies and shown to have good coding accuracy (121,200–204).

5.2.2. Patient population

Patients aged 18 years old or above with PCa who received any ADT (medical castration or bilateral orchidectomy (BO)) between 1st January 1993 and 31st March 2021 were analysed.

Patients with a prior history of myocardial infarction (MI), stroke, or heart failure (HF) were excluded from all analyses of the primary outcome. These patients were excluded for two reasons. Firstly, patients with prior occurrence of MI, stroke, or HF were likely to have further recorded attendances to follow up on these conditions, and as all diagnoses were extracted using ICD-9 codes, it would have been difficult to reliably distinguish follow-up attendances from true, recurrent occurrences of events. Second, as patients with prior occurrence of MI, stroke, or HF were likely to have had varying severity or multiple prior occurrences of these events, both of which would have caused substantial increase in the heterogeneity of their cardiovascular risks that were difficult to account for. Therefore, excluding these patients avoided this heterogeneity and allowed a better reflection of the cardiovascular risks associated with ADT.

5.2.3. Data collected

The following baseline variables were collected: age, type of ADT (medical castration or bilateral orchiectomy; medical castration included usage of leuprorelin, triptorelin, goserelin, or degarelix, as other gonadotropin-releasing hormone agonists and antagonists were not available in Hong Kong during the study period), duration of castration, comorbidities (hypertension, diabetes mellitus, dyslipidaemia, chronic kidney disease, chronic liver disease, stroke, MI, ischaemic heart disease, HF, anaemia, atrial fibrillation, ventricular tachyarrhythmia, chronic obstructive pulmonary disease, and known malignancy), use of medications or prior procedures (radiotherapy, chemotherapy, radical prostatectomy, angiotensinogen-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, dihydropyridine calcium channel blockers, non-dihydropyridine calcium channel blockers, metformin, sulphonylurea, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonist, insulin, antiplatelet, anticoagulant, corticosteroid, percutaneous coronary intervention,

and coronary artery bypass graft), the number of cardiovascular medications being used at baseline, and the number of diabetic medications being used at baseline. Patients were also recorded for ever receiving radiotherapy, chemotherapy, radical prostatectomy, and any androgen receptor signalling inhibitor (ARSI; prescriptions of first-generation ARSIs (flutamide and bicalutamide) and second-generation ARSIs (abiraterone and enzalutamide) were recorded separately; other ARSIs were not available in Hong Kong during the study period). Additionally, the number of patients with available baseline records (within 3 years prior to index date which is the date of ADT initiation) of serum total cholesterol level, high-density lipoprotein cholesterol (HDL-C) level, and haemoglobin A1c (HbA1c) level were recorded, and these variables were described for patients with available records. All comorbidities were identified using ICD-9 codes, listed in **Supplementary Table 5.1**.

5.2.4. Follow-up and outcome

All patients were followed up from the date of ADT initiation until September 31st, 2021. The primary outcome was major adverse cardiovascular event (MACE), which was defined as the first occurrence of cardiovascular mortality, MI, stroke, or HF. The secondary outcome was all-cause mortality. MI, stroke, and HF were identified by ICD-9 codes as listed in **Supplementary Table 5.1**. The cause of death was identified by ICD-9 or ICD-10 codes as listed in **Supplementary Table 5.2**.

5.2.5. Statistical analysis

Continuous variables were expressed as mean ± standard deviation. The cohort was subdivided into four groups by the year of ADT initiation, i.e. 1993-2000, 2001-2007, 2008-2014, and 2015-2021. All baseline characteristics were described for patients in each group. Continuous variables were compared between groups using one-way analysis of variance (ANOVA), while categorical variables were compared using Chi-square test. Between-group trends were tested using the Wilcoxon-type test developed by Cuzick (205). Due to the nature of the database, missing values could only exist for laboratory test results. The number of patients with missing values were described, and only non-missing values were included in between-group comparisons without any imputation performed.

Kaplan-Meier incidence curves were constructed to visualize the cumulative incidence of the outcomes for each group. As the group of patients with the most recent ADT initiation (i.e. the 2015-2021 group) could be expected to have the shortest follow-up duration, several approaches were deployed to compare the outcomes between groups. First, incidence rates of the outcomes were calculated for each group with the follow-up duration of the groups restricted to the longest follow-up duration of the 2015-2021 group. The incidence rates (IR) were then compared against that of the group with the earliest ADT initiation (i.e. the 1993-2000 group) using the Mantel-Haenszel method with calculation of the corresponding incidence rate ratios (IRR), and the trends in incidence rates between groups were tested using the log-linear trend test. These analyses on IR and IRR were also repeated without any restriction on the follow-up duration. Second, survival analysis was conducted with the

aforementioned restriction on follow-up duration. As no important violation of the proportional hazards assumption was found by the Schoenfield's residuals-based test and visual inspection of the log-log plot and Kaplan-Meier plot, univariable Cox regression analysis was used to compare the cumulative incidence of the outcomes between groups with the 1993-2000 group as reference, and with hazard ratio (HR) and 95% confidence interval (CI) as summary statistics. Third, the five-year risk of the outcomes were estimated for each group using life tables.

Two sensitivity analyses were performed. First, the restricted mean survival time (RMST) for each group were calculated. Second, as some patients died without having MACE, non-cardiovascular mortality was a competing event for MACE. Hence, univariable competing risk regression was performed for MACE using the Fine and Gray sub-distribution model with non-cardiovascular mortality as the competing events; sub-hazard ratio (SHR) and 95% CI were used as summary statistics.

Lastly, to better understand the risk factors for the outcomes, all baseline variables except laboratory test results were entered for backward stepwise Cox regression with $p \geqslant 0.10$ as the threshold for removal and $p<0.05$ as the threshold for entry. The year of ADT initiation was also entered as a categorical variable to account for any temporal difference in the outcomes. This also accounted for the temporal difference in follow-up duration; thus, no restriction was placed on the follow-up duration in this analysis.

All p values were two-sided, with $p<0.05$ considered statistically significant. All statistical analyses were performed on Stata v16.1 (StataCorp LLC, College Station, Texas, USA).

5.3. Results

In total, 13,537 patients were identified and analysed (mean age 75.5±8.5 years old). Baseline characteristics of included patients were summarized in **Table 5.1**. There was a trend favouring medical castration and against BO in more recent years (85.8% with medical castration and 24.4% with BO in 2015-2021 group vs 11.1% with medical castration and 91.2% with BO in 1993-2000 group; Chi-square $p<0.001$ and $p_{trend}<0.001$ for both). Fewer of those receiving ADT in more recent years had received radiotherapy (2.5% in 2015-2021 group vs 6.1% in 1993-2000 group, Chi-square $p<0.001$, $p_{trend}<0.001$) or radical prostatectomy (19.4% in 2015-2021 group vs 47.3% in 1993-2000 group, Chi-square $p<0.001$, $p_{trend}<0.001$). Meanwhile, more of those who received ADT in more recent years have ever received first-generation (44.4% in 2015-2021 group vs 8.4% in 1993-2000 group, Chi-square $p<0.001$, $p_{trend}<0.001$) or second-generation (19.8% in 2015-2021 group vs 0.3% in 1993-2000 group, Chi-square $p<0.001$, $p_{trend}<0.001$) ARSI, as well as chemotherapy (16.1% in 2015-2021 group vs 0.8% in 1993-2000 group, Chi-square $p<0.001$, $p_{trend}<0.001$). Amongst those who received medical castration, the duration of medical castration was shorter in the most recent group (596±564 days in 2015-2021 group vs 974±1409 days in 1993-2000 group, ANOVA $p<0.001$, $p_{trend}<0.001$), although this may have been due to the shorter follow-up duration inherent to this group.

Table 5.1 Characteristics for all patients and stratified by the year of androgen deprivation therapy initiation.

	All patients	1993-2000	2001-2007	2008-2014	2015-2021	P value between groups	P for trend
Number of patients, N	13,537	1134	3017	4641	4745	NA	NA
Follow-up duration, years	4.7±4.3	5.7±6.6	6.5±5.6	5.4±3.7	2.6±1.7	<0.001	<0.001
Age, years	75.5±8.5	74.9±7.8	75.2±7.8	75.7±8.5	75.8±9.0	<0.001	<0.001
Medical castration, N (%)	8178 (60.4)	126 (11.1)	1213 (40.2)	2768 (59.6)	4071 (85.8)	<0.001	<0.001
Bilateral orchidectomy, N (%)	6593 (48.7)	1034 (91.2)	2075 (68.8)	2326 (50.1)	1158 (24.4)	<0.001	<0.001
Duration of ADT, days [1]	891±905	842±1160	1066±1287	1116±1026	687±558	<0.001	<0.001
Hypertension, N (%)	3624 (26.8)	123 (10.9)	549 (18.2)	1293 (27.9)	1659 (35.0)	<0.001	<0.001
Diabetes mellitus, N (%)	2886 (21.3)	87 (7.7)	484 (16.0)	1014 (21.9)	1301 (27.4)	<0.001	<0.001
Dyslipidaemia, N (%)	1270 (9.4)	9 (0.8)	97 (3.2)	364 (7.8)	800 (16.9)	<0.001	<0.001
Chronic kidney disease, N (%)	452 (3.3)	18 (1.6)	70 (2.3)	177 (3.8)	187 (3.9)	<0.001	<0.001
Chronic liver disease, N (%)	146 (1.1)	5 (0.4)	14 (0.5)	56 (1.2)	71 (1.5)	<0.001	<0.001
Stroke, N (%)	1216 (9.0)	42 (3.7)	221 (7.3)	424 (9.1)	529 (11.2)	<0.001	<0.001
Myocardial infarction, N (%)	427 (3.2)	9 (0.8)	73 (2.4)	156 (3.4)	189 (4.0)	<0.001	<0.001
Ischaemic heart disease, N (%)	1407 (10.4)	76 (6.7)	260 (8.6)	507 (10.9)	564 (11.9)	<0.001	<0.001
Heart failure, N (%)	695 (5.1)	35 (3.1)	116 (3.8)	278 (6.0)	266 (5.6)	<0.001	<0.001
Anaemia, N (%)	966 (7.1)	34 (3.0)	112 (3.7)	418 (9.0)	402 (8.5)	<0.001	<0.001
Atrial fibrillation, N (%)	610 (4.5)	24 (2.1)	90 (3.0)	212 (4.6)	284 (6.0)	<0.001	<0.001
COPD, N (%)	804 (5.9)	53 (4.7)	193 (6.4)	316 (6.8)	242 (5.1)	0.001	0.341
Known malignancy, N (%)	1003 (13.3)	130 (11.5)	403 (13.4)	701 (15.1)	569 (12.0)	<0.001	0.558
Prior PCI, N (%)	432 (3.2)	6 (0.5)	47 (1.6)	157 (3.4)	222 (4.7)	<0.001	<0.001
Prior CABG, N (%)	55 (0.4)	1 (0.1)	10 (0.3)	17 (0.4)	27 (0.6)	0.088	0.015
Prior radiotherapy, N (%)	493 (3.6)	69 (6.1)	105 (3.5)	199 (4.3)	120 (2.5)	<0.001	<0.001
Prior RP, N (%)	3735 (27.6)	536 (47.3)	1071 (35.5)	1206 (26.0)	922 (19.4)	<0.001	<0.001
Prior chemotherapy, N (%)	61 (0.5)	0 (0)	3 (0.1)	11 (0.2)	47 (1.0)	<0.001	<0.001
Ever received radiotherapy, N (%)	3114 (23.0)	328 (28.9)	799 (26.5)	1294 (27.9)	693 (14.6)	<0.001	<0.001
Ever received RP, N (%)	4601 (34.0)	603 (53.2)	1286 (42.6)	1456 (31.4)	1256 (26.5)	<0.001	<0.001
Ever received chemotherapy, N (%)	1311 (9.7)	9 (0.8)	121 (4.0)	416 (9.0)	765 (16.1)	<0.001	<0.001

		All patients	1993-2000	2001-2007	2008-2014	2015-2021	P value between groups	P for trend
Ever received first-generation ARSI, N (%)		4239 (31.5)	92 (8.4)	663 (22.1)	1377 (29.7)	2107 (44.4)	<0.001	<0.001
Ever received second-generation ARSI, N (%)		1582 (11.7)	3 (0.3)	77 (2.6)	563 (12.1)	939 (19.8)	<0.001	<0.001
Ever received chemotherapy or ARSI, N (%)		5116 (37.8)	101 (8.9)	724 (24.0)	1638 (35.3)	2653 (55.9)	<0.001	<0.001
Number of cardiovascular medications		1.5±1.7	0.2±0.6	1.0±1.3	1.7±1.6	2.0±1.8	<0.001	<0.001
Number of antidiabetic medications		0.30±0.73	0.05±0.28	0.21±0.57	0.32±0.74	0.40±0.85	<0.001	<0.001
ACEI/ARB users, N (%)		3383 (25.0)	23 (2.0)	481 (15.9)	1303 (28.1)	1576 (33.2)	<0.001	<0.001
Beta-blocker users, N (%)		4130 (30.5)	42 (3.7)	696 (23.1)	1638 (35.3)	1754 (37.0)	<0.001	<0.001
Dihydropyridine CCB users, N (%)		5396 (39.9)	58 (5.1)	886 (29.4)	2058 (44.3)	2394 (50.5)	<0.001	<0.001
Non-dihydropyridine CCB users, N (%)		575 (4.3)	11 (1.0)	134 (4.4)	226 (4.9)	201 (4.3)	<0.001	0.002
Metformin users, N (%)		1480 (10.9)	14 (1.2)	194 (6.4)	584 (12.6)	688 (14.5)	<0.001	<0.001
Sulphonylurea users, N (%)		1744 (12.9)	29 (2.6)	347 (11.5)	661 (14.2)	707 (14.9)	<0.001	<0.001
DPP4 inhibitor users, N (%)		150 (1.1)	0 (0)	0 (0)	29 (0.6)	121 (2.6)	<0.001	<0.001
GLP1 receptor agonist users, N (%)		2 (0.0)	0 (0)	0 (0)	1 (0.0)	1 (0.0)	0.829	0.423
Insulin users, N (%)		722 (5.3)	10 (0.9)	90 (3.0)	222 (4.8)	400 (8.4)	<0.001	<0.001
Antiplatelet users, N (%)		2962 (21.9)	43 (3.8)	531 (17.6)	1112 (24.0)	1276 (27.9)	<0.001	<0.001
Anticoagulant users, N (%)		458 (3.4)	3 (0.3)	58 (1.9)	148 (3.2)	249 (5.3)	<0.001	<0.001
Corticosteroid users, N (%)		2342 (17.3)	29 (2.6)	510 (16.9)	933 (20.1)	870 (18.3)	<0.001	<0.001
With available total cholesterol, HDL-C, and HbA1c levels, N (%)		3940 (29.1)	5 (0.4)	265 (8.8)	1220 (26.3)	2450 (51.6)	<0.001	<0.001
Total cholesterol	Available, N (%)	6727 (49.7)	28 (2.5)	806 (26.7)	2458 (53.0)	3435 (72.4)	<0.001	<0.001
	Level, mmol/L	4.41±1.01	5.25±2.20	4.79±0.95	4.56±1.01	4.21±0.96	<0.001	<0.001
HDL-C	Available, N (%)	6478 (47.9)	15 (1.3)	626 (20.8)	2415 (52.0)	3422 (72.1)	<0.001	<0.001
	Level, mmol/L	1.27±0.37	1.17±0.31	1.28±0.37	1.27±0.37	1.28±0.37	0.335	0.299
HbA1c	Available, N (%)	4295 (31.7)	22 (1.9)	403 (13.4)	1320 (28.4)	2550 (53.7)	<0.001	<0.001
	Level, %	6.49±1.16	7.85±1.76	6.94±1.46	6.64±1.18	6.33±1.06	<0.001	<0.001

ACEI, angiotensinogen-converting enzyme inhibitor. ARB, angiotensin receptor blocker. ARSI, androgen receptor signaling inhibitor. CABG, coronary artery bypass graft. CCB, calcium channel blocker. COPD, chronic obstructive pulmonary disease. DPP4, dipeptidyl peptidase-4. GLP1, glucagon-like peptide-1. HbA1c, haemoglobin A1c. HDL-C, high density lipoprotein cholesterol. NA, not applicable. RP, radical prostatectomy.

[1] Only including patients who received medical castration

A total of 2059 (15.2%) had a prior diagnosis of MI, stroke, or HF, and were thus excluded from all analyses of MACE, resulting in a sample size of 11,478 patients for the MACE analyses. Over a mean follow-up duration of 4.7±4.3 years, 2727 patients (23.8%) had MACE, and 9124 (67.4) died. Kaplan-Meier curves showing the cumulative incidence of MACE and all-cause mortality without any restriction on follow-up durations were shown in **Supplementary Figure 5.1** and **5.2**, respectively. As expected, patients with the most recent ADT initiation had the shortest follow-up duration, with the longest observed follow-up duration being 6.7 years.

5.3.1. Cardiovascular risk factors and medications

Overall, patients who were initiated on ADT more recently had more cardiovascular risk factors (**Table 5.1**), with higher rates of prior hypertension, diabetes mellitus, stroke, myocardial infarction, ischaemic heart, heart failure, chronic kidney disease, atrial fibrillation, and dyslipidaemia. These patients were also slightly older. Correspondingly, more of those who had ADT initiated more recently were using cardiovascular or antidiabetic medications at baseline. Also, more of those who had ADT initiated more recently had received percutaneous coronary intervention.

Additionally, more of those who had ADT initiated recently had been checked for levels of total cholesterol, HDL-C, and HbA1c prior to initiating ADT. This was accompanied by lower total cholesterol and HbA1c amongst those with available test results whose ADT was initiated recently, but without any significant differences in HDL-C levels. Overall, despite an increasing proportion of patients having all three laboratory markers profiled prior to ADT initiation, only 51.6% of the 2015-2021 group had all three markers profiled (vs 0.4% in 1993-2000 group, Chi-square $p<0.001$, $p_{trend}<0.001$).

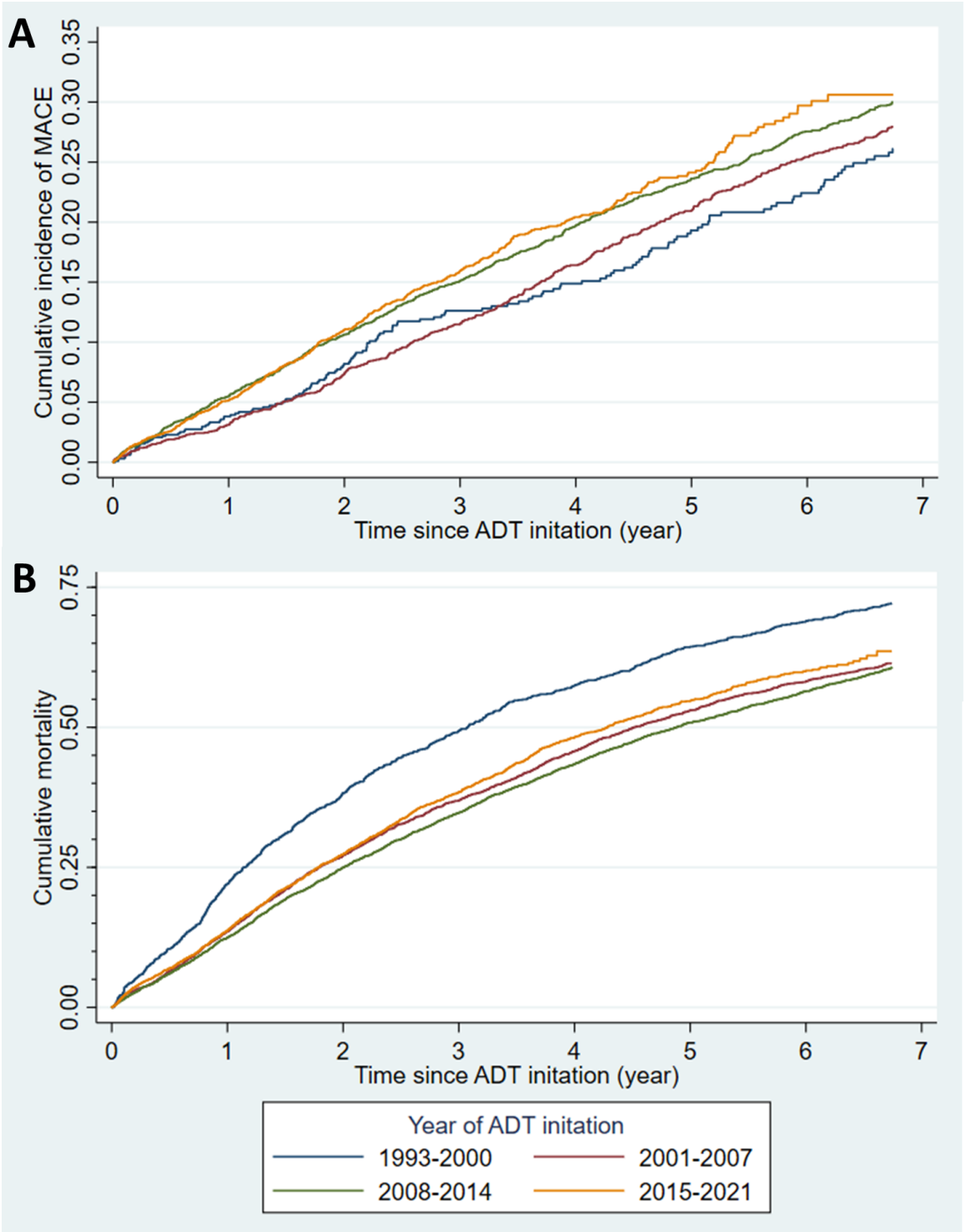
5.3.2. Major adverse cardiovascular event

With follow-up durations restricted to the longest observed follow-up duration of the 2015-2021 group (6.7 years), patients initiated on ADT more recently had higher IR of MACE (IR 5.7 [5.3, 6.2] events per 100 person-year in the 2015-2021 group vs 4.4 [95% CI 3.7, 5.1] events per 100 person-year in the 1993-2000 group; IRR 1.32 [1.10, 1.58], p=0.003 for the 2015-2021 group compared to the 1993-2000 group; log-linear trend test $p<0.001$; **Table 5.2**). Similar observations were made with IR and IRR calculated without any restriction on follow-up durations (**Supplementary Table 5.3**).

A similar trend was observed in the Cox regression analysis ($p_{trend}<0.001$), where the patients with ADT initiated in years 2015-2021 had an estimated 33% higher risk of MACE compared to those with ADT initiation in years 1993-2000 (HR 1.33[1.11, 1.59], p=0.002; **Figure 5.1A** and **Table 5.3**). Correspondingly, the estimated five-year risk of MACE was the highest in the 2015-2021 group (22.5% [20.9%, 24.2%]), followed by the 2008-2014 group (23.0% [21.6%,

24.5%]), the 2001-2007 group (19.4% [17.7%, 21.1%], and lastly, with the lowest five-year risk, the 1993-2000 group (17.0% [14.4%, 19.9%]).

Figure 5.1 Kaplan-Meier curves showing the cumulative incidence of (A) major adverse cardiovascular event (MACE) and (B) all-cause mortality with the follow-up duration restricted to the longest observed follow-up duration of the 2015-2021 group (6.7 years). ADT, androgen deprivation therapy.



Sensitivity analyses with RMST demonstrated similar results (RMST 5.59 [5.51, 5.68] years for the 2015-2021 group vs 5.86 [5.73, 6.00] years for the 1993-2000 group; **Supplementary Table 5.4**). Competing risk regression also found similar results, with the 2015-2021 group having an estimated 43% higher cumulative incidence of MACE than the 1993-2000 group (SHR 1.43 [1.19, 1.71], p<0.001; **Supplementary Table 5.5**).

Backward stepwise Cox regression showed that increased age, diabetes mellitus, hypertension, anaemia, known malignancy, anticoagulant use, and using more cardiovascular medications were independently associated with higher risk of MACE, while statin use, and metformin use were independently associated with lower risk of MACE (**Supplementary Table 5.6**).

5.3.3. All-cause mortality

With follow-up durations restricted to the longest observed follow-up duration of the 2015-2021 group (6.7 years), patients initiated on ADT more recently had lower IR of all-cause mortality (IR 15.9 [15.2, 16.6] deaths per 100 person-year in the 2015-2021 group vs 20.3 [19.0, 21.8] deaths per 100 person-year in the 1993-2000 group; IRR 0.78 [0.72, 0.85], p<0.001; for the 2015-2021 group compared to the 1993-2000 group; log-linear trend test p=0.003; **Table 5.2**). However, analysis without any restriction on follow-up duration showed no significant difference between the 2015-2021 group and 1993-2000 group in the IR of all-cause mortality (IRR 0.98 [0.91, 1.06], p=0.660; **Supplementary Table 5.3**), which was driven by a markedly lower IR in the 1993-2000 group (IR 16.2 [15.2, 17.2] deaths per 100 person-year when analyzed without any restriction on follow-up duration vs 20.3 [19.0, 21.8] deaths per 100 person-year when analyzed with restricted follow-up duration). Such difference likely resulted from the mortality rate being higher in the initial years after ADT initiation before levelling off in later years, as apparent from the Kaplan-Meier curve without any restriction on follow-up duration (**Supplementary Figure 5.2**).

Cox regression with restricted follow-up duration showed that patients with ADT initiated more recently had lower risk of mortality (p_{trend}<0.001), with the 2015-2021 group having an estimated 24% lower risk of all-cause mortality than those in the 1993-2000 group (HR 0.69 [0.64, 0.74], p<0.001; **Figure 5.1B** and **Table 5.3**). The estimated five-year risk of all-cause mortality was 64.5% [61.7%, 67.4%] for the 1993-2000 group, 53.0% [51.2%, 54.8%] for the 2001-2007 group, 50.8% [49.4%, 52.3%] for the 2008-2014 group, and 52.9% [51.3%, 54.6%] for the 2015-2021 group.

Sensitivity analysis with RMST showed similar results as Cox regression (RMST 3.55 [3.40, 3.70] years for the 1993-2000 group vs 4.14 [4.06, 4.22] years for the 2015-2021 group; **Supplementary Table 5.4**).

Table 5.2 Incidence rates of both outcomes with the follow-up duration restricted to the longest observed follow-up duration of the 2015-2021 group (6.7 years), stratified by the year of androgen deprivation therapy initiation. Incidence rate ratios displayed were referenced against the 1993-2000 group.

Year of androgen deprivation therapy initiation	Major adverse cardiovascular events		All-cause mortality	
	Incidence rate [1]	Incidence rate ratio	Incidence rate [1]	Incidence rate ratio
1993-2000	4.4 [3.7, 5.1]	1 (reference)	20.3 [19.0, 21.8]	1 (reference)
2001-2007	4.7 [4.3, 5.1]	1.07 [0.89, 1.28], p=0.479	14.5 [13.9, 15.2]	0.71 [0.66, 0.78], p<0.001
2008-2014	5.4 [5.0, 5.7]	1.23 [1.04, 1.47], p=0.019	13.9 [13.4, 14.5]	0.69 [0.63, 0.74], p<0.001
2015-2021	5.7 [5.3, 6.2]	1.32 [1.10, 1.58], p=0.003	15.9 [15.2, 16.6]	0.78 [0.72, 0.85], p<0.001

[1] Per 100 person-year

Table 5.3 Hazard ratios and accompanying 95% confidence intervals from Cox regression analysis with the follow-up duration restricted to the longest observed follow-up duration of the 2015-2021 group (6.7 years). Hazard ratios displayed were referenced against the 1993-2000 group.

Year of androgen deprivation therapy initiation	Major adverse cardiovascular event	All-cause mortality
1993-2000	1 (reference)	1 (reference)
2001-2007	1.07 [0.89, 1.28], p=0.493	0.72 [0.66, 0.78], p<0.001
2008-2014	1.23 [1.03, 1.46], p=0.021	0.69 [0.64, 0.74], p<0.001
2015-2021	1.33 [1.11, 1.59], p=0.002	0.76 [0.70, 0.83], p<0.001

ADT, androgen deprivation therapy.

Backward stepwise Cox regression showed that increased age, diabetes mellitus, anaemia, atrial fibrillation, chronic liver disease, chronic obstructive pulmonary disease, known malignancy, prior chemotherapy, prior radiotherapy, insulin use, sulphonylurea use, and using more cardiovascular medications were independently associated with higher risk of all-cause mortality, while medical castration, statin use, prior radical prostatectomy, angiotensinogen-converting enzyme inhibitor / angiotensin receptor blocker use, and metformin use were independently associated with lower risk of all-cause mortality (**Supplementary Table 5.7**). ADT initiation during or after 2001 was identified to be independently associated with lower risk of all-cause mortality as well. There was a trend of chronic kidney disease being associated with numerically higher risk of all-cause mortality which approached statistical significance (p=0.056).

5.4. Discussion

This population-based study demonstrated that cardiovascular risk factors were increasingly prevalent amongst Asian patients with PCa receiving ADT. This was accompanied by an increasing risk of MACE, despite reducing risk of mortality and an increasing proportion of patients with laboratory profiling relevant to cardiovascular risks.

This was one of the first studies that systematically quantified the temporal trends of cardiovascular burden in patients with PCa receiving ADT. We observed an increase in the risk of MACE but a decrease in the risk of mortality over time. The latter has been observed in other studies and have been postulated to be due to better treatment of PCa (197); other factors possibly at play may include changes in lifestyle and access to healthcare over the years. Meanwhile, the former occurred despite better contemporary understanding and recognition of the adverse cardiovascular effects of ADT (40), hence more patients being tested or monitored for cardiovascular risks. While it is immediately apparent that the increasing prevalence of cardiovascular risk factors over time may have contributed significantly to this observation, the factors driving the increase in MACE incidence were likely multifactorial and intertwined. For instance, the increasing use of ARSI and chemotherapy may have contributed to such increase in the risk of MACE, as both classes of agents have been shown to carry significant cardiovascular risks (206), with the newer generation of ARSI having been shown specifically to carry significantly higher cardiovascular risks than conventional ADT (41,207). Nonetheless, disentangling these factors, which may further include but are not limited to the patterns of cardiometabolic screening, usage and duration of specific types of ADT, and the stage of disease when PCa was detected or when ADT was initiated, was outside the scope of the current study.

The increasing prevalence of cardiovascular risk may have been a direct result of the well-characterized, general increase in the prevalence of cardiovascular diseases (196). Systemic factors, such as patient selection for ADT, and patients' knowledge and perception of ADT, may have played a role also. Indeed, we showed that the preference for specific modalities of ADT changed over time. This change maybe partly related to the change in local medical reimbursement system, as well as an overwhelming preference for medical castration over BO

in more recent years which was consistent with survey studies showing an estimated two-third of clinicians not considering or offering BO to eligible patients with PCa (208,209). It was possible that similar changes in the selection of patients for ADT have influenced the cardiovascular outcomes. This was especially relevant since the use of ADT is heavily dependent on patient preferences even within guidelines (194,210), with studies having shown significant variations in practice (211,212). It may thus be reasonable to speculate that changes in patient preferences outside the scope of this study may have contributed to the differences in cardiovascular burden and outcomes, either directly or by influencing patient selection for ADT.

Previous studies have shown that cardiovascular risk factors are prevalent amongst patients with PCa. In a large, prospective Canadian cohort of 2492 patients with PCa, 22% had known cardiovascular diseases (213). Similarly, in another smaller cohort of patients with PCa undergoing ADT, a quarter had established cardiovascular diseases (214). We observed similar results particularly in the most contemporary subgroup of patients, with 35.0% having hypertension and 27.4% having diabetes mellitus at baseline, and over 11% having had stroke or MI. In addition, we observed that only half of the patients in the most contemporary group had had total cholesterol, HDL-C, and HbA1c profiled prior to ADT initiation, which was despite substantial improvement in such proportions over time. This was echoed by a recent study by Sun and colleagues, who found that only 68.1% of an American cohort of veterans with PCa received comprehensive cardiovascular risk factor assessment (215).

5.4.1. Direct clinical relevance and further directions

Given the increasing risk of MACE observed in the current study, this study serves as a timely reminder for clinicians to be vigilant in screening and managing cardiovascular burden amongst patients with PCa undergoing ADT. The increasing risk of MACE in spite of increasing metabolic screening prior to initiating ADT showed that it is insufficient to only screen these patients, and that more efforts are required to adequately manage and reduce their cardiometabolic risk, including referral of patients with multiple cardiovascular risk factors to cardiology or cardio-oncology services before initiating ADT. Such multidisciplinary approach has been recommended by the 2022 European Society of Cardiology cardio-oncology guideline (13). This was not only relevant to urologists and oncologists, but also primary care physicians and cardiologists who may also take care of patients with PCa receiving ADT. Furthermore, the observed five-year risks of MACE and mortality reported in this study should allow clinicians to better inform patients of the risks associated with ADT, thereby facilitating shared decision-making regarding therapeutic options. It is important for clinicians to comprehensively inform patients and involve them actively in such decision-making, as greater involvements have been shown to be associated with lower risks of decision regret and higher health-related quality of life (216). Additionally, the independent risk factors for MACE and all-cause mortality hereby identified may improve identification of patients who are possibly at higher risk of these events. Given the relatively old mean age and long duration of ADT in this study, and as the duration of ADT may be proportionally associated with the risk of adverse cardiovascular outcomes (60), the current results are the most relevant to elderly patients with PCa who will be receiving long-term ADT, especially medical castration which was the

predominant modality of ADT in the most contemporary group of patients in the current study. Although the results may not be as relevant to young, otherwise healthy patients who are to be initiated on short-term ADT, the findings remain a valid reminder for clinicians to be vigilant of cardiovascular risks in patients with PCa undergoing ADT in general.

With this study demonstrating the significant and increasing cardiovascular burden amongst patients with PCa undergoing ADT, there are several gaps in evidence that are more relevant than ever. First, evidence pertinent to the optimal screening strategy for cardiovascular diseases in these patients is scarce. While previous studies have used the Framingham risk score as a surrogate of cardiovascular risk (213–215), its accuracy and validity for this specific patient group has not been adequately explored. This was echoed by the 2022 European Society of Cardiology cardio-oncology guideline (13) which pointed out the lack of cardiovascular risk scores for patients receiving ADT. More macroscopically, it is unclear, and therefore remains at clinicians' discretion, which patients are in particular need for cardiovascular screening and monitoring. To this end, prognostic studies, possibly with exploration of novel risk scores, are sorely needed to allow better stratification of high-risk patients; our reported independent risk factors for MACE and all-cause mortality may be a starting point which such studies may reference.

Second, there has not been any investigation of strategies to mitigate the adverse cardiovascular effects of ADT. Whilst Bhatia and colleagues have proposed a management algorithm for ADT-related adverse cardiovascular effects, the algorithm was based on previous paradigm established for patients with breast cancer, and direct evidence supporting the algorithm or any specific management approach remains lacking (217,218). This was in stark contrast to many other classes of antineoplastic medications that causes adverse cardiovascular effects, for which evidence-based management algorithms have been established (219,220). Future studies should therefore investigate approaches and therapeutics to mitigate the adverse cardiovascular effects brought by ADT. Screening, risk stratification, and management of cardiovascular risk factors have all been specified as key areas of focus for future research by an American Heart Association scientific statement as well (221).

Last but not least, further studies are required to elucidate the factors driving the observed worsening of cardiovascular outcome in patients with PCa undergoing ADT, which are likely complex, intertwined, and multifactorial in nature. A better understanding of these factors is necessary for stifling further worsening of cardiovascular outcomes in these patients.

5.4.2. Generalizability, strengths, and limitations

This study included a large cohort of patients from a population-based database, meaning that the findings are representative of real-life practice locally, and likely generalizable to other developed Asian cities. The consistent findings from multiple, different statistical approaches also reinforced the validity of our findings. However, Hong Kong operates a heavily subsidized public healthcare system, from which an estimated 90% of all Hong Kong citizens receive

healthcare. Given that healthcare financing structures have significant impact on access to care and the choice of therapeutics (222,223), the findings of this study may not be directly generalizable to countries with different healthcare financing structures, such as those that are predominantly privatized. Sociodemographic and cultural differences in the population may also affect generalizability of our findings to other countries and regions.

This study had a few limitations. First, the retrospective, observational nature predisposed to residual and unmeasured confounders which may influence findings. Whilst we acknowledge that there were likely unmeasured factors that may have driven our findings, it was not within the scope of this study to disentangle these underlying drivers – we invite the readers and colleagues to further explore this topic indeed. Second, owing to the nature of the database used, cancer staging and some cardiovascular risk factors that are prognostic in cardiovascular diseases, such as blood pressure and smoking status, were not available, which may have been important confounders, and which limited the interpretation of our findings. Specifically, there have been reports showing earlier diagnosis of PCa in recent years (224), which may have contributed to differences in the incidence and risk of both all-cause mortality and MACE – this remains to be investigated in the future. Third, as the data was retrieved from a deidentified, administrative database, it could not be individually adjudicated. Nonetheless, data entry was performed by treating clinicians without the involvement of any of the authors, and none of the authors had the right or authority to alter the data. Furthermore, previous studies have demonstrated that data recorded in the database (CDARS) had good accuracy, particularly for cardiovascular outcomes (225,226).

5.5. Conclusions

Over the past three decades, cardiovascular risk factors have become increasingly prevalent amongst patients with PCa receiving ADT in Hong Kong. This was accompanied by an increasing incidence of MACE but a decreasing incidence of all-cause mortality. Factors underlying such observations remain to be elucidated.

6. Chapter 6: Long-term cardiovascular burden in prostate cancer patients receiving androgen deprivation therapy

This chapter is based on the following publication: **Chan JSK**, Lee YHA, Liu K, Hui JMH, Dee EC, Ng K, Satti DI, Tang P, Tse G, Ng CF. Long-term cardiovascular burden in prostate cancer patients receiving androgen deprivation therapy. *Eur J Clin Invest*. 2023; 53(4): e13932. doi: 10.1111/eci.13932

6.1. Introduction

Androgen deprivation therapy (ADT), which pharmacologically or surgically suppresses androgen activity, is a key treatment for prostate cancer (PCa).(210) However, it is associated with increased cardiovascular risks, including elevated risks of cardiovascular mortality, myocardial infarction, and stroke.(40,195) Nonetheless, prior studies have focused on the first occurrence of adverse cardiovascular events,(60,195,227) and the burden of cardiovascular hospitalizations in patients with PCa receiving ADT has remained unexplored. Similarly, the long-term burden of cardiovascular mortality amongst ADT users have been underexplored.(228,229) Given the adverse cardiovascular effects of ADT, it is important to better understand the long-term burden of cardiovascular mortality and hospitalizations in these patients. Henceforth, this study aimed to describe the long-term burden of cardiovascular mortality and hospitalizations in patients with PCa receiving ADT.

6.2. Methods

6.2.1. Study design and source of data

This prospective cohort study was approved by The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (reference number 2022.051), and was conducted according to the Declaration of Helsinki. Reporting of the study conforms to broad EQUATOR guidelines.(230) Since only deidentified data were used, the need for individual consent was waived. Data was acquired from the Clinical Data Analysis and Reporting System (CDARS), a population-based database that prospectively records data of patients attending public hospitals and clinics in Hong Kong. CDARS encodes diagnoses using the International Classification of Diseases, Ninth revision (ICD-9) codes regardless of the time of data input, as ICD-10 codes have not been implemented in CDARS to date. Mortality data were acquired from the linked Hong Kong Death Registry, a governmental mortality registry for Hong Kong citizens which records causes of death in ICD-9 or ICD-10 codes. Both databases have been used extensively in research and demonstrated to have good coding accuracy and data completeness.(121,231–233)

6.2.2. Eligibility criteria, follow-up, outcomes, and covariates

Patients with PCa who received ADT (medical castration or bilateral orchiectomy) between 1/1/1993 and 31/3/2021 were identified. There were no exclusion criteria. All patients were followed up until 30/9/2021 or death, whichever occurred earlier. The causes of mortality (cardiovascular mortality, PCa mortality, or mortality from other causes, defined using ICD

codes in **Supplementary Table 6.1**) was recorded. The number and length of stay (LOS) of hospitalizations during follow-up were recorded, with specific analysis of emergency hospitalizations (i.e. hospitalizations via the accident and emergency department) and cardiovascular hospitalizations (defined using ICD-9 codes in **Supplementary Table 6.2**). In addition, the following data were collected for all patients: age, type of androgen deprivation therapy, comorbidities (hypertension, diabetes mellitus, dyslipidaemia, chronic kidney disease, chronic liver disease, stroke, myocardial infarction, ischaemic heart disease, heart failure, anaemia, atrial fibrillation, ventricular tachyarrhythmia, chronic obstructive pulmonary disease, and known malignancy), and use of medications or prior procedures (radiotherapy, chemotherapy, radical prostatectomy, androgen receptor signalling inhibitor (ARSI; no patient had baseline prescription of ARSI), angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, dihydropyridine calcium channel blockers, non-dihydropyridine calcium channel blockers, metformin, sulphonylurea, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonist, insulin, antiplatelet, anticoagulant, corticosteroid, percutaneous coronary intervention, and coronary artery bypass graft).

6.2.3. Statistical analysis

Continuous variables were described as medians with interquartile ranges. There is no missing value due to the nature of the database. As the Kaplan-Meier method overestimates cumulative incidence of events in the presence of competing risks, the Aalen-Johansen estimator was used to visualize the cause-specific cumulative incidence of different types of mortality (cardiovascular mortality, prostate cancer mortality, and mortality from other causes). The 5-year cause-specific cumulative incidence of the outcomes were estimated with consideration of competing risks. The overall incidence rate (IR) and annualized LOS of hospitalizations were estimated using negative binomial regression with the follow-up duration as exposure. As a large number of patients did not have emergency hospitalizations, cardiovascular hospitalizations, or emergency cardiovascular hospitalizations, the IR, and annualized LOS of these types of hospitalizations were estimated for those who had the respective type of hospitalization using zero-inflated negative binomial regression with the follow-up duration as exposure, and constant inflation.

An *a priori* subgroup analysis was performed to describe the outcomes in greater detail, in which all analyses were stratified by the type of androgen deprivation therapy (medical castration, bilateral orchiectomy, or both). Additionally, a *post hoc* exploratory subgroup analyses was performed with stratification for ever-prescription of ARSI. All p-values were two-sided, and $p<0.01$ was considered statistically significant. Statistical analyses were performed on Stata v16.1 (StataCorp LLC, College Station, Texas, United States of America).

6.3. Results

In total, 13,537 patients were identified and analyzed (median age 75.9 years old [interquartile range 70.0-81.5 years old]; **Table 6.1**); 6944 received medical castration, 5359 received bilateral orchiectomy, and 1234 received both.

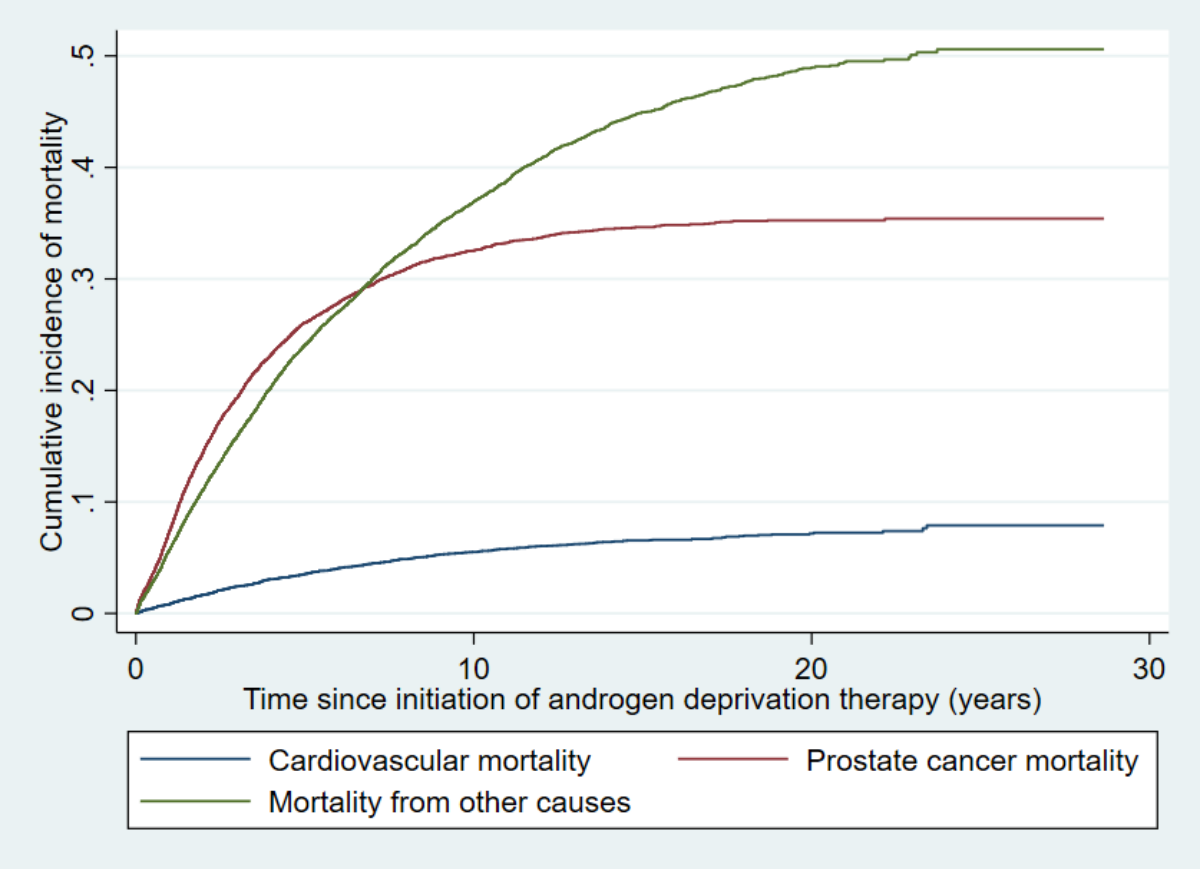
Table 6.1 Characteristics of all included patients.

Number of patients, N	13,537
Follow-up duration, years	4.7±4.3
Age, years	75.5±8.5
Medical castration, N (%)	8178 (60.4)
Bilateral orchidectomy, N (%)	6593 (48.7)
Hypertension, N (%)	3624 (26.8)
Diabetes mellitus, N (%)	2886 (21.3)
Dyslipidaemia, N (%)	1270 (9.4)
All of hypertension, diabetes mellitus, and dyslipidaemia, N (%)	501 (3.7)
Chronic kidney disease, N (%)	452 (3.3)
Chronic liver disease, N (%)	146 (1.1)
Stroke, N (%)	1216 (9.0)
Myocardial infarction, N (%)	427 (3.2)
Ischaemic heart disease, N (%)	1407 (10.4)
Heart failure, N (%)	695 (5.1)
Anaemia, N (%)	966 (7.1)
Atrial fibrillation, N (%)	610 (4.5)
Chronic obstructive pulmonary disease, N (%)	804 (5.9)
Prior percutaneous coronary intervention, N (%)	432 (3.2)
Prior CABG, N (%)	55 (0.4)
Prior radiotherapy, N (%)	493 (3.6)
Prior radical prostatectomy, N (%)	3735 (27.6)
Prior chemotherapy, N (%)	61 (0.5)
Ever received radiotherapy, N (%)	3114 (23.0)
Ever received radical prostatectomy, N (%)	4601 (34.0)
Ever received chemotherapy, N (%)	1311 (9.7)
Ever received ARSI, N (%)	4792 (35.4)
Ever received chemotherapy or ARSI, N (%)	5116 (37.8)
ACEI/ARB users, N (%)	3383 (25.0)
Beta-blocker users, N (%)	4130 (30.5)
Dihydropyridine CCB users, N (%)	5396 (39.9)
Non-dihydropyridine CCB users, N (%)	575 (4.3)
Metformin users, N (%)	1480 (10.9)
Sulphonylurea users, N (%)	1744 (12.9)
DPP4 inhibitor users, N (%)	150 (1.1)
GLP1 receptor agonist users, N (%)	2 (0.0)
Insulin users, N (%)	722 (5.3)
Antiplatelet users, N (%)	2962 (21.9)
Anticoagulant users, N (%)	458 (3.4)
Corticosteroid users, N (%)	2342 (17.3)

ACEI, angiotensin-converting enzyme inhibitor. ARB, angiotensin receptor blocker. ARSI, androgen receptor signaling inhibitor. CABG, coronary artery bypass graft. CCB, calcium channel blocker. DPP4, dipeptidyl peptidase 4. GLP1, glucagon-like peptide-1.

Over a median follow-up duration of 3.3 years [1.5-6.7 years], 9124 patients (67.4%) died (**Figure 6.1**), of whom 671 had cardiovascular mortality (7.4% of patients who died; 5.0% of all patients), 3926 had PCa mortality (43.0% of patients who died; 29.0% of all patients), and 4529 had mortality from other causes (49.6% of patients who died; 33.5% of all patients). The five-year risk of cardiovascular mortality was 3.5% [3.2%, 3.9%], while that of PCa mortality was 26.1% [25.3%, 26.9%], and that of mortality from other causes was 24.1% [23.3%, 24.8%].

Figure 6.1 Cause-specific cumulative incidence curve of mortality for all included patients.



Subgroup analysis by the type of ADT found that 3.2-6.0% of patients had cardiovascular mortality (**Supplementary Tables 6.3-6.4** and **Figure 6.2**). Furthermore, in the exploratory subgroup analysis, more of those who were never prescribed ARSI had cardiovascular mortality than their counterparts who were prescribed ARSI at some point during follow-up, with more of the former dying from PCa and less from other causes than the latter (**Supplementary Table 6.5** and **Figure 6.3**). The cause-specific five-year risks of mortality showed similar trends (**Supplementary Table 6.6**).

Figure 6.2 Cause-specific cumulative incidence curves of mortality for patients with each type of androgen deprivation therapy (A: medical castration; B: bilateral orchiectomy; C: both medical castration and bilateral orchiectomy).

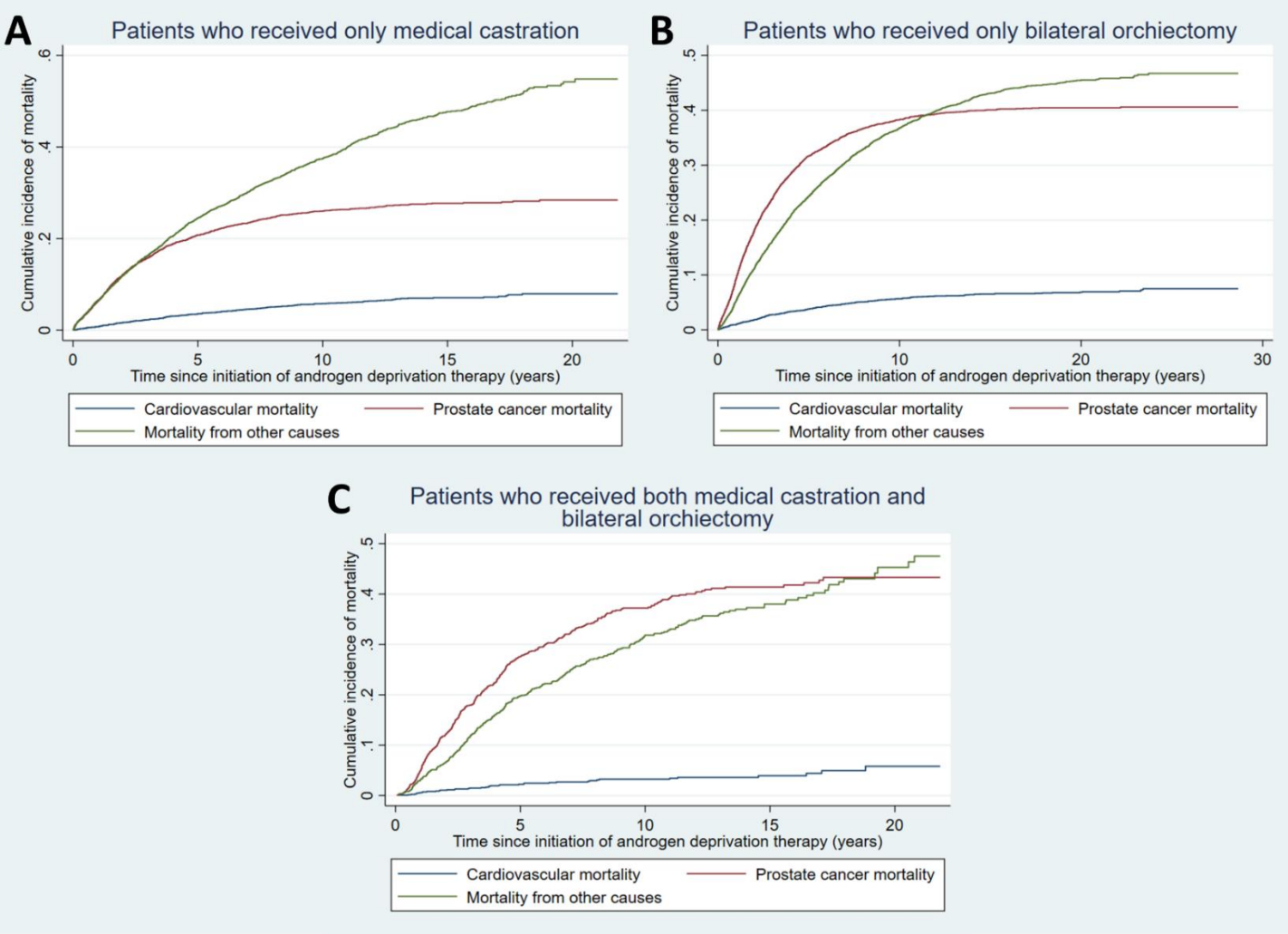
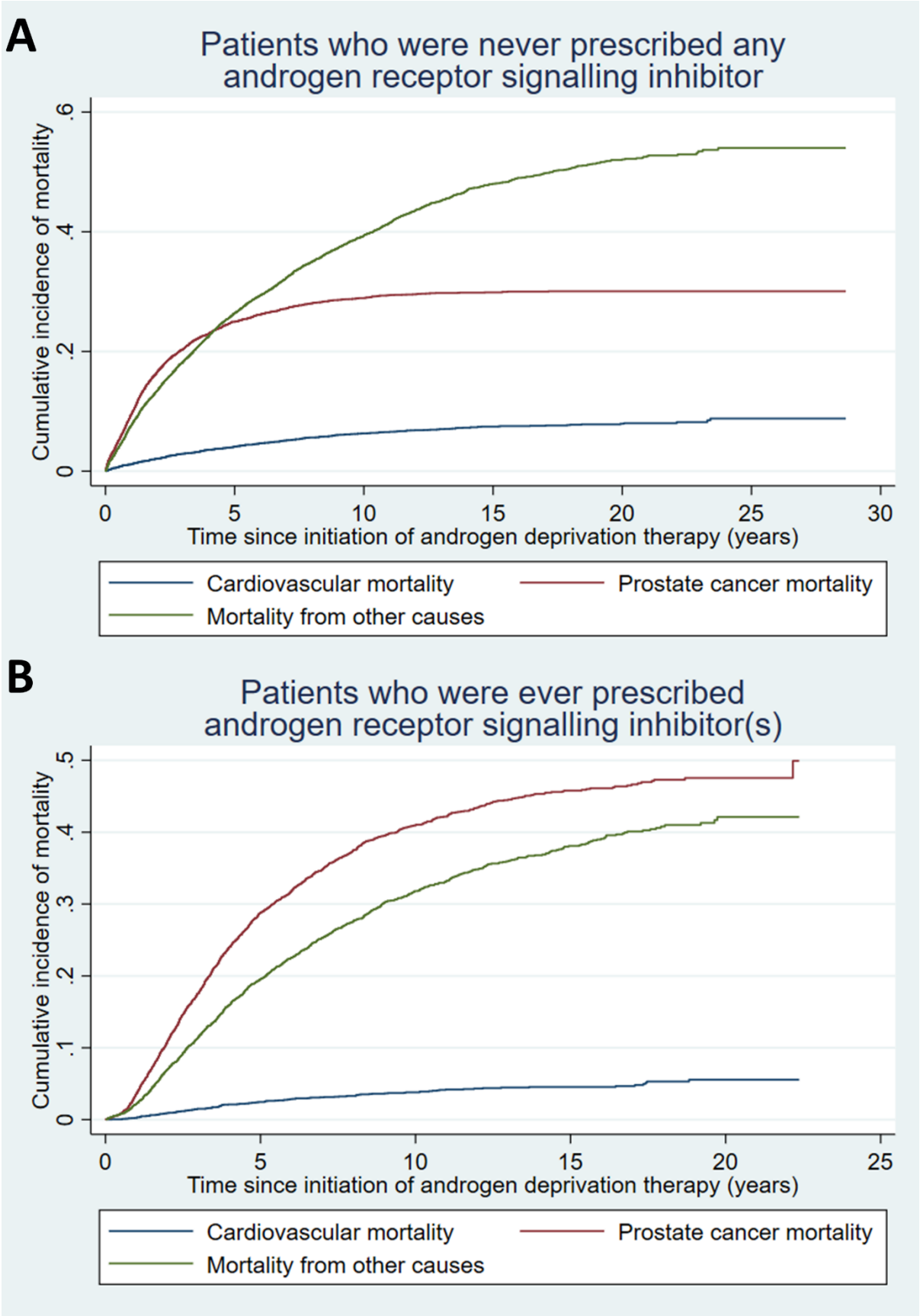


Figure 6.3 Cause-specific cumulative incidence curves of mortality for patients who were never (A) or ever (B) prescribed androgen receptor signalling inhibitor(s).



Altogether, 139,085 episodes of hospitalizations were observed, with 6831 episodes (4.9%) being cardiovascular hospitalizations, 57,632 (41.4%) being emergency hospitalizations, and 4553 (3.3%) being emergency cardiovascular hospitalizations. These corresponded to 763,963 days of hospitalization, with 50,912 days (6.7%) being cardiovascular hospitalizations, 372,477 (48.8%) being emergency hospitalizations, and 30,526 (4.0%) being emergency cardiovascular hospitalizations. Of the 6831 episodes of cardiovascular hospitalizations, 1609 episodes (23.6%) were due to myocardial infarction or ischaemic heart disease, 1532 (22.4%) were due to heart failure, 1002 (14.7%) were due to arrhythmias, 1175 (17.2%) were due to stroke, and 1513 (22.1%) were due to other cardiovascular causes. Furthermore, of the 4553 episodes of emergency cardiovascular hospitalizations, 1225 episodes (26.9%) were due to heart failure, 922 (20.3%) were due to myocardial infarction or ischaemic heart disease, 797 (17.5%) were due to stroke, 741 (16.3%) were due to arrhythmia, and 868 (19.1%) were due to other cardiovascular causes. **Table 6.2** summarizes the IR and annualized LOS of hospitalizations for all included patients.

Table 6.2 Incidence rate (IR) and length of stay (LOS) of different types of hospitalizations.

	Number of patients with event, N (%)	IR [95% CI], event per 100 person-years	LOS [95% CI], days per 100 person-years
Any hospitalization	13,118 (96.9)	353.5 [347.2, 359.8]	2653.4 [2594.0, 2714.2]
Cardiovascular hospitalizations	3055 (22.6)	13.3 [12.7, 13.9] [1]	138.7 [129.2, 148.9] [1]
Emergency hospitalizations	11,463 (84.7)	138.4 [135.5, 141.4] [1]	1228.5 [1195.6, 1232.4] [1]
Emergency cardiovascular hospitalizations	2562 (18.9)	8.7 [8.2, 9.1] [1]	83.8 [77.7, 90.4] [1]

CI, confidence interval.

[1] Estimated for those who had the respective type of hospitalization using zero-inflated negative binomial regression.

The IR and annualized LOS of hospitalizations were largely comparable between the three types of ADT (medical castration, bilateral orchiectomy, and both medical castration and bilateral orchiectomy; **Supplementary Table 6.7**). When stratified by ever-prescription of ARSI (**Supplementary Table 6.8**), patients who were never prescribed ARSI had higher IR and annualized LOS across all subtypes of hospitalizations, except the annualized LOS of emergency cardiovascular hospitalizations which was comparable between the two subgroups.

6.4. Discussion

In this study, we quantified the long-term burden of cardiovascular mortality and hospitalizations in a representative, prospective, population-based cohort of Hong Kong

patients with PCa receiving ADT. We observed a crude cardiovascular mortality rate of 5.0%, comparable with a recent study of patients with metastatic PCa that reported a 6.9% crude cardiovascular mortality rate.(229) We also observed that 4.9% of hospitalization episodes and 6.7% of the days of hospitalizations were attributable to cardiovascular causes, with an estimated 13.3 episodes per 100 person-years. Governmental figures in 2019 reported 171,331 episodes of cardiovascular mortality and hospitalizations in Hong Kong,(234) which, given a then-7.5-million population,(234) translated to 2.3 cardiovascular hospitalizations or deaths per 100 person-year. These higher observed rates were expected, as ADT, often but not always in combination with other treatments such as radiotherapy, is indicated for patients with advanced PCa who are older and often have significant pre-existing cardiovascular risks that are further compounded by ADT use.(210) This was evident in our cohort, with over 20% of patients having hypertension or diabetes, and over 10% having ischaemic heart disease which was likely a dominant driver of cardiovascular mortality and hospitalizations. This was further reinforced by the observation that myocardial infarction or ischaemic heart disease was the leading cause of cardiovascular hospitalizations, which also suggested that myocardial ischaemia may be a priority for treatment and monitoring in these patients. Additionally, we observed that compared to those who never received ARSI, those who were prescribed ARSI had lower cumulative incidence of cardiovascular mortality but higher PCa mortality – the former likely reflected how clinicians' awareness of the increase in cardiovascular risks associated with ARSI(40) influenced prescribing practice, while the latter was likely due to ARSI being indicated for more advanced diseases.(210)

Our findings highlighted the cardiovascular burden amongst patients with PCa receiving ADT. Clinically, our results may facilitate discussions regarding treatment modalities in light of cardiovascular risk. With only a small proportion of deaths being cardiovascular-related, clinicians may be reassured that in many cases, oncologic benefits of ADT likely outweigh cardiovascular risks. However, careful cardiac workup and follow-up would still be necessary particularly for patients with known cardiovascular risk factors. Overall, it is important to note that although cardiovascular risks are elevated, PCa remains a substantially more common cause of mortality in these patients, and the risks of cardiotoxicity must be balanced against the oncological benefits of ADT which, in turn, depends on numerous disease and patient factors that must be assessed meticulously. The emerging concept of 'permissive cardiotoxicity', which emphasizes a proactive and not reactive approach to cancer therapy-related cardiotoxicity, may be useful in this instance to minimize interruptions of ADT whilst simultaneously mitigating cardiovascular risks.(94) How this is to be implemented in reality, however, remains to be investigated. Our findings may form the basis on which such studies may be based, as may studies exploring other aspects of ADT-related cardiotoxicity that warrant further investigation, including but not limited to the associations between the duration of ADT and cardiovascular mortality and burden, and the relationship between metabolic syndrome and ADT-related cardiotoxicity.

This is the first study quantifying the long-term burden of cardiovascular hospitalizations amongst patients with PCa receiving ADT, for which the literature remains lacking. It is also one of the first studies of mortality causes in these patients. Utilizing a prospective population-

based database, our findings were representative of Hong Kong and likely generalizable to other Asian regions. Nonetheless, cancer staging was not available, preventing more detailed breakdown of observed events. Moreover, the data could not be individually adjudicated. Nonetheless, all data were input by treating clinicians independent of the authors, and CDARS has been shown to have good data completeness and coding accuracy.(232)

6.5. Conclusion

This population-based study quantified the long-term burden of cardiovascular mortality and hospitalization amongst Hong Kong patients with PCa receiving ADT, with comparable event rates between different types of ADT.

7. Chapter 7: Long-term prognostic impact of cardiovascular comorbidities in patients with prostate cancer receiving androgen deprivation therapy: a population-based competing risk analysis

This chapter is based on the following publication: **Chan JSK**, Lee YHA, Hui JMH, Liu K, Dee EC, Ng K, Liu T, Tse G, Ng CF. Long-term prognostic impact of cardiovascular comorbidities in patients with prostate cancer receiving androgen deprivation therapy: a population-based competing risk analysis. *Int J Cancer.* 2023; 153(4): 756-764. doi: 10.1002/ijc.34557

7.1. Introduction

Androgen deprivation therapy (ADT) involves pharmacological or surgical suppression of androgen activity, and has long been a cornerstone of prostate cancer (PCa) treatment.(210) Whilst the efficacy of ADT for treating PCa is undoubted, the past decade has seen studies demonstrating an association between ADT and adverse cardiovascular outcomes. Ever since the landmark study by Keating and colleagues,(195) ADT has been shown to be associated with increased risks of myocardial infarction, arrhythmia, stroke, heart failure, and cardiovascular mortality, with many also demonstrating other aspects of adverse cardiometabolic outcomes.(40)

Given the rising prevalence of PCa and the important role played by ADT in PCa treatment, increasing attention has been given to the adverse cardiovascular effects of ADT. In the 2022 European Society of Cardiology Guidelines on cardio-oncology, one of the first major societal guidelines in cardio-oncology, a separate section was dedicated to the surveillance for ADT-related cardiotoxicity.(13) The same guideline recommended the use of the Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) risk assessment tool for cardiovascular risk stratification of cardio-oncology patients, in which numerous cardiovascular risk factors were designated categories that reflect their relative prognostic significance for cardiotoxicity related to a specific class of anti-cancer medications.(13,71) However, this important risk assessment tool did not include such designations for ADT. Indeed, little is known about the relative impact of different cardiovascular risk factors on adverse cardiovascular outcomes. Similarly, studies of relationships between different cardiovascular risk factors in patients receiving ADT are lacking. These represent important gaps in the understanding and stratification of cardiovascular risk and burden in these patients. Therefore, we aimed to investigate the interrelationship between different major cardiovascular comorbidities, and their impact on cardiovascular outcomes in patients with PCa receiving ADT.

7.2. Materials and methods

This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guideline.

7.2.1. Source of data

Data were collected from the Clinical Data Analysis and Reporting System (CDARS), a population-based administrative database that prospectively records basic demographics, diagnoses, laboratory tests, and medical procedures of all patients attending public hospitals and clinics in Hong Kong, which cover the entire Hong Kong and serve 90% of the population.(199) Diagnoses are encoded by the International Classification of Diseases, Ninth revision (ICD-9) codes regardless of the time of data input, as ICD-10 codes have not been implemented in CDARS to date. Mortality data were collected from the linked Hong Kong Death Registry, a governmental registry of all Hong Kong citizens' death records. Both databases have been used extensively in research, and have been shown to have good coding accuracy and data completeness.(121,231,232,235–238)

7.2.2. Patient population

Adult (aged 18 years old or above) patients with PCa who received ADT between 1/1/1993-31/3/2021 were identified. ADT included medical castration and bilateral orchiectomy (BO). There were no exclusion criteria. This cohort has been published before.(120)

The following baseline characteristics were recorded: age, type of androgen deprivation therapy, comorbidities (hypertension, diabetes mellitus, dyslipidaemia, chronic kidney disease, chronic liver disease, stroke, myocardial infarction (MI), heart failure (HF), and arrhythmias (atrial fibrillation, ventricular tachycardia, or ventricular fibrillation)), and use of medications or prior procedures (radiotherapy, chemotherapy, radical prostatectomy, androgen receptor signalling inhibitor (ARSI), dihydropyridine calcium channel blockers, metformin, sulphonylurea, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonist, insulin, antiplatelet, anticoagulant, and corticosteroid).

7.2.3. Follow-up and outcomes

All patients were followed up from the date of ADT initiation until 31/9/2021, death, or the primary endpoint, whichever occurred earlier. The primary endpoint was a composite of cardiovascular hospitalization and cardiovascular mortality. Cardiovascular hospitalizations were identified by ICD-9 codes listed in **Supplementary Table 1**, while cardiovascular mortality was identified by ICD-9 or ICD-10 codes listed in **Supplementary Table 2**.

7.2.4. Major cardiovascular comorbidities and their relative impact

We focused on prior history of HF, MI, stroke, and arrhythmia as the major cardiovascular comorbidities of interest. These comorbidities were chosen amongst broader cardiometabolic conditions, such as hypertension and diabetes mellitus, as (1) we had shown that these accounted for >75% of cardiovascular hospitalizations in patients with PCa receiving ADT,(120) (2) they are clinically more severe conditions that are likely to lead to substantially worse morbidity, and (3) the inclusion of broader cardiometabolic comorbidities would have

created too many combinations of comorbidities with limited sample sizes, preventing any meaningful analysis. Patients were categorized into the following groups by the presence of these major cardiovascular comorbidities for comparisons: none of HF/MI/stroke/arrhythmia, HF only, MI only, stroke only, arrhythmia only, and at least two of HF/MI/stroke/arrhythmia. To explore the effects of stroke subtypes, we carried out a *post hoc* analysis in which patients with stroke only were split into those having had ischaemic stroke, haemorrhagic stroke, or both ischaemic and haemorrhagic stroke.

As these comorbidities commonly overlap, we further explored the relative impact of each major cardiovascular comorbidity in those with overlapping comorbidities (i.e. with ≥2 major cardiovascular comorbidities). This was done by comparing patients with both a condition of focus and any of the 'non-focus' conditions against patients with ≥2 of the 'non-focus' conditions. For instance, to explore the relative impact of HF, we compared patients with HF and any of MI/stroke/arrhythmia against those with ≥2 of MI/stroke/arrhythmia.

7.2.5. Statistical analyses

Continuous variables were expressed as medians with interquartile ranges (IQRs). There was no missing value due to the nature of database and variables used. All variables used for multivariable adjustments were determined based on clinical expertise. The number of major cardiovascular comorbidities was compared between groups using multivariable Poisson regression adjusting for all recorded baseline variables, with the ratio of cardiovascular comorbidity counts and corresponding 95% confidence intervals (CIs) as summary statistics. Non-cardiovascular mortality constituted a competing event for the primary outcome. As Kaplan-Meier curves over-estimate cumulative incidences in the presence of competing events,(120,239) the cause-specific cumulative incidence of the primary endpoint was estimated and visualized using the Aalen-Johansen estimator.(120,239) The 3-, 5-, and 10-year cause-specific cumulative incidences were estimated for each group (none of HF/MI/stroke/arrhythmia, HF only, MI only, stroke only, arrhythmia only, and at least two of HF/MI/stroke/arrhythmia). The cumulative incidence of the primary endpoint was quantitatively compared between groups using multivariable Fine-Gray competing risk regression, with sub-hazard ratios (SHRs) and 95% CIs as summary statistics and adjusting for all collected baseline variables. All reported SHRs and corresponding CIs are adjusted estimates.

As the exploratory analysis for the relative impact of each major cardiovascular comorbidity focused on patients with ≥2 of these comorbidities, the corresponding Fine-Gray regressions were additionally adjusted for the number of major cardiovascular comorbidities present to account potential imbalances in the number of comorbidities between groups. Furthermore, in view of the results from the exploratory analysis, a *post hoc* analysis was conducted to explore the prognostic effects of the number of major cardiovascular comorbidities on the primary endpoint among patients with ≥2 of these comorbidities. Because very few patients had all four of these comorbidities, this *post hoc* analysis compared those with two of these comorbidities against those with ≥3 of these comorbidities.

Fine-Gray regression was separately performed in two pre-specified and one *post hoc* subgroup analyses. First, to clarify any impact that heterogeneity in the type of ADT may have on the observed effects, subgroup analysis was performed for each type of ADT (medical castration, bilateral orchidectomy, and both; all patients received bilateral orchidectomy after medication castration, mostly because, until recently, the local reimbursement system did not subsidize medical castration, and bilateral orchidectomy was often performed as a cost-saving long-term alternative to medical castration). On the other hand, as cancer staging and histology were not available from the database used, we used ever-prescription of ARSI or chemotherapy as a surrogate for metastatic disease, as these were only indicated in metastatic PCa.(193,240) The second subgroup analysis thus stratified patients by whether they were ever prescribed ARSI or chemotherapy, as a surrogate of whether they had metastatic disease. The third, *post hoc* subgroup analysis explored the effects of metabolic dysfunction or hypertension on our findings, with stratification for the presence of hypertension, diabetes mellitus, or dyslipidaemia. Due to the small sample sizes for each risk category, interactions between subgroups were not tested. Additionally, due to the relatively small number of patients with ≥2 major cardiovascular comorbidities, these subgroup analyses were not performed for the exploratory analysis of the relative impact of each comorbidity in those with overlapping comorbidities.

Two-sided $p<0.05$ were considered statistically significant. All analyses were performed on Stata version 16.1 (StataCorp LLC, College Station, Texas, United States).

7.3. Results

Altogether, 13,537 patients were included (median age 75.9 [IQR 70.0-81.5] years old; **Table 7.1**). Most patients (11,102, 82.0%) had none of prior HF/MI/stroke/arrhythmia, 357 (2.6%) had prior HF only, 240 (1.8%) had MI only, 968 (7.2%) had prior stroke only, 319 (2.4%) had arrhythmia only (602 (4.5%) had only atrial fibrillation, 22 (0.2%) had only ventricular tachycardia or fibrillation, and eight (0.1%) had both atrial fibrillation and ventricular tachycardia or fibrillation), and 494 (3.6%) had ≥2 of HF/MI/stroke/arrhythmia. Among patients who had one to three of the four major cardiovascular comorbidities, patients who had HF, MI, or arrhythmia had significantly more major cardiovascular comorbidities than those who did not have each of these conditions ($p<0.001$ for all; **Table 7.2**), but not for those who had stroke ($p=0.303$). The number of patients with each possible combination of major cardiovascular comorbidities are shown in **Supplementary Table 7.3**.

Table 7.1 Characteristics of included patients.

Number of patients, N	13,537
Age, years	75.5±8.5
Medical castration, N (%)	8178 (60.4)
Bilateral orchidectomy, N (%)	6593 (48.7)
Ischaemic stroke, N (%)	1052 (7.8%)
Haemorrhagic stroke, N (%)	241 (1.8%)
Myocardial infarction, N (%)	427 (3.2)
Heart failure, N (%)	695 (5.1)
Arrhythmia, N (%)	632 (4.7)
Hypertension, N (%)	3624 (26.8)
Diabetes mellitus, N (%)	2886 (21.3)
Dyslipidaemia, N (%)	1270 (9.4)
Chronic kidney disease, N (%)	452 (3.3)
Prior radiotherapy, N (%)	493 (3.6)
Prior radical prostatectomy, N (%)	3735 (27.6)
Prior chemotherapy, N (%)	61 (0.5)
Ever received chemotherapy or ARSI, N (%)	5116 (37.8)
Dihydropyridine CCB users, N (%)	5396 (39.9)
Metformin users, N (%)	1480 (10.9)
Sulphonylurea users, N (%)	1744 (12.9)
DPP4 inhibitor users, N (%)	150 (1.1)
GLP1 receptor agonist users, N (%)	2 (0.0)
Insulin users, N (%)	722 (5.3)
Antiplatelet users, N (%)	2962 (21.9)
Anticoagulant users, N (%)	458 (3.4)
Corticosteroid users, N (%)	2342 (17.3)

ARSI, androgen receptor signaling inhibitor. CCB, calcium channel blocker. DPP4, dipeptidyl peptidase 4. GLP1, glucagon-like peptide-1.

Table 7.2 Comparison of the number of major cardiovascular comorbidities among those who had one to three of such these conditions.

Category	Number of major cardiovascular comorbidities, N (%)			Ratio of cardiovascular comorbidity counts [95% confidence interval]	p-value
	1	2	3		
With HF	357 (51.9)	255 (37.1)	76 (10.9)	1.44 [1.34, 1.56]	<0.001
Without HF (reference)	1527 (90.7)	148 (8.8)	8 (0.5)		
With MI	240 (57.1)	130 (31.0)	50 (11.9)	1.34 [1.22, 1.47]	<0.001
Without MI (reference)	1644 (84.3)	273 (14.0)	34 (1.7)		
With stroke	968 (80.1)	187 (15.5)	54 (4.5)	1.04 [0.97, 1.12]	0.303
Without stroke (reference)	916 (78.8)	216 (18.6)	30 (2.6)		
With arrhythmia	319 (51.0)	234 (37.4)	72 (11.5)	1.39 [1.27, 1.52]	<0.001
Without arrhythmia (reference)	1565 (89.6)	169 (9.7)	12 (0.7)		

HF, heart failure. MI, myocardial infarction.

7.3.1. Impact of cardiovascular comorbidities

Over a median follow-up of 3.3 [1.5-6.7] years, 3225 (23.8%) met the primary endpoint, and 6662 (49.2%) died of non-cardiac causes without meeting the primary endpoint; 9113 (67.6%) died in total. Of the 3225 patients who met the primary endpoint, one had cardiovascular mortality, and 3224 had cardiovascular hospitalization (amongst whom 670 [4.9% of all patients; 20.8% of those who had cardiovascular hospitalization] went on to have cardiovascular mortality). Cumulative incidence of the primary endpoint is shown in **Figure 7.1**, and each group's estimated 3-, 5-, and 10-year cumulative incidences of the primary endpoint are summarized in **Supplementary Table 7.4**. Compared to patients who had none of prior HF/MI/stroke/arrhythmia, patients with only prior HF (SHR 1.67 [95% confidence interval: 1.37, 2.02], p<0.001), prior arrhythmia (SHR 1.63 [1.35, 1.98], p<0.001), or prior MI (SHR 1.43 [1.14, 1.79], p=0.002) had significantly higher incidence of the primary endpoint, but not those who only had prior stroke (SHR 1.06 [0.92, 1.23], p=0.391). Those who had ≥2 of HF/MI/stroke/arrhythmia had the highest incidence of the primary endpoint (SHR 1.94 [1.62, 2.33], p<0.001). In *post hoc* analysis, patients with stroke only did not have significantly different incidence of the primary endpoint regardless of the type of stroke (ischaemic stroke: SHR 1.07 [0.92, 1.24], p=0.408; haemorrhagic stroke: SHR 1.10 [0.77, 1.56], p=0.598; both ischaemic and haemorrhagic stroke: SHR 0.93 [0.53, 1.63], p=0.808), compared to those without any of major cardiovascular comorbidities.

Amongst the 1881 patients with only one of the major cardiovascular comorbidities, HF (SHR 1.51 [1.21, 1.89], p<0.001), arrhythmia (SHR 1.39 [1.11, 1.73], p=0.004), and MI (SHR 1.31 [1.03, 1.66], p=0.026) were all associated with significantly higher incidences of the primary endpoint compared to those with only stroke.

7.3.2. Subgroup analysis

Subgroup analysis by the type of ADT (**Table 7.3**) showed mostly consistent trends in patients who received only medical castration (N=6944) or only bilateral orchidectomy (N=5116), with those having ≥2 of HF/MI/stroke/arrhythmia having the highest incidence of the primary endpoint, and with only HF, MI, and arrhythmia being associated with significantly higher incidence of the primary endpoint when compared to those without any of HF/MI/stroke/arrhythmia. However, no significant association was observed in the 1234 patients who received both medical castration and bilateral orchidectomy.

Figure 7.1 Cumulative incidence curves for the primary endpoint, stratified by different major cardiovascular comorbidities. HF, heart failure. MI, myocardial infarction.

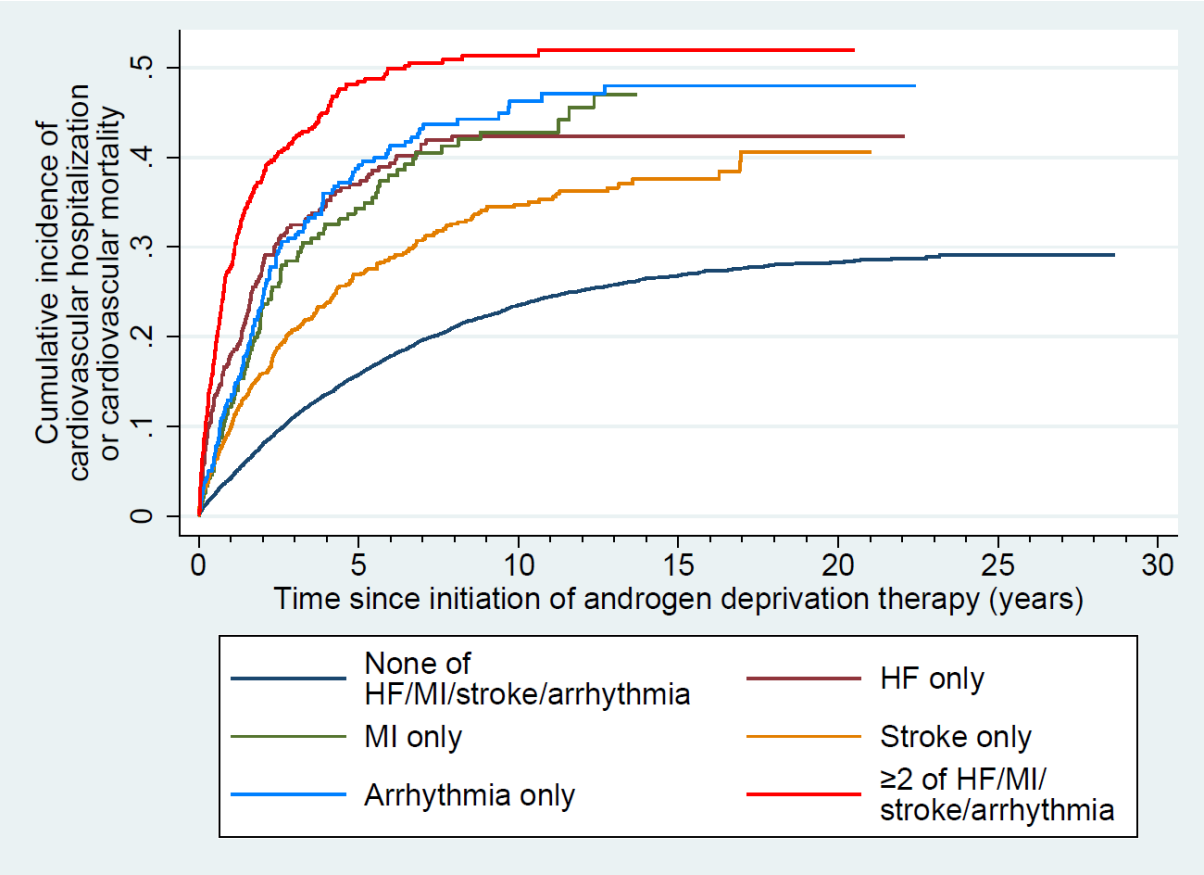


Table 7.3 Results of subgroup analysis by the type of androgen deprivation therapy received. All values shown are adjusted sub-hazard ratios with corresponding 95% confidence intervals.

Major cardiovascular comorbidities	Medical castration (N=6944)	Bilateral orchidectomy (N=5359)	Both medical castration and bilateral orchidectomy (N=1234)
None of HF/MI/stroke/arrhythmia	1 (reference)	1 (reference)	1 (reference)
HF only	1.65 [1.25, 2.17], p<0.001	1.77 [1.31, 2.38], p<0.001	1.15 [0.56, 2.38], p=0.704
MI only	1.36 [1.01, 1.84], p=0.045	1.65 [1.13, 2.42], p=0.009	1.02 [0.39, 2.64], p=0.972
Stroke only	1.01 [0.83, 1.23], p=0.915	1.20 [0.96, 1.51], p=0.109	0.74 [0.44, 1.23], p=0.243
Arrhythmia only	1.76 [1.36, 2.28], p<0.001	1.67 [1.22, 2.30], p=0.002	0.52 [0.22, 1.22], p=0.133
⩾2 of HF/MI/stroke/arrhythmia	1.81 [1.43, 2.29], p<0.001	2.38 [1.75, 3.24], p<0.001	1.34 [0.61, 2.94], p=0.463

HF, heart failure. MI, myocardial infarction.

On the other hand, while MI and arrhythmia remained to be associated with significantly higher incidence of the primary endpoint regardless of whether patients had metastatic disease (i.e. prescribed ARSI or chemotherapy; **Supplementary Table 7.5**), such association for HF was significant in those who did not have metastatic disease (i.e. never prescribed ARSI or chemotherapy), but only approached significance in those with metastatic disease (p=0.059). Having ≥2 of HF/MI/stroke/arrhythmia remained to be associated with the highest incidence of primary endpoint regardless of whether patients had metastatic disease.

In the *post hoc* subgroup analysis by the presence of hypertension, diabetes mellitus, or dyslipidaemia, findings in both subgroups were largely consistent with the main analysis (**Supplementary Table 7.6**), although the association for patients with only MI amongst those with hypertension, diabetes mellitus, or dyslipidaemia only approached statistical significance (p=0.055).

7.3.3. Relative impact of each comorbidity in patients with overlapping comorbidities

The relative impact of each specified major cardiovascular comorbidity were explored among the 494 patients with ≥2 of HF/MI/stroke/arrhythmia, with cumulative incidences of the primary endpoint stratified by different combinations of cardiovascular comorbidities (**Figure 7.2**). HF, MI, stroke, and arrhythmia did not have significantly different impact on the incidence of the primary endpoint (**Table 7.4**). *Post hoc* analysis suggested that compared to those with two of HF/MI/stroke/arrhythmia, those who had ≥3 of these comorbidities had significantly higher incidence of the primary endpoint (SHR 1.42 [1.02, 1.97], p=0.037).

Figure 7.2 Cumulative incidence curves for the primary endpoint, stratified by different combinations of major cardiovascular comorbidities. The relative impact of **(A)** heart failure (HF), **(B)** myocardial infarction (MI), **(C)** stroke, and **(D)** arrhythmia was explored, which showed that the impact of these comorbidities on the cumulative incidence of the primary endpoint were not significantly different from each other.

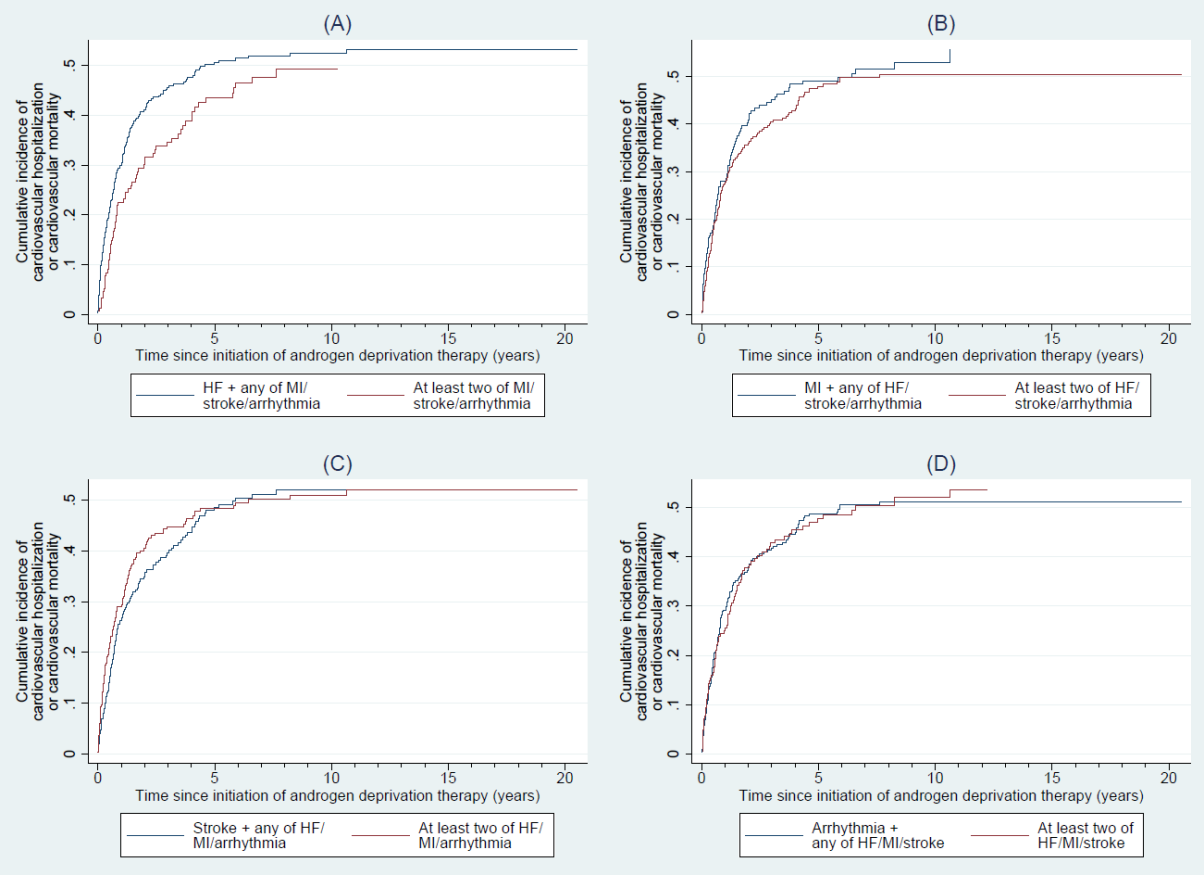


Table 7.4 Results from the exploratory analysis for the impact of each major cardiovascular comorbidity among those with ⩾2 of heart failure (HF) / myocardial infarction (MI) / stroke / arrhythmia. Sub-hazard ratios displayed were adjusted for all recorded baseline variables and the number of major cardiovascular comorbidities present.

Comparator (comorbidity of interest ***highlighted***)	Reference group	Sub-hazard ratio [95% CI]	p-value
HF + any of MI/stroke/arrhythmia (N=338)	≥2 of MI/stroke/arrhythmia (N=156)	1.15 [0.86, 1.55]	0.343
MI + any of HF/stroke/arrhythmia (N=187)	≥2 of HF/stroke/arrhythmia (N=307)	0.99 [0.73, 1.34]	0.934
Stroke + any of HF/MI/arrhythmia (N=248)	≥2 of HF/MI/arrhythmia (N=246)	0.91 [0.69, 1.19]	0.490
Arrhythmia + any of HF/MI/stroke (N=313)	≥2 of HF/MI/stroke (N=181)	0.98 [0.70, 1.37]	0.924

CI, confidence interval.

7.4. Discussion

This prospective, population-based study had three main findings. First, the presence of HF, MI, and arrhythmia, but not stroke, were associated with more cardiovascular comorbidities. Second, in those with only one of HF/MI/stroke/arrhythmia, HF, MI, and arrhythmias conferred similarly elevated cardiovascular risks compared to those without any of these conditions, but stroke was not associated with any significant increase in cardiovascular risks, regardless of the type of stroke. Third, in those with ≥2 of HF/MI/stroke/arrhythmia, these conditions may have similar impact on cardiovascular risks, and the overall number of comorbidities was likely a significant prognosticator for cardiovascular events.

The first finding was within expectations. Most intuitively, HF, MI, and arrhythmia are all cardiac disorders with many similarities in the underlying pathophysiological pathways, most of which are directly cardiac in nature. In contrast, although atherosclerosis and thromboembolism from underlying atrial fibrillation represent some pathophysiological overlap between stroke and HF/MI/arrhythmia, brain pathologies and mechanisms leading to bleeding diathesis are likely to contribute significantly to stroke, but not HF/MI/arrhythmia. The extent of similarities between stroke and HF/MI/arrhythmia are thus not comparable to that between HF, MI, and arrhythmia.

For our second finding, it was not surprising that patients with HF, MI, or arrhythmia only had significantly higher incidence of the primary endpoint than those without any of the major cardiovascular comorbidities. The cardiovascular effects of ADT are mediated by several different mechanisms, including changes in body composition and circulating adipocytokines, insulin resistance, disordered lipid metabolism, hypercoagulability, endothelial dysfunction, and immune activation,(241) which are also pathophysiological pathways underlying HF, MI, and arrhythmia. A prior history signifies probable disorders in these regards, thereby driving the observed associations. These associations were mostly consistent regardless of the type of ADT received, with the lack of associations in the subgroup who received both medical castration and bilateral orchidectomy likely due to the small sample size. Interestingly, the association for HF only approached significance in those who were ever prescribed ARSI / chemotherapy. This may have been because many chemotherapeutic agents have direct cardiotoxic effects unrelated to atherosclerosis and inflammation which underlie most cases of HF at baseline(242) – the lack of overlap in pathophysiology of chemotherapy-related cardiovascular events and prior HF could have diluted the association.

It is less clear why patients with stroke only did not have significantly different incidence of the primary endpoint compared to those without any of the major cardiovascular comorbidities, regardless of the type of stroke. A probable explanation may be that significant physical disability and immobility are not uncommon in patients with major stroke, which are likely to deter clinicians from initiating ADT in these patients. Therefore, the observed patients with only stroke likely had relatively mild stroke, implying a less prominent association with underlying atherosclerotic burden and inflammatory activity which thus did not confer any significant increase in the risk of adverse cardiovascular outcomes. This was further supported

by our finding that patients with a history of stroke did not have significantly different number of major cardiovascular comorbidities than those without stroke (**Table 7.2**).

The third finding of this study showed that the overall number of comorbidities, instead of the exact type of comorbidities, may be more important for cardiovascular prognostication. This is clinically important. Although both the HFA-ICOS cardiovascular risk stratification tool and the European Society of Cardiology Guidelines recommended using general cardiovascular risk scores such as the SCORE2 or SCORE2-OP risk calculators for patients receiving ADT,(13,71) these were developed for the general population, and thus do not include existing cardiovascular comorbidities in the models, and were not validated in patients with cancer undergoing cardiotoxic cancer therapies.(243,244) This lack of evidence was also reflected in the above guideline recommendations which were only supported by expert consensus. Although this may be a reasonable compromise given the absence of tools developed specifically for cardiovascular risk stratification in patients receiving ADT,(13) the epidemiology and natural history of PCa imply that a substantial portion of patients with PCa undergoing ADT would be at relatively old age with pre-existing cardiovascular comorbidities, who are the ones in the most need for specialized cardio-oncology referrals and follow-ups, but who are unaccounted for by most, if not all general cardiovascular risk calculators. Our finding thus complements these recommended cardiovascular risk stratification tools, allowing clinicians to rapidly identify high-risk patients from an easy count of their cardiovascular comorbidities. This should facilitate timely referral of high-risk patients to specialists and optimize distribution of healthcare resources.

Moving forward, our findings should prompt and facilitate further research into the cardiovascular risk stratification of patients with PCa undergoing ADT. Although our findings may complement existing cardiovascular risk stratification tools as a rough, qualitative guidance of the risks associated with the studied cardiovascular comorbidities, they were certainly not meant for quantitatively estimating cardiovascular risks. Much work remains to be done in this regard, and more comprehensive multivariable modelling with internal and external validation is necessary for developing an accurate, representative, and actionable cardiovascular risk score for the captioned patients. Our findings may inform these future studies in terms of variable selection and modelling choices. In addition, we noted that despite an increasing understanding of the adverse cardiovascular risks of ADT, very little has been done to understand the baseline cardiovascular risk profile in patients receiving ADT. With this study, we hoped to inspire more in-depth studies of the risk profile and interactions between different cardiometabolic risk factors in these patients.

7.4.1. Strengths and limitations

Using data from a prospectively recorded population-based database, our study is representative of the clinical practice in Hong Kong, a modern Asian metropolitan, and our findings are likely generalizable to many other Asian cohorts. The population-based nature also allowed a sizeable cohort, reinforcing the validity of our findings. Furthermore, we carefully considered and modelled for the important issue of competing risks in this study. Competing

risks is critically important in cardio-oncology studies, as many patients die of cancer or non-cardiovascular causes before experiencing cardiovascular events. By recognizing this issue and modelling for it using appropriate statistical models, we likely avoided significant biases in estimates that likely would have occurred if other methods not accounting for competing risks were used.

Nonetheless, this study is not without limitations. First, owing to the nature of the database used, cancer staging and histology were not available. Nonetheless, ADT is unlikely to be used for non-advanced disease.(193,240) Additionally, we attempted to mitigate this by using prescription of ARSI or chemotherapy as a surrogate for metastatic disease(120,193,233,240) and performing a subgroup analysis accordingly. The results appeared qualitatively similar for most risk groups with all confidence intervals showing substantial overlaps, supporting that the associations were likely to be independent of whether the PCa is metastatic or not.

Second, owing to the observational nature of this study, unmeasured and residual confounders may be present. For instance, due to the nature of the database used, some important cardiovascular risk factors, such as smoking, metabolic syndrome, and obesity, could not be accounted for. We adjusted for the widest range of relevant risk factors available to us, which should sufficiently account for a significant proportion of confounders. Nonetheless, further studies with greater data granularity are required to verify our findings. Third, the database used (CDARS) did not allow individual adjudication of data. However, CDARS has been demonstrated to have good data completeness and accuracy,(232) and all data was input by treating clinicians independent of the authors.

7.5. Conclusions

In patients with PCa receiving ADT, the sole presence of a history of HF, MI, and arrhythmia, but not stroke, were associated with more major cardiovascular comorbidities. The sole presence of HF, MI, or arrhythmia, but not stroke, may be associated with significantly elevated cardiovascular risks. In those with ≥2 of prior HF/MI/stroke/arrhythmia, the number of cardiovascular comorbidities may be prognostically more important than the type of comorbidities present.

8. Chapter 8: HbA1c variability and cardiovascular events in patients with prostate cancer receiving androgen deprivation therapy

This chapter is based on the following publication: **Chan JSK**, Lee YHA, Liu K, Hui JMH, Dee EC, Ng K, Satti DI, Liu T, Tse G, Ng CF. HbA1c variability and cardiovascular events in patients with prostate cancer receiving androgen deprivation therapy. *Eur Urol Open Sci*. 2023; 47: 3-11. doi: 10.1016/j.euros.2022.11.002

8.1. Introduction

Prostate cancer (PCa) was the third most common cancer globally in 2020, with 1.4 million incident cases and accounting for over 375,000 deaths(192). Androgen deprivation therapy (ADT) is one of key therapies for PCa, in which testosterone activity is suppressed pharmacologically and/or surgically(193,194). ADT is recommended alone or in combination with other therapeutic modalities for diseases of intermediate or higher risks(194,210). Despite its established oncological efficacy, studies have shown associations between ADT and increased risks of diabetes mellitus (DM), cardiovascular mortality, myocardial infarction (MI), and stroke(40,195,245), and among diabetic patients, worsened diabetic control and higher risk of diabetic complications(246–248). Currently, risk factors and prognosticators for adverse cardiovascular events among patients with PCa receiving ADT remain actively investigated.

Studies of the glycaemic effects of ADT focused on glycaemic markers, such as HbA1c, as point estimates at fixed timepoints(246–248). Emerging evidence suggested that visit-to-visit HbA1c variability (VVHV) has incremental prognostic value atop point estimates which neglect longitudinal variations in HbA1c levels. Higher VVHV, reflecting more fluctuating HbA1c levels between hospital or clinic visits (i.e. less stable glycaemic control), has been associated with increased risks of mortality and adverse cardiovascular events in patients with and without DM(249–253). Nonetheless, the effect of ADT on VVHV, as well as the prognostic value of VVHV in patients with PCa receiving ADT are unexplored. Given the adverse cardiometabolic effects of ADT and the prognostic value of VVHV, this study aimed to test the hypothesis that ADT adversely affects VVHV, and that VVHV is prognostic of cardiovascular outcomes in patients with PCa receiving ADT.

8.2. Methods

This retrospective cohort study was approved by Joint Chinese University of Hong Kong– New Territories East Cluster Clinical Research Ethics Committee, and was conducted according to the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology guideline. As only retrospective, deidentified data were used, the need for individual consent was waived.

8.2.1. Source of data

Data were acquired from the Clinical Data Analysis and Reporting System (CDARS), a population-based administrative database recording basic demographics, diagnoses, laboratory tests, medication prescriptions, and medical procedures of all patients attending public hospitals and clinics in Hong Kong, which cover the entire Hong Kong and serve 90% of the population(199). CDARS encodes diagnoses using the International Classification of Diseases, Ninth revision (ICD-9) codes regardless of the time of data input, as ICD-10 codes have not been implemented in CDARS to date. Mortality data were acquired from the linked Hong Kong Death Registry, a governmental registry of mortality data for Hong Kong citizens. CDARS and the linked Hong Kong Death Registry have been used extensively in research, and have been demonstrated to have good coding accuracy and data completeness(60,121,231,232,235,238).

8.2.2. Patient population

Adult (aged 18 years old or above) patients with PCa who received ADT between 1/1/1993-31/3/2021 were retrospectively identified and included. ADT included medical castration (leuprorelin, triptorelin, goserelin, or degarelix; other gonadotropin-releasing hormone agonists and antagonists were not available in Hong Kong during the study period) and bilateral orchiectomy (BO). Patients with less than three HbA1c measurements available within three years after ADT initiation, less than six months' ADT, missing baseline HbA1c level (within three years prior to ADT initiation), known heart failure (HF), MI, or stroke, and those with the primary outcome occurring within three years were excluded. The following baseline covariates were recorded: age, type of androgen deprivation therapy (ADT), duration of ADT, comorbid conditions defined using ICD-9 codes listed in **Supplementary Table 8.1** (hypertension, diabetes mellitus (DM), dyslipidaemia, ischaemic heart disease, chronic kidney disease, atrial fibrillation, known malignancy), prior radiotherapy, prior radical prostatectomy, use of medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, androgen receptor signaling inhibitors, beta-blockers, metformin, sulphonylureas, insulins, dihydropyridine calcium channel blockers, antiplatelets, anticoagulants, chemotherapeutic agents, and steroids), and baseline HbA1c level.

8.2.3. Follow-up and outcomes

All patients were followed up from the date of ADT initiation until 31/9/2021. The primary outcome was major adverse cardiovascular events (MACE) that occurred after at least three years after initiation of ADT, a composite of HF, MI, stroke, and cardiovascular mortality. HF, MI, and stroke were identified by ICD-9 codes listed in **Supplementary Table 8.1**, while cardiovascular mortality was identified by ICD-9 or ICD-10 codes listed in **Supplementary Table 8.2**.

8.2.4. Statistical analyses

VVHV was calculated using all HbA1c measurements within three years after ADT initiation. For patients with at least three HbA1c measurements available within three years before ADT initiation, mean HbA1c and VVHV prior to ADT initiation were also calculated; no imputations were performed for patients with less than three HbA1c measurements within three years prior to ADT initiation. VVHV was measured by the coefficient of variation (CV; $\frac{standard\ deviation}{mean}$), and average real variability (ARV; $\frac{\sum_{k=1}^{N-1}|HbA1c_{k+1}-HbA1c_k|}{N-1}$, where N is the number of HbA1c measurements available, and k ranges from 1 to N-1)(254,255). For patients who had at least three HbA1c measurements available within three years prior to ADT initiation, per-unit change in VVHV was defined as $[Post-ADT\ VVHV]-[Pre-ADT\ VVHV]$, and percentage change was defined as $\frac{[Post-ADT\ VVHV]-[Pre-ADT\ VVHV]}{[Pre-ADT\ VVHV]}\times 100\%$.

Continuous variables were expressed as medians with interquartile ranges (IQRs). For patients who had at least three HbA1c test results available in the three years prior to ADT initiation, the CV, and ARV of HbA1c before and after ADT initiation were compared using the Wilcoxon signed rank test.

As the test for proportional hazards assumption based on Schoenfield's residuals showed no significant violation of the proportional hazards assumption, Cox proportional hazards models were used to evaluate the prognostic value of VVHV after ADT initiation, and the per-unit and percentage changes in VVHV. Exposure to medical and surgical castration were separately modelled as time-varying variables. Univariable Cox regression was performed for baseline variables to identify significant confounders (**Supplementary Table 8.3**; defined as $p<0.10$ on univariable Cox regression). These identified confounders were subsequently used for multivariable adjustment in multivariable Cox models with VVHV and changes in VVHV as continuous variables. Measures of VVHV were standardized, such that the results represent estimates per standard deviation (SD) increase in VVHV measures. Patients were then divided into quartiles by VVHV, and multivariable Cox models were fitted again with the first quartile as reference. Kaplan-Meier incidence curves were used to visualize the cumulative incidence of MACE over the study duration, and hazard ratios with 95% confidence intervals (CIs) were used as summary statistics. Furthermore, the HR across the observed spectrum of VVHV as compared to the observed mean of VVHV was modelled and visualized using fractional polynomial curves.

Three *a priori* subgroup analyses were performed for both changes in VVHV and the prognostic value of VVHV. To better understand if the prognostic value of VVHV differ between diabetic and non-diabetic patients, a subgroup analysis was performed with stratification by known diagnosis of diabetes mellitus. Similarly, a subgroup analysis was performed with stratification by the use of any antidiabetic medication, with testing for interaction. Another subgroup analysis was performed for the type of ADT (medical castration, BO, or both) to understand in greater detail the prognostic power of VVHV in different types

of ADT. Per-unit and percentage changes in the markers of VVHV were compared between subgroups using Mann-Whitney test or Kruskal-Wallis test as appropriate, while interaction terms were used in multivariable Cox regression to compare the prognostic value of the markers of VVHV between subgroups.

Three sensitivity analyses were performed. As non-cardiovascular mortality prohibits the observation of any potential major adverse cardiovascular event (MACE) in those who had not experienced MACE, non-cardiovascular mortality constitutes a competing event for MACE. Therefore, an *a priori* sensitivity analysis was performed using multivariable competing risk regression under the Fine and Gray sub-distribution model, with non-cardiovascular mortality as the competing event and the same adjusting variables as in the fully adjusted Cox model; sub-hazard ratios with 95% CIs were used as summary statistics.

Additionally, as the cumulative incidence curves crossed each other, a post hoc sensitivity analysis was performed where differences in restricted mean survival time were used to compare between groups. This approach does not rely on the proportional hazards assumption(256).

Finally, to reduce heterogeneity in the duration of ADT, a second post hoc sensitivity analysis was performed where only patients with at least 18 months of androgen deprivation therapy were analyzed. This was also done in an effort to mitigate the herein lack of staging and disease risk profile data, as androgen deprivation therapy of one year or longer is unlikely to be used in patients with low-risk prostate cancer(193,240).

All p-values were two-sided, with $p<0.05$ considered statistically significant. All analyses were performed on Stata v16.1 (StataCorpLLC, College Station, Texas, USA).

8.3. Results

Altogether, 13,537 patients were identified, of whom 2198 had at least three HbA1c results available within three years after ADT initiation. After applying the exclusion criteria, 1065 patients were included (**Figure 8.1;** median age 74.4 years old [IQR 68.3-79.5 years old]), of whom 850 (79.8%) had DM. Characteristics of included patients are summarized in **Table 8.1**. Within the three years after ADT initiation, the patients had a median of 5 [4-6] available HbA1c measurements. The median CV of HbA1c was 0.081 [0.046-0.135], and the median ARV was 0.57% [0.31%-1.03%]. The 25th percentile, median, and 75th percentile values were also used for defining the cut-off values for categorizing the VVHV markers into quartiles.

Figure 8.1 Study flowchart. ADT, androgen deprivation therapy.

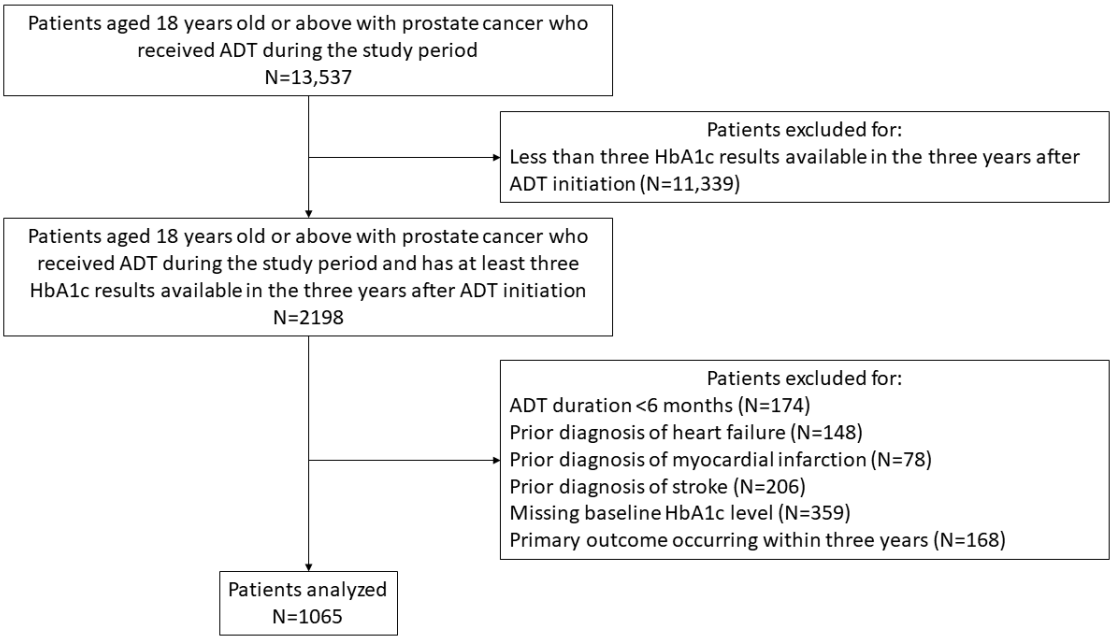


Table 8.1 Baseline characteristics of included patients.

Total number of patients, N	1065
Age, years [IQR]	74.4 [68.3-79.5]
Medical castration, N (%)	762 (71.6)
Bilateral orchiectomy, N (%)	430 (40.4)
ADT duration, years [IQR]	3.4 [2.3-5.7]
Hypertension, N (%)	401 (37.7)
Diabetes mellitus, N (%)	850 (79.8)
Dyslipidaemia, N (%)	166 (15.6)
Ischaemic heart disease, N (%)	155 (14.6)
Chronic kidney disease, N (%)	41 (3.9)
Atrial fibrillation, N (%)	37 (3.5)
Known malignancy, N (%)	103 (9.7)
Prior radiotherapy, N (%)	41 (3.9)
Prior radical prostatectomy, N (%)	269 (25.3)
ACEI/ARB use, N (%)	599 (56.2)
Beta-blocker use, N (%)	476 (44.7)
Metformin use, N (%)	627 (58.9)
Sulphonylurea use, N (%)	565 (53.1)
Insulin use, N (%)	183 (17.2)
Dihydropyridine CCB use, N (%)	623 (58.5)
Antiplatelet use, N (%)	298 (28.0)
Anticoagulant use, N (%)	36 (3.4)
Chemotherapy use, N (%)	6 (0.6)
Steroid use, N (%)	164 (15.4)
HbA1c, % [IQR]	6.7 [6.1-7.4]

ACEI, angiotensin-converting enzyme inhibitor. ADT, androgen deprivation therapy. ARB, angiotensin receptor blocker. CCB, calcium channel blocker. IQR, interquartile range.

8.3.1. Change in VVHV after ADT initiation

Seven-hundred-and-nine patients (66.6%) had at least three HbA1c measurements within the three years prior to ADT initiation, with a median of 5 [3-7] measurements in the three years prior to ADT initiation, and 5 [4-7] measurements in the three years after ADT initiation.

VVHV increased significantly after ADT initiation, as measured by both CV (0.059 [0.036-0.103] pre-ADT vs 0.089 [0.054, 0.139] post-ADT, p<0.001) and ARV (0.44% [0.26%-0.77%] pre-ADT vs 0.63% [0.39%-1.08%] post-ADT, p<0.001). The median per-unit change in CV was 0.023 [-0.013-0.071], and the median percentage change was 43.0% [-17.3%-147.5%]. The median per-unit change in ARV was 0.17% [-0.09%-0.50%], and the median percentage change was 43.1% [-18.0%-138.1%]. In total, 473 (66.2%) and 474 (66.9%) had increased CV and ARV of HbA1c after initiating ADT, respectively.

Subgroup analysis by prior diagnosis of DM (**Supplementary Table 8.4**), prior use of antidiabetic medication(s) (**Supplementary Table 8.5**), and type of ADT (**Supplementary Table 8.6**) found that there were generally no differences between subgroups in the change in VVHV after ADT initiation, except for the percentage change in CV of HbA1c which was significantly smaller in those who used antidiabetic medication(s) as compared to those who did not use such medication(s) at baseline (p=0.025). There was also a numerical trend for a smaller percentage change in the ARV of HbA1c in those who used antidiabetic medication(s) which approached, but did not reach, statistical significance (p=0.072).

8.3.2. Prognostic value of VVHV

Over a median follow-up of 4.3 years [2.8-6.7 years], 159 patients (14.9%) had MACE. Higher VVHV was associated with higher risk of MACE, as measured by both CV (adjusted hazard ratio (aHR; per SD) 1.21 [95% confidence interval 1.02, 1.43], p=0.029; **Table 8.2** and **Figure 8.2A**) and ARV (aHR (per SD) 1.25 [1.06, 1.48], p=0.008; **Table 8.2** and **Figure 8.3A**); one SD of CV corresponded to 0.082, and one SD of ARV corresponded to 0.72%. When analyzed as quartiles, patients in the highest quartile of both the CV (aHR 1.69 [1.03, 2.77], p=0.037; **Table 8.2** and **Figure 8.2B**) and ARV (aHR 1.90 [1.14, 3.16], p=0.014; **Table 8.2** and **Figure 8.3B**) of HbA1c had significantly higher risk of MACE than the lowest quartile. However, among patients who had at least three HbA1c results within the three years prior to ADT initiation, neither per-unit changes nor percentage changes in VVHV were significantly associated with the risk of MACE (**Supplementary Table 8.7**).

Table 8.2 Results of Cox regression examining the associations between visit-to-visit HbA1c variability and the risk of major adverse cardiovascular events.

Variability measure		Variability as continuous variable (per SD increase)		Variability as quartiles			
		Univariable	Multivariable [1]	Q1	Q2 [1]	Q3 [1]	Q4 [1]
CV	Median [IQR]	0.081 [0.046-0.135]		0.030 [0.020-0.039]	0.063 [0.054-0.072]	0.104 [0.092-0.116]	0.186 [0.157-0.239]
	HR [95% CI]	1.23 [1.06, 1.44], p=0.008	1.21 [1.02, 1.43], p=0.029	1 (reference)	0.85 [0.51, 1.42], p=0.532	1.29 [0.80, 2.08], p=0.306	1.69 [1.03, 2.77], p=0.037
ARV	Median [IQR], %	0.57 [0.31-1.03]		0.20 [0.15-0.27]	0.43 [0.38-0.50]	0.75 [0.65-0.85]	1.50 [1.20-2.05]
	HR [95% CI]	1.31 [1.12, 1.53], p=0.001	1.25 [1.06, 1.48], p=0.008	1 (reference)	1.25 [0.76, 2.08], p=0.383	1.31 [0.80, 2.17], p=0.283	1.90 [1.14, 3.16], p=0.014

ARV, average real variability. CI, confidence interval. CV, coefficient of variation. HR, hazard ratio. SD, standard deviation.

[1] Adjusted for age, medical castration, bilateral orchiectomy, ADT duration, hypertension, atrial fibrillation, and baseline HbA1c.

Figure 8.2 (A) Fractional polynomial plot showing the association between the coefficient of variation (CV) of HbA1c and the risk of major adverse cardiovascular events (MACE) across the observed range of HbA1c CV; and (B) Kaplan-Meier curves curves showing the cumulative incidence of MACE in patients in each quartile of the CV of HbA1c. ADT, androgen deprivation therapy.

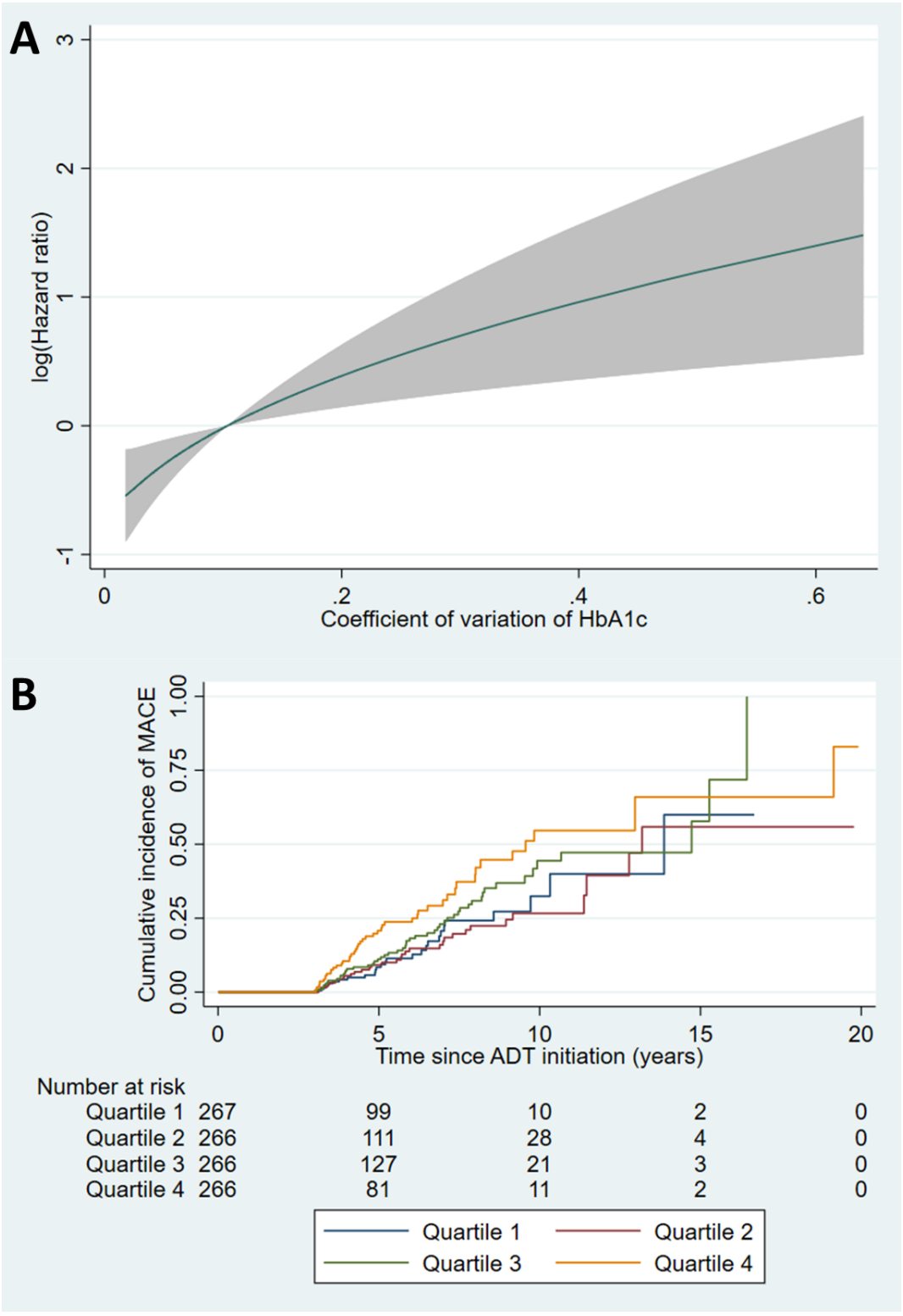
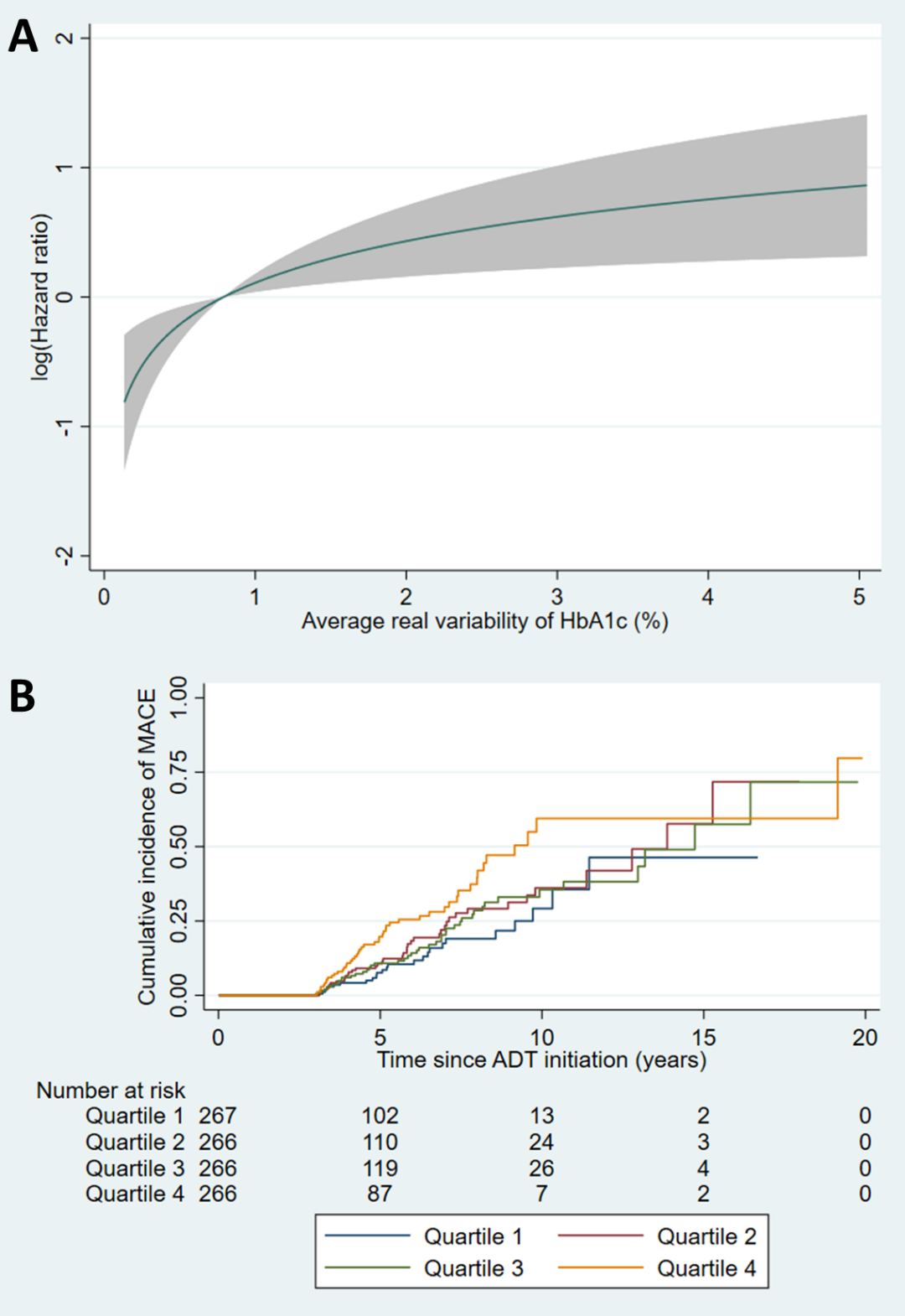


Figure 8.3 (A) Fractional polynomial plot showing the association between the average real variability (ARV) of HbA1c and the risk of major adverse cardiovascular events (MACE) across the observed range of HbA1c ARV; and (B) Kaplan-Meier curves showing the cumulative incidence of MACE in patients in each quartile of the ARV of HbA1c. ADT, androgen deprivation therapy.



8.3.3. Subgroup analysis of the prognostic value of VVHV

In the subgroup analysis by prior diagnosis of DM (**Supplementary Table 8.8**), higher VVHV, as measured by CV (aHR (per SD) 1.25 [1.03, 1.52], p=0.024) and ARV (aHR (per SD) 1.27 [1.06, 1.52], p=0.009), was associated with a higher risk of MACE in patients with prior diagnosis of DM (N=850), but not in those without (N=215). There was no significant interaction between neither CV ($p_{interaction}$=0.396) nor ARV ($p_{interaction}$=0.603) of HbA1c and prior diagnosis of DM in terms of the risk of MACE.

Similarly, in the subgroup analysis by prior use of any antidiabetic medication(s) (**Supplementary Table 8.9**), higher VVHV, as measured by CV (aHR (per SD) 1.23 [1.01, 1.50], p=0.041) and ARV (aHR (per SD) 1.24 [1.04, 1.49], p=0.020), was associated with a higher risk of MACE in patients with prior use of any antidiabetic medication(s) (N=788), but not in those without (N=277). There was no significant interaction between neither CV ($p_{interaction}$=0.583) nor ARV ($p_{interaction}$=0.972) of HbA1c and prior use of any antidiabetic medication(s) in terms of the risk of MACE.

Subgroup analysis by the type of ADT found similar results (**Supplementary Table 8.10**), with higher VVHV, as measured by CV (aHR (per SD) 1.32 [1.05, 1.67], p=0.017) and ARV (aHR (per SD) 1.31 [1.04, 1.65], p=0.024), being associated with a higher risk of MACE in patients who only underwent medical castration (N=635), but not in those who only underwent BO (N=303), nor those who underwent both medical castration and BO (N=127), as summarized in **Supplementary Table 8.10**. No significant interactions were found between the type of ADT and VVHV in terms of the risk of MACE.

8.3.4. Sensitivity analysis of the prognostic value of VVHV

In total, 367 patients (34.5%) died without having MACE. Sensitivity analysis using multivariable Fine and Gray competing risk regression found that higher ARV of HbA1c was associated with a higher cumulative incidence of MACE (adjusted sub-hazard ratio (per SD) 1.15 [1.01, 1.32], p=0.037). However, CV of HbA1c was not significantly associated with the cumulative incidence of MACE (adjusted sub-hazard ratio (per SD) 1.11 [0.96, 1.29], p=0.142).

The post hoc sensitivity analysis using restricted mean survival time (**Supplementary Table 8.11**) showed consistent results, where patients in the highest quartile of both CV and ARV having significantly shorter restricted mean survival time compared to those in the lowest quartile. The second post hoc sensitivity, which analyzed only patients with at least one year of ADT (N=1030), also showed consistently that increases in both CV (aHR (per SD) 1.21 [1.02, 1.44], p=0.026) and ARV (aHR (per SD) 1.26 [1.07, 1.49], p=0.006) of HbA1c were associated with increased risk of MACE.

8.4. Discussion

In this study, we showed that ADT may increase VVHV, and that higher VVHV, but not changes in VVHV, was associated with a higher risk of MACE among patients with PCa receiving ADT. To the best of the authors' knowledge, this is the first study that explored the effects of ADT on VVHV, as well as the prognostic value of VVHV in the context of ADT.

We found that VVHV increased after ADT, consistent with prior findings of ADT being associated with poor glycaemic control(195,245–248). Previous studies about glycaemic control in patients receiving ADT focused on timepoint-specific HbA1c or fasting glucose levels, which captures only a snapshot of a patient's glycaemic metabolism and ignores temporal variations in glycaemic indices. VVHV adds a longitudinal element to the assessment of glycaemic control, with higher VVHV indicating lower glycaemic stability. Numerous measures of VVHV exist(250,252,257). Here, we chose CV and ARV as measures of VVHV. CV is one of the most common measures of VVHV, as its definition (SD divided by mean) inherently considers the effects of mean HbA1c on VVHV. Meanwhile, ARV focuses on differences between consecutive measurements and has been found to be superior to SD in terms of prognostic significance(255). Originally devised for blood pressure measurements, ARV has been adopted for VVHV(250), as well as visit-to-visit fasting glucose variability(258,259). We showed that both CV and ARV of HbA1c increased after ADT initiation, providing robust evidence that ADT adversely affects glycaemic stability.

Our finding that higher VVHV was prognostic of MACE agrees with prior studies of VVHV in other populations(249–253). Notably, our results indicated that a threshold effect may exist in the relationship between VVHV and the risk of MACE, as only the highest quartile, but not the 2nd or 3rd quartiles, was associated with increased risk of MACE compared to the lowest quartile. Clinically, this may necessitate determination of an upper limit of normal VVHV, rather than aiming to minimize VVHV; further, larger studies are required. Additionally, our subgroup analysis found no significant interaction between VVHV and prior diagnosis of DM, use of antidiabetic medications, or the type of ADT, suggesting that VVHV is prognostic regardless of these factors. Although associations were insignificant in several subgroups, the statistical insignificance was probably due to the small sample sizes. Nevertheless, competing risk regression found significant association only between HbA1c ARV and the risk of MACE. Kim and colleagues have made similar observations in patients with type 2 DM, possibly indicating that ARV is a more robust measure of VVHV and prognosticator(250).

8.4.1. Clinical relevance and future directions

Clinically, our findings reinforced the potential utility of VVHV as a tool for cardiovascular risk stratification. Little has been done in terms of cardiovascular risk stratification for patients with PCa receiving ADT. VVHV may be a simple marker that can be explored for such purposes. More generally, our findings should raise clinicians' awareness of the importance of VVHV, and prevent fluctuations in HbA1c from being dismissed as random or measurement errors.

Nonetheless, much work remains before VVHV may be adopted for clinical use. Having observed a possible threshold effect, normal values of VVHV need to be established for patients with PCa receiving ADT. Additionally, drivers of VVHV remain unclear: whilst medication adherence may be an intuitive driver, studies have demonstrated associations between VVHV, inflammation, and oxidative stress(260,261). Given the intimate relationships between inflammation and both cancer and cardiovascular diseases(262,263), the association between VVHV and the risk of MACE may vary depending on a patient's inflammatory state. Lastly, whilst it is enticing to suggest VVHV to be a treatment target of glycaemic control, it remains unclear how interventions, both pharmacological and non-pharmacological, influence VVHV. Findings from our subgroup analysis suggested that usage of antidiabetic medication(s) may be associated with smaller changes in VVHV as compared to non-usage. However, it remained unclear whether such association was independent of confounders, and such findings should be viewed as hypothesis-generating only. These areas require further investigation before VVHV may be utilized clinically.

8.4.2. Strengths and limitations

Utilizing data from a population-based database, this study included as many patients as pragmatically possible from Hong Kong, increasing the representativeness of our findings. Additionally, we demonstrated robust associations between VVHV and the risk of MACE in multiple subgroup and sensitivity analyses, reinforcing the validity of our findings. Nonetheless, this study has some limitations. First, many patients had less than three HbA1c levels recorded within the three years after ADT initiation, with only 1065 of 13,537 patients (7.9%) who fulfilled the inclusion criteria analyzed, limiting the generalizability of our findings, and necessitating larger studies to validate our findings. Furthermore, this study selected patients with high cardiometabolic risks, as they were more likely to receive frequent HbA1c testing than those with low metabolic risks. Therefore, it is unclear whether VVHV would be as prognostic in patients with lower metabolic risks. Similarly, our selection criteria for patients with at least six months of ADT limited generalizability of our findings to patients receiving shorter durations of ADT. Future studies should therefore further explore the effects that shorter courses of ADT may have on VVHV, as well as the prognostic value of VVHV in these patients. Nonetheless, our findings were consistent with prior findings, including those in the general population(257), meaning VVHV is likely prognostic in patients with lower metabolic risks as well.

Additionally, the observational nature of this study predisposed to residual and unmeasured confounders. Specifically, some studies have suggested that gonadotropin-releasing hormone agonists and antagonists may differ in the risk of MACE(264), although this has remained highly controversial following the publication of the PRONOUNCE trial, the first randomized controlled trial specifically designed to compare the cardiovascular safety of gonadotropin-releasing hormone agonists and antagonists, which found no significant difference in the risk of MACE between these agents(95). Moreover, cancer staging, histology, disease risk profile, and individual indications for specific treatment regimens were not available. Nevertheless, we have considered many important cardiovascular risk factors for multivariable adjustment. Lastly, due to the deidentified nature of the database used (CDARS), the data could not be

individually adjudicated, and miscoding of diagnoses and outcomes was possible. Nonetheless, all data input were performed by the patients' treating clinicians who were independent of the authors, and none of the authors had the rights to alter recorded data. Previous studies of CDARS have also demonstrated good data completeness and coding accuracy(232).

8.5. Conclusions

In patients with PCa receiving ADT, VVHV increased after ADT initiation. Higher VVHV was associated with increased risk of MACE, independent of prior diagnosis of DM, use of antidiabetic medication(s), and the type of ADT. Further studies are required to validate our findings, and to further explore VVHV as a potential tool for cardiovascular risk stratification in patients with PCa receiving ADT.

9. Chapter 9: Long-term cardiovascular risks of gonadotropin-releasing hormone agonists and antagonists: a population-based cohort study

This chapter is based on the following publication: **Chan JSK**[*], Lee YHA[*], Hui JMH, Liu K, Dee EC, Ng K, Tang P, Tse G, Ng CF. Long-term cardiovascular risks of gonadotropin-releasing hormone agonists and antagonists: a population-based cohort study. *Clin Oncol.* 2023; 35(6): E376-E383. doi: 10.1016/j.clon.2023.03.014 * co-first authors

9.1. Introduction

Androgen deprivation therapy, which may be pharmacological or surgical (bilateral orchiectomy) castration, is the cornerstone of advanced prostate cancer (PCa) treatment. In particular, pharmacological androgen deprivation therapy commonly consist of the use of gonadotropin-releasing hormone (GnRH) agonists or antagonists; whilst both of these drug classes include more than one agent, they are considered equivalent within their respective classes from the oncological perspective (240). Whilst studies have suggested the GnRH antagonists may be superior to agonists in terms of oncological outcomes or survival (265,266), both agents remain in use and are recommended by international guidelines (194).

Due to its modulation of sex hormones which have substantial downstream cardiovascular effects, androgen deprivation therapy has been shown to be associated with increased cardiovascular risks in general (40). Specifically, studies have suggested that two major types of pharmacological androgen deprivation therapy, namely GnRH agonists and antagonists, may display different cardiovascular safety profiles (40). Although the recent PRONOUNCE randomized controlled trial (RCT) attempted to compare the cardiovascular risks associated with these agents, its insufficient power prevented definitive conclusions to be drawn (95). Furthermore, both cardiovascular epidemiology and outcome of PCa are known to have significant inter-ethnic variations, with Asians having higher burden of atherosclerotic cardiovascular diseases than those of other ethnicities but, amongst patients with hormone-sensitive metastatic PCa, better overall survival than those of other ethnicities (267–269). The relative cardiotoxicity of androgen-depriving agents observed in non-Asian cohorts therefore may not be directly applicable to Asians. Thus, we aimed to compare the long-term cardiovascular safety of GnRH agonists and antagonists in Asian patients with PCa.

9.2. Materials and methods

This prospective cohort study was in line with the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology guideline. This study has been approved by The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee. Requirement for consent was waived due to the use of anonymised data.

9.2.1. Data source

All data were retrieved from the Clinical Data Analysis and Reporting System (CDARS), a population-based electronic health records database prospectively recording data of all patients attending public healthcare institutions in Hong Kong which serve an estimated 90% of Hong Kong's population (199). Diagnoses were coded by the *International Classification of Diseases, Ninth revision* (ICD-9) codes regardless of the time of data entry, as ICD-10 codes have not been implemented in CDARS to date. Mortality data were obtained from the linked Hong Kong Death Registry, a governmental registry that holds all Hong Kong citizen's death records. Causes of mortality were recorded using either ICD-9 or ICD-10. All the codes used for comorbid conditions or outcomes and causes of death were summarized in **Supplementary Tables 9.1 and 9.2**, respectively**.** CDARS has been used in previous studies and shown to have good coding accuracy (60,121,201,232,270).

9.2.2. Patients

Adult patients (≥18 years old) with PCa receiving either GnRH agonists (leuprorelin, triptorelin, or goserelin) or antagonist (degarelix; relugolix is not available in Hong Kong to date) in Hong Kong between January 2013 and March 2021 were included. Patients with less than six months' prescriptions of GnRH agonists or antagonists, switching between both classes, missing baseline (pre-treatment) prostate-specific antigen level, or prior stroke or myocardial infarction (MI) were excluded. Six months was chosen as the minimum duration of GnRH agonist or antagonist use to increase confidence that any observed differences in cardiovascular risk were attributable to the GnRH agonist or antagonist instead of pre-morbid conditions, and to reduce heterogeneity in disease aggressiveness of the cohort as four to six months of androgen deprivation therapy is recommended for intermediate-risk PCa only (194).

9.2.3. Follow-up and outcomes

A new-user design was used, with the index date defined as the first-ever date of GnRH agonist or antagonist prescription. All patients were followed up until 31st September 2021.

The primary outcome was major adverse cardiovascular events (MACE) as defined in the PRONOUNCE trial ($MACE_{PRONOUNCE}$), that is the first occurrence of all-cause mortality, stroke, or MI.(95) The secondary outcome ($MACE_{CVM}$) was a modified MACE that evaluated cardiovascular mortality (CVM) instead of all-cause mortality.

9.2.4. Statistical analyses

Continuous variables were expressed as medians and interquartile ranges (IQRs). Inverse probability of treatment weighting was used to balance covariates between groups. The propensity scores were constructed using a generalized boosted model with a maximum of 10,000 regression trees and an iteration stopping point that minimized the absolute standardized mean difference of the mean effect size. The covariates selected for inverse probability

treatment weighting were age, comorbid conditions (hypertension, diabetes mellitus, hyperlipidaemia, ischaemic heart disease, heart failure, chronic obstructive pulmonary disease, atrial fibrillation, chronic kidney disease, and known metastatic malignancy), GnRH agonist or antagonist use duration, bilateral orchiectomy, use of other medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, statins, dihydropyridine calcium channel blockers, and androgen receptor signalling inhibitors), and baseline prostate-specific antigen level. Standardized mean difference reflected covariate balance, with values less than 0.25 considered acceptable.

The proportional hazards assumption was found to be violated using Schoenfield residuals. As the baseline status of hypertension had a weighted standardized mean difference of 0.231, log-rank tests stratified for the baseline status of hypertension was used to compare the cumulative incidence of the outcomes between groups. The cumulative incidence of $MACE_{PRONOUNCE}$ was visualized using the Kaplan-Meier method. However, as non-cardiovascular death would prohibit the occurrence of $MACE_{CVM}$ in those who have not had the event, non-cardiovascular death constitutes a competing event for $MACE_{CVM}$. Of note, the Kaplan-Meier method is known to over-estimate cumulative incidences in the presence of competing events (239). Therefore, the cumulative incidence of $MACE_{CVM}$ was estimated and visualized using the Aalen-Johansen estimator (239,271). A restricted cubic spline with three knots placed at Harrell's recommended percentiles of survival time was used to visualize the estimated time-varying hazard ratio with 95% confidence interval for both outcomes during the study period (136,272).

An *a priori* exploratory analysis was performed for both outcomes in addition to the main analysis above, restricting follow-up to a maximum of one year which was the duration of follow-up in the PRONOUNCE trial in order to maximize the findings' comparability with the PRONOUNCE trial (95). Additionally, to understand the impact of prior cardiovascular risk factors on observed effects, an *a priori* subgroup analysis was performed by the presence of cardiovascular risk factors at baseline, which were defined as any diagnosis of hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, heart failure, or ischaemic heart disease. Log-rank test with stratification for baseline hypertension diagnosis was only performed for the subgroup of patients with known cardiovascular risk factors, as those who had none of these risk factors could not have had hypertension by definition. Finally, an *a priori* sensitivity analysis was performed, including only patients who did not undergo bilateral orchiectomy due to the well-established differences in cardiovascular risks associated with bilateral orchiectomy (40).

All p values were two-sided, with $p<0.05$ considered significant. All analyses were performed using Stata v16.1 (StataCorp LLC, USA).

9.3. Results

In total, 5007 patients were identified for inclusion. After applying the exclusion criteria (**Figure 9.1**), 2479 patients (162 GnRH antagonist users and 2317 agonist users; median age 75.0 years old, IQR 68.0-81.6 years old) were analysed. Inverse probability treatment weighting achieved acceptable balance for all covariates (standardized mean difference <0.25; **Table 9.1**). In total, 1161 patients (46.8%) had known cardiovascular risk factor(s), of whom 92 (7.9%) were GnRH antagonist users; 70 of the 1318 patients (5.3%) without known cardiovascular risk factors were GnRH antagonist users.

Figure 9.1 Study flowchart. ADT, androgen deprivation therapy. GnRH, gonadotropin-releasing hormone. PSA, prostate-specific antigen.

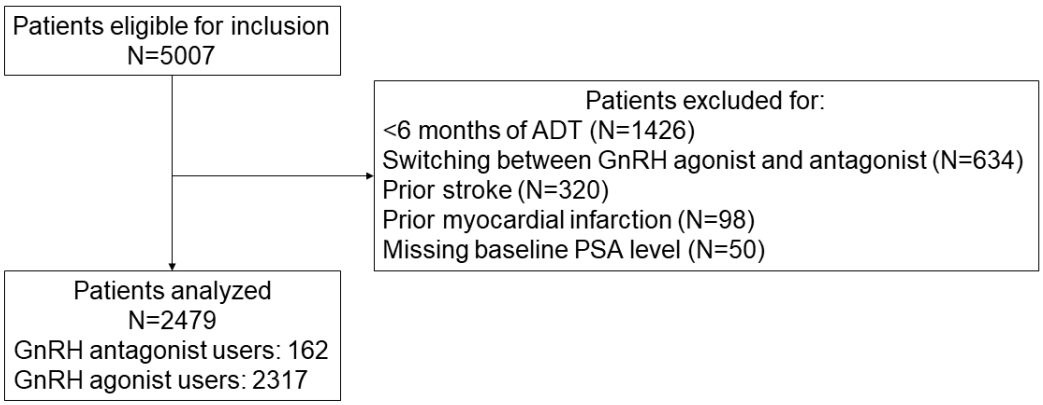


Table 9.1 Unweighted baseline characteristics between gonadotropin-releasing hormone (GnRH) antagonist and agonist users.

	GnRH antagonist users (N=162)	GnRH agonist users (N=2317)	Unweighted SMD	SMD with IPTW
Duration of ADT prescription, days	420 [272-660]	882 [528-1235]	0.713	0.146
6 months to 2 years, N (%)	130 (80.3)	946 (40.8)	0.880	0.147
>2 years, N (%)	32 (19.8)	1371 (59.2)		
Age, years	76.8 [69.5-82.6]	74.9 [67.9-81.6]	0.115	0.157
Bilateral orchidectomy, N (%)	27 (16.7)	98 (4.2)	0.568	0.138
Hypertension, N (%)	67 (41.4)	680 (29.3)	0.262	0.231
Diabetes mellitus, N (%)	40 (24.7)	561 (24.2)	0.011	0.037
Hyperlipidaemia, N (%)	24 (14.8)	256 (11.0)	0.119	0.023
Ischaemic heart disease, N (%)	24 (14.8)	189 (8.2)	0.238	0.181
Heart failure, N (%)	7 (4.3)	74 (3.2)	0.063	0.067
Chronic obstructive pulmonary disease, N (%)	8 (4.9)	105 (4.5)	0.019	0.019
Atrial fibrillation, N (%)	12 (7.4)	95 (4.1)	0.163	0.196
Chronic kidney disease, N (%)	8 (4.9)	66 (2.8)	0.123	0.028
Any known malignancy, N (%)	20 (12.4)	231 (10.0)	0.079	0.054
Ever underwent radiotherapy, N (%)	24 (14.8)	412 (17.8)	0.078	0.119
Ever underwent radical prostatectomy, N (%)	32 (19.8)	575 (24.8)	0.118	0.014
Anti-diabetic medication(s), N (%)	34 (21.0)	497 (21.5)	0.011	0.025
ACEI/ARB, N (%)	53 (32.7)	664 (28.7)	0.089	0.105
Beta-blocker, N (%)	64 (39.5)	763 (32.9)	0.139	0.133
Statin, N (%)	68 (42.0)	797 (34.4)	0.158	0.005
Dihydropyridine calcium channel blocker, N (%)	81 (50.0)	1023 (44.2)	0.118	0.048
Ever received chemotherapy, N (%)	34 (21.0)	373 (16.1)	0.132	0.073
Ever received ARSI, N (%)	83 (51.2)	1328 (57.3)	0.123	0.025
Baseline prostate-specific antigen, ng/mL	397 [109-1339]	40 [11-166]	0.798	0.126

ACEI, angiotensin-converting enzyme inhibitor. ARB, angiotensin receptor blocker. ADT, androgen deprivation therapy. ARSI, androgen receptor signalling inhibitor. IPTW, inverse probability of treatment weighting. SMD, standardized mean difference.

Over a median follow-up duration of 3.0 years (IQR 1.7-5.0 years; 1.4 years (0.9-2.6 years) for antagonist users, and 3.1 years (1.8-5.2 years) for agonist users), 1115 patients (45.0%) had $MACE_{PRONOUNCE}$ and 344 (13.9%) had $MACE_{CVM,}$ of which 178 (7.2%) and 67 (2.7%) had $MACE_{PRONOUNCE}$ and $MACE_{CVM}$ in the first year, respectively; 771 patients (31.1%) had died before $MACE_{CVM}$ occurred. Specifically, 571 (43.3%) and 164 (12.4%) of the 1318 patients without known cardiovascular risk factors had $MACE_{PRONOUNCE}$ and $MACE_{CVM}$, respectively, whilst 544 (46.9%) and 180 (15.5%) of the 1161 patients with known cardiovascular risk factor(s) had $MACE_{PRONOUNCE}$ and $MACE_{CVM}$, respectively. The overall observed incidence rate of $MACE_{PRONOUNCE}$ was 13.3 [95% confidence interval: 12.6, 14.1] events per 100 person-years, and that of $MACE_{CVM}$ was 4.1 [3.7, 4.6] events per 100 person-years. **Table 9.2** summarizes the events that contributed to $MACE_{PRONOUNCE}$ and $MACE_{CVM}$.

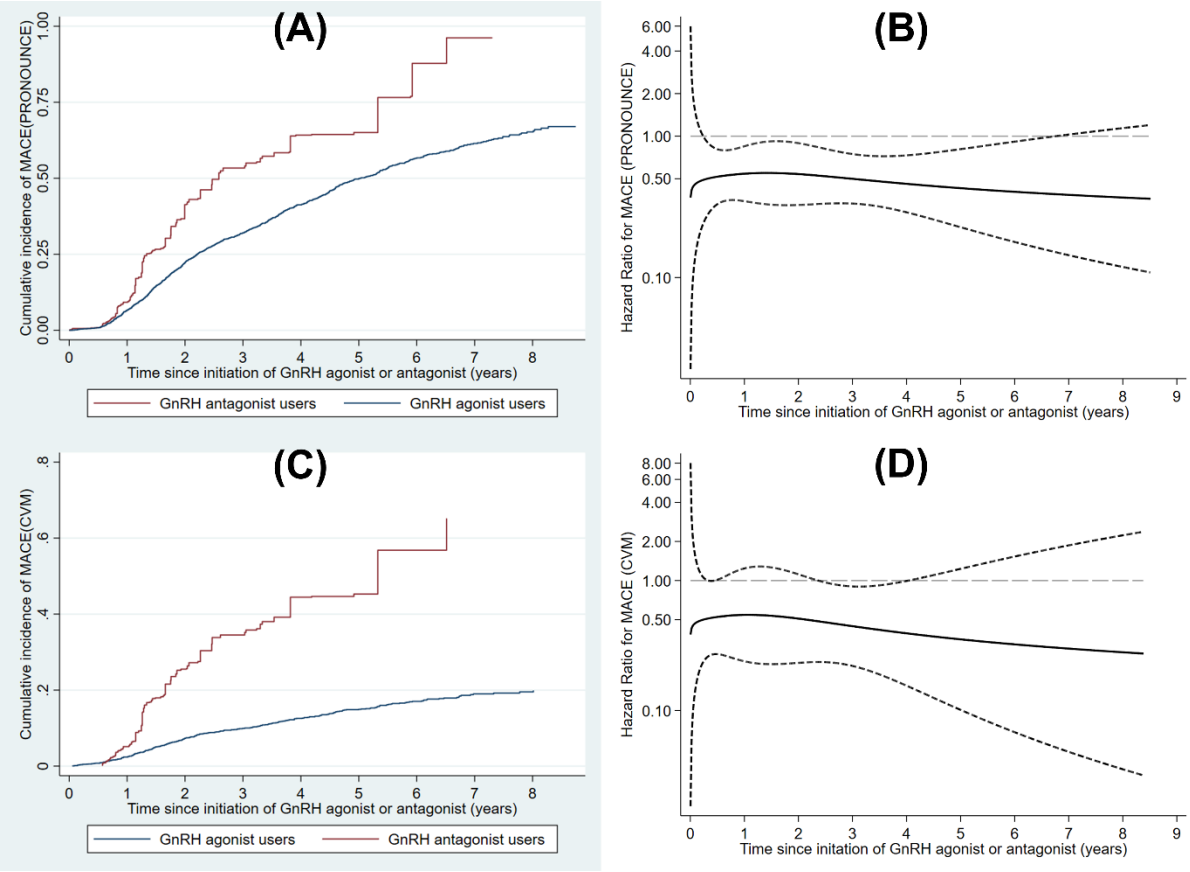
Table 9.2 Events contributing to the primary and secondary outcomes. Mortality, myocardial infarction, and stroke were mutually exclusive, while all-cause mortality and cardio-vascular mortality were not mutually exclusive as they contributed to different outcomes.

	GnRH antagonist users (N=162)	GnRH agonist users (N=2317)
All-cause mortality, N (%)	86 (53.1)	824 (35.6)
Cardiovascular mortality, N (%)	3 (1.9)	48 (2.1)
Myocardial infarction, N (%)	9 (5.6)	50 (2.2)
Stroke, N (%)	11 (6.8)	135 (5.8)

Gonadotropin-releasing hormone, GnRH.

Overall, GnRH agonist users had significantly lower risks of $MACE_{PRONOUNCE}$ (both unstratified and stratified log-rank tests $p<0.001$; **Figure 9.2A**) and $MACE_{CVM}$ (unstratified log-rank test $p=0.016$, stratified log-rank test $p=0.027$; **Figure 9.2C**). Restricted cubic splines showed that the hazard ratio for $MACE_{PRONOUNCE}$ was clearly significant throughout the study period (**Figure 9.2B**), but less so for $MACE_{CVM}$ (**Figure 9.2D**).

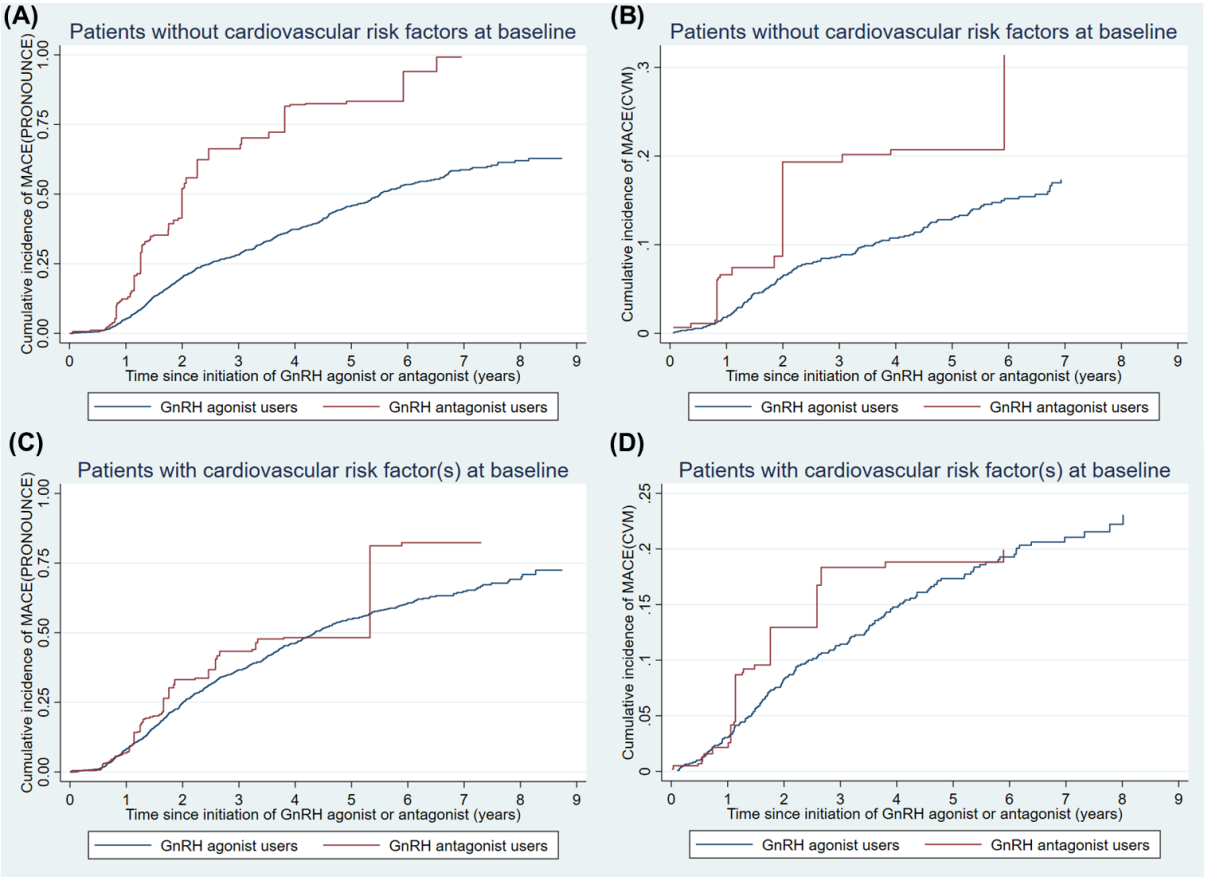
Figure 9.2 On the left, cumulative incidence curves visualize the cumulative incidence of major adverse cardiovascular events (MACE) as defined by the PRONOUNCE trial (A), and MACE defined as cardiovascular mortality (CVM), myocardial infarction, and stroke (C) amongst gonadotropin-releasing hormone (GnRH) agonist and antagonist users. On the right, restricted cubic splines visualize the variation of hazard ratio throughout the study period for MACE as defined by the PRONOUNCE trial (B) and MACE defined as CVM, myocardial infarction, and stroke (D); hazard ratios were referenced against GnRH antagonist users, and the dash lines indicate the 95% confidence intervals.



However, exploratory analysis restricting the follow-up duration to a maximum of one year found no significant difference between GnRH agonist and antagonist users in terms of the risks of both MACE$_{PRONOUNCE}$ (unstratified log-rank test p=0.233, stratified p=0.308) and MACE$_{CVM}$ (unstratified log-rank test p=0.300, stratified p=0.357).

Subgroup analysis by the presence of cardiovascular risk factors at baseline showed that in those without known cardiovascular risk factors, GnRH antagonist users had significantly higher risk of MACE$_{PRONOUNCE}$ (log-rank test p<0.001; **Figure 9.3A**) and MACE$_{CVM}$ (log-rank test p=0.008; **Figure 9.3B**), while no significant difference was observed in the risks of both MACE$_{PRONOUNCE}$ (unstratified log-rank test p=0.532, stratified p=0.624; **Figure 9.3C**) and MACE$_{CVM}$ (unstratified log-rank test p=0.587, stratified p=0.650; **Figure 9.3D**) in those with known cardiovascular risk factors.

Figure 9.3 Cumulative incidence curves visualizing the cumulative freedom from major adverse cardiovascular events (MACE) as defined by the PRONOUNCE trial (**A, C**) and MACE defined as cardiovascular mortality (CVM), myocardial infarction, and stroke (**B, D**) in those without cardiovascular risk factors at baseline (**A, B**), and in those with cardiovascular risk factor(s) at baseline (**C, D**). GnRH, gonadotropin-releasing hormone.



Sensitivity analysis showed that amongst patients who did not undergo bilateral orchiectomy (N=2354), GnRH agonist users remained to have significantly lower risks of $MACE_{PRONOUNCE}$ (both unstratified and stratified log-rank tests $p<0.001$) and $MACE_{CVM}$ (unstratified log-rank test $p=0.022$, stratified log-rank test $p=0.031$).

9.4. Discussion

In this population-based prospective cohort study, we found that GnRH agonists may be associated with lower long-term, but not short-term, cardiovascular risks than antagonists, specifically among patients without known cardiovascular risk factors at baseline.

Existing evidence comparing the cardiovascular safety of GnRH agonists and antagonists is inconclusive (96). In an international observational study, GnRH antagonist users with known cardiovascular risk factors had higher risks of MI and arrythmia compared to GnRH agonist users (97). Nonetheless, a meta-analysis of RCTs suggested that GnRH antagonists were

associated with lower risks of cardiovascular events, though it was noted that the trials generally had short durations of follow-up, and that cardiovascular events were not reported as pre-specified outcomes (264). Indeed, a post-hoc analysis of six RCTs by Albertsen and colleagues, one of the earliest work in this area, only analysed cardiovascular events up to one year after initiation of GnRH agonists or antagonists, with none of the RCTs powered or designed for detecting differences in cardiovascular events (273). Similarly, the aforementioned PRONOUNCE trial, the first RCT intended to compare the cardiovascular safety of these agents, only followed up patients for one year.(95) These were in contrast to the generally longer follow-up duration in observational studies, which may have influenced the observed effects.(96) Our results suggested that short-term risks may not be directly extrapolatable to longer terms, with the observation that GnRH antagonists may be associated with higher cardiovascular risk over longer terms, but not within the first year. Having observed comparable first-year events rates (4.8% in the PRONOUNCE trial and 7.2% in this study) and no significant differences between GnRH agonists and antagonists within the first year, our findings agree with and build on the results of the PRONOUNCE trial. Furthermore, we noted that, likely for maximizing power, the PRONOUNCE trial defined MACE as a composite of all-cause mortality, MI, and stroke (i.e. $MACE_{PRONOUNCE}$ in this study), instead of the conventional definition of cardiovascular mortality, MI, and stroke (i.e. $MACE_{CVM}$ in this study) which was recommended by both the Food and Drug administration of the United States of America and the European Medicines Agency (274,275). This discrepancy led to our exploration of $MACE_{CVM}$ in this study, the results of which further supported that GnRH antagonists may carry significantly higher long-term cardiovascular risks than GnRH agonists. Overall, further studies should consider specific exploration of short- and long-term outcomes, as well as standardized definitions of cardiovascular events.

In addition, we observed that differences in the risk of MACE were only observed amongst those without any known cardiovascular risk factor at baseline. George and colleagues have also observed that baseline cardiovascular risk factors may be an effect modifier, observing that the relative effect on the risk of arrhythmia was higher in those without known cardiovascular risk factors, though the relative effect on the overall risk of any cardiovascular disease was only significant in those with known cardiovascular risk factor(s) (97). Whilst the reasons underlying such differences in effects were unclear, a possible reason could be that GnRH agonists or antagonists and cardiovascular risk factors do not interact in an additive nor synergistic manner, such that in patients with known cardiovascular risk factor(s), cardiovascular risk factors were the predominant drivers of cardiovascular events, masking the effects by GnRH agonists or antagonists; contrastingly, among those without such risk factors, the effects by GnRH agonists or antagonists were not masked, resulting in statistically significant differences. Nonetheless, the above reasoning is speculative, and these findings from subgroup analyses should be viewed cautiously as hypothesis-generating only. Further studies exploring the impact of cardiovascular risk factors on GnRH agonist and antagonist-related cardiotoxicity are required.

Nonetheless, observational studies, as is this study, are prone to biases and confounders which may significantly skew the results. Unfortunately, no RCT to date has been adequately powered

to compare the cardiovascular safety of these agents, including the recent HERO trial which suggested that relugolix, a GnRH antagonist, may be associated with a >50% reduction in cardiovascular events when compared to leuprolide, a GnRH agonist (276). The aforementioned PRONOUNCE trial, the first RCT designed to compare the cardiovascular safety of these agents, was eventually underpowered due to recruitment issues and low event rates (95). A recent analysis by Tiwari and colleagues demonstrated that with the event rates observed in PRONOUNCE, an estimated 2170 patients, over twice the planned sample size and four times the eventual sample size of PRONOUNCE, would be required to achieve a 80% power for a hazard ratio of 0.49 with a two-sided alpha of 0.05 (96). Such sample sizes are unlikely to be logistically and financially feasible. Tiwari and colleagues further argued that the results of PRONOUNCE and their post-hoc analysis showed that any difference between GnRH agonists and antagonists would be small and not clinically meaningful (96). However, as aforementioned, the one-year risks examined in PRONOUNCE may not be extrapolatable to longer terms. Therefore, we believe that continued efforts of investigating the cardiovascular safety of these agents remain warranted, and prospective registries with clear documentation of baseline cardiovascular risks and long follow-up may be the most pragmatic way in which one may attempt to bridge this gap in evidence.

9.4.1. Strengths and limitations

With a mean follow-up duration of 3.5 years, our study is, to the best of our knowledge, the first to compare the long-term cardiovascular safety of GnRH agonists and antagonists in Asian patients with PCa. Making use of population-based data, our findings are likely representative and widely generalizable, at least within Asia.

Nonetheless, this study was limited by its observational nature which predisposes to confounding and biases, including bias by indication. Specifically, Albertsen and colleagues published their analysis, which favoured GnRH antagonists in terms of cardiovascular outcomes, in 2014 (273). As we included patients prescribed GnRH agonists or antagonists between 2013 and 2021, clinicians may have been influenced and were inclined to prescribe GnRH antagonists for those at higher cardiovascular risks, driving a worse cardiovascular outcome. Nevertheless, this has been mitigated as much as possible by including multiple key prognostic factors in the inverse probability treatment weighting. This study's inclusion and exclusion criteria, which excluded patients with <6 months of ADT use or those who had no available baseline prostate-specific antigen level, may also predispose to selection bias, selecting for patients who did not have mortality nor any event that prevented continued use of ADT, and those who had less comprehensive workup prior to ADT initiation which may reflect quality of care. Having only included patients in Hong Kong, it is also possible that the prescription patterns of GnRH agonists and antagonists were influenced by the predominantly public and heavily subsidized nature of the local healthcare system, which may introduce further selection bias and limit applicability of our findings to regions with other types of healthcare systems or health-financing structures.

Additionally, our study is limited by the lack of details with regard to prostate cancer risk group, staging, and disease severity, which are taken into consideration when planning the type and extent of ADT given to a patient. Metastatic PCa may also increase cardiovascular risks via multiple mechanisms, including the requirement for other systemic, cardiotoxic PCa treatments such as androgen receptor signalling inhibitors (40). However, is important to note that our study assesses the duration and type of ADT and the subsequent association with cardiovascular toxicity, rather than the association between the primary prostate cancer and cardiovascular outcomes. This limitation was also partially mitigated by only including patients who used GnRH agonist or antagonist for more than six months, whose indication for androgen deprivation therapy was most likely high-risk PCa according to guideline (194). The use of other systemic PCa treatments, such as chemotherapy and androgen receptor signalling inhibitors, were also balanced between treatment groups by inverse probability treatment weighting. Furthermore, we excluded patients with prior MI or stroke, which may reduce the generalizability of our findings. Additionally, the data could not be individually adjudicated; nonetheless, CDARS captures data entered by treating clinicians, independent of the authors. Previous studies have also demonstrated that CDARS has good coding accuracy (232). Lastly, as a metropolitan, Hong Kong's population is not 100% Asian. As a result, some patients included in this study may be non-Asians. Nonetheless, the 2021 Hong Kong census found that 91.6% of the population were Chinese, and an additional 6.6% were non-Chinese Asians (277). It is thus likely that the overwhelming majority of the patients included in this study were Asians, and our conclusion remains valid.

9.5. Conclusion

In conclusion, GnRH antagonists may be associated with worse long-term, but not short-term, cardiovascular safety than GnRH agonists amongst Asian patients with PCa, particularly amongst those without cardiovascular risk factors at baseline. Further studies exploring the long-term cardiovascular safety of these agents, as well as investigations of the impact of cardiovascular risk factors on the effects of these agents, are warranted.

10. Chapter 10: Cardiovascular outcomes and hospitalizations in Asian patients receiving immune checkpoint inhibitors: a population-based study

This chapter is based on the following publication: **Chan JSK**, Lakhani I, Lee TTL, Chou OHI, Lee YHA, Cheung YM, Yeung HW, Tang P, Ng K, Dee EC, Liu T, Wong WT, Tse G, Leung FP. Cardiovascular outcomes and hospitalizations in Asian patients receiving immune checkpoint inhibitors: a population-based study. *Curr Probl Cardiol.* 2023; 48(1): 101380. doi: 10.1016/j.cpcardiol.2022.101380

10.1. Introduction

Whilst immune checkpoint inhibitors (ICI) have become an established treatment option for a number of malignancies,(278) such as those of lung, head and neck, skin, and other organs, recent years have seen an increasing understanding of ICI-related adverse effects, such as hepatotoxicity, colitis, and cardiotoxicity.(279–281) ICI is associated with increased risks of myocarditis, heart failure (HF), and myocardial infarction (MI), most of which are mechanistically inflammatory: cardio-immune crosstalk disruptions and T-cell and macrophage mediated response to cardiac antigens, which may be direct results of immune checkpoint inhibition, lead to autoantibody-independent processes including inflammatory cell infiltration and myocardial fibrosis, alongside other processes such as IgG deposition and loss of PD-L1-dependent cardioprotection.(282,283)

Despite many reports demonstrating ICI-related cardiotoxicity, studies focusing on the effect of ICI on cardiovascular hospitalization have been scarce. Additionally, despite some studies having explored ICI-related adverse events in Asian cohorts,(284) a representative quantification of the cardiovascular risks amongst Asian patients treated with ICI remains lacking. Therefore, we aimed to quantify the burden of cardiovascular hospitalizations and the risk of adverse cardiovascular events amongst Asian users of ICI.

10.2. Methods

This retrospective cohort study was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. Requirement for individual patient consent was waived as deidentified data was used. All underlying data are available upon reasonable request to the corresponding authors.

10.2.1. Source of data

Data were extracted from the Clinical Data Analysis and Reporting System (CDARS), a population-based, administrative electronic medical records system in Hong Kong. CDARS records all diagnostic, procedural and prescription records of patients attending public healthcare institutions in Hong Kong, which serve an estimated 90% of the population.(199)

Diagnoses were encoded by *International Classification of Diseases, Ninth Revision* (ICD-9) codes (**Supplementary Table 10.1**) regardless of the time of data entry, as ICD-10 has not been implemented in CDARS to date. Mortality data and death causes were obtained from the linked Hong Kong Death Registry, a governmental registry of all Hong Kong citizens' death records; causes of death were encoded by ICD-9 or ICD-10 codes (**Supplementary Table 10.2**). Both CDARS and the Hong Kong Death Registry have been used extensively in prior studies and shown to have good coding accuracy and data completeness.(60,200,231,235,238)

10.2.2. Patients, follow-up, and outcome

All patients receiving any ICI in Hong Kong between 1st January 2013 and 31st December 2021 were identified. ICI included PD-1 inhibitors (pembrolizumab or nivolumab), PD-L1 inhibitors (atezolizumab, avelumab, or durvalumab), and CTLA4 inhibitor (ipilimumab); no other ICI were available in Hong Kong during the study period. There were no exclusion criteria for estimating cardiovascular hospitalizations. Patients with prior myocardial infarction (MI), stroke, or HF were excluded when analysing the primary outcome, which was major adverse cardiovascular event (MACE), defined as the first occurrence of MI, stroke, HF, or cardiovascular mortality. All patients were followed up until 31st December 2021.

10.2.3. Data collected

The total number of hospitalization episodes with their respective length of stay (LOS) during the follow-up period were recorded for each patient. Specifically, the total number of cardiovascular hospitalizations, as determined by ICD-9 diagnostic (**Supplementary Table 10.1**) and procedural (**Supplementary Table 10.3**) codes, was recorded. Overnight hospitalizations were recorded. Additionally, baseline variables were also recorded, which included: age, sex, type of cancer, comorbid conditions (hypertension (defined by both ICD-9 codes and the use of antihypertensive(s)), ischaemic heart disease, MI, HF, atrial fibrillation, diabetes mellitus (defined by both ICD-9 codes and the use of antidiabetic medication(s)), dyslipidaemia (defined by both ICD-9 codes and the use of anti-lipid medication(s)), chronic kidney disease, chronic obstructive pulmonary disease, chronic liver disease, stroke, and peripheral arterial disease), and the use of other medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, metformin, sulfonylurea, insulin, dipeptidyl peptidase-4 inhibitors, beta-blockers, statins, dihydropyridine calcium channel blockers, and chemotherapeutic agents).

10.2.4. Statistical analysis

Continuous variables were expressed as median with interquartile range (IQR). The IR of MACE was estimated. Kaplan-Meier curves were used to visualize the cumulative incidence of MACE over the study period. The six-month, one-year, 1.5-year, and two-year risks of MACE were estimated using life tables. Similar to above, the IR of MACE within the first year of follow-up were also calculated specifically, and a sensitivity analysis was performed in which the IR of MACE was estimated only for patients with at least one year of follow-up.

Incidence rate (IR) of hospitalizations and annualized length of stay (LOS) were estimated with respective confidence intervals (CI) using negative binomial regression with follow-up duration as the exposure variable. As many patients did not have overnight or cardiovascular hospitalizations, the corresponding IR were estimated for patients who had such events using zero-inflated negative binomial regression with constant inflation. Hospitalization-related costs were estimated by multiplying the estimated LOS with the latest per-day cost of in-patient hospital stay (HKD5100, corresponding to €637.5 with a conversion factor of 0.125 at the time of writing) published by the Hong Kong Hospital Authority in 2020.(285) To account for potential changes in IR over time, the IR of hospitalizations within the first year of follow-up were calculated specifically. For similar reasons, a sensitivity analysis was performed with analyses restricted to patients with at least one year of follow-up.

Two-sided $p<0.05$ were considered statistically significant. All statistical analyses were performed on Stata v 16.1 (StataCorp LLC, College Station, Texas, United States of America).

10.3. Results

In total, 4324 patients were identified and included in the analysis (2905 (67.2%) males; median age 63.5 years old, IQR 55.4-70.7 years old). Most patients received a PD-1 inhibitor (3527 patients, 81.6%), and 59.4% (2567 patients) had chemotherapy use at baseline. Half had lung cancer (2179 patients, 50.4%). Hypertension was documented in 1993 patients (46.1%), dyslipidaemia in 1227 (28.4%), and diabetes mellitus in 793 (18.3%); 153 patients had prior diagnosis of stroke, MI, or HF, and were therefore excluded from all MACE analyses. The baseline characteristics of the study cohort were summarized in **Table 10.1**.

10.3.1. Major adverse cardiovascular event

Amongst the 4171 patients included in the MACE analysis, MACE occurred in 116 patients (2.8%) over a median follow-up duration of 1.0 year (IQR 0.4-2.3 years), of which 18 (18.1% of those with MACE; 0.4% of all patients) had cardiovascular mortality, 34 (29.3% of those with MACE; 0.8% of all patients) had MI, 15 (12.9% of those with MACE; 0.4% of all patients) had HF, and 55 (47.4% of those with MACE; 1.3% of all patients) had stroke; more than one component of MACE occurred concomitantly in 9 patients (7.8% of those with MACE; 0.2% of all patients). Patients who had MACE had higher rates of cardiovascular risk factors, including hypertension, diabetes mellitus, dyslipidaemia, and ischaemic heart disease, and used more cardiovascular and antidiabetic medications (**Supplementary Table 10.4**).

Among the 116 patients who had MACE, 90 (77.6%) had MACE within the first year, with a median time-to-event of 0.5 year (IQR 0.2-0.9 year). This early clustering of events was also demonstrated by the Kaplan-Meier curve (**Figure 10.1**). The six-month risk of MACE was estimated to be 1.7% [95% CI: 1.4%, 2.2%], the one-year risk 2.8% [2.3%, 3.5%], the 1.5-year risk 3.2% [2.6%, 4.0%], and the two-year risk 4.3% [3.6%, 5.3%]. Concordantly, the IR of MACE within the first year was 2.9 [2.3, 3.5] events per 100 patient-years, with a lower overall

IR of 1.7 [1.4, 2.0] events per 100 patient-years throughout the study period. Sensitivity analysis of patients with at least one year of follow-up (N=2048) also yielded a lower IR of MACE, which was estimated to be 0.9 [0.7, 1.2] events per 100 person-years.

Table 10.1 Baseline characteristics of included patients.

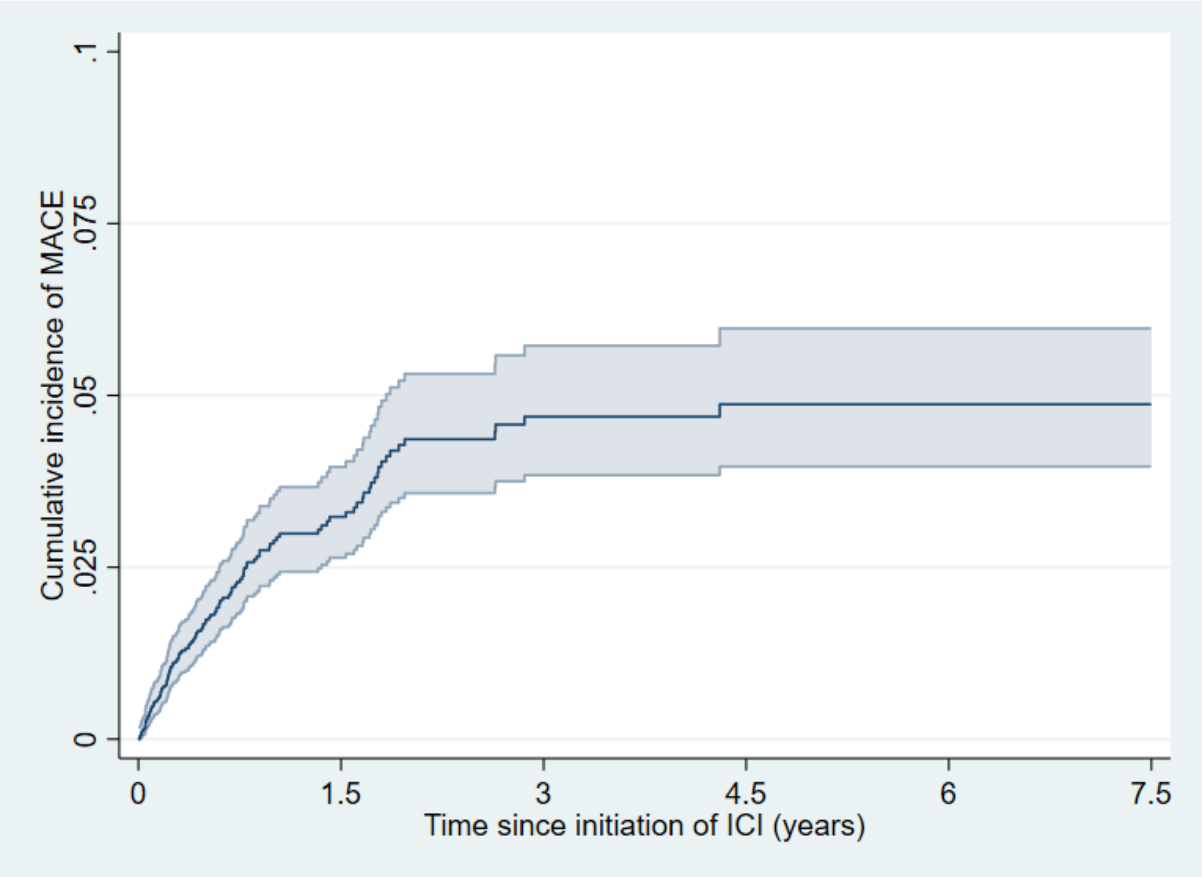
	All patients	Patients with cardiovascular hospitalization(s)	Patients without cardiovascular hospitalization(s)
Number of patients, N	4324	188	4136
Type of immune checkpoint inhibitor			
Anti-PD-1 user, N (%)	3527 (81.6)	160 (85.1)	3367 (81.4)
Anti-PD-L1 user, N (%)	873 (20.2)	35 (18.6)	838 (20.3)
Anti-CTLA4 user, N (%)	322 (7.5)	16 (8.5)	306 (7.4)
Type of cancer			
Lung cancer, N (%)	2005 (46.4)	103 (54.8)	1902 (46.0)
Head and neck cancer, N (%)	154 (3.6)	3 (1.6)	151 (3.7)
Nasopharyngeal cancer, N (%)	76 (1.8)	1 (0.5)	75 (1.8)
Breast cancer, N (%)	138 (3.2) [1]	6 (3.2)	132 (3.2)
Colorectal cancer, N (%)	102 (2.4)	5 (2.7)	97 (2.4)
Liver cancer, N (%)	540 (12.5)	22 (11.7)	518 (12.5)
Stomach cancer, N (%)	97 (2.2)	2 (1.1)	95 (2.3)
Melanoma, N (%)	109 (2.5)	1 (0.5)	108 (2.6)
Renal cell carcinoma, N (%)	182 (4.2)	13 (6.9)	169 (4.1)
Esophageal cancer, N (%)	46 (1.1)	0 (0)	46 (1.1)
Cervical cancer, N (%)	26 (0.6)	1 (0.5)	25 (0.6)
Lymphoma, N (%)	181 (4.2)	7 (3.7)	174 (4.2)
Leukaemia, N (%)	43 (1.0)	0 (0)	43 (1.0)
Plasma cell dyscrasia, N (%)	8 (0.2)	0 (0)	8 (0.2)
Demographics			
Male, N (%)	2905 (67.2)	127 (67.6)	2778 (67.2)
Age, years	63.5 [55.4-70.7]	67.7 [58.7-75.9]	63.4 [55.2-70.5]
Comorbid conditions			
Hypertension, N (%)	1993 (46.1)	109 (58.0)	1884 (45.6)
Ischaemic heart disease, N (%)	201 (4.7)	28 (14.9)	173 (4.2)
Myocardial infarction, N (%)	46 (1.1)	6 (3.2)	40 (1.0)
Heart failure, N (%)	52 (1.2)	10 (5.3)	42 (1.0)

Atrial fibrillation, N (%)	97 (2.2)	12 (6.4)	85 (2.1)
Diabetes mellitus, N (%)	793 (18.3)	40 (21.3)	753 (18.2)
Dyslipidaemia, N (%)	1227 (28.4)	78 (41.5)	1149 (27.8)
Chronic kidney disease, N (%)	39 (0.9)	2 (1.1)	37 (0.9)
Stroke, N (%)	76 (1.8)	6 (3.2)	70 (1.7)
Peripheral arterial disease, N (%)	7 (0.2)	0 (0)	7 (0.2)
Use of other medications			
ACEI/ARB user, N (%)	984 (22.8)	64 (34.0)	920 (22.2)
Metformin user, N (%)	594 (13.7)	34 (18.1)	560 (13.5)
Sulfonylurea user, N (%)	380 (8.8)	19 (10.1)	361 (8.7)
Insulin user, N (%)	370 (8.6)	14 (7.5)	356 (8.6)
DPP4 inhibitor user, N (%)	185 (4.3)	12 (6.4)	173 (4.2)
Beta-blocker user, N (%)	974 (22.5)	65 (34.6)	909 (22.0)
Statin user, N (%)	1144 (26.5)	76 (40.4)	1068 (25.8)
Dihydropyridine CCB user, N (%)	1576 (36.5)	85 (45.2)	1491 (36.1)
Chemotherapy user, N (%)	2567 (59.4)	99 (52.7)	2468 (59.7)

[1] 9.7% of female patients

ACEI, angiotensin-converting enzyme inhibitor. ARB, angiotensin receptor blocker. CCB, calcium channel blocker. CTLA4, cytotoxic T-lymphocyte associated protein 4. DPP4, dipeptidyl peptidase 4. PD-1, programmed cell death protein 1. PD-L1, programmed cell death ligand 1.

Figure 10.1 Kaplan-Meier curve showing the cumulative incidence of major adverse cardiovascular event (MACE). ICI, immune checkpoint inhibitor.



10.3.2. Hospitalization and costs

Over a median follow-up duration of 1.0 year (IQR 0.4-2.3 years), 50,578 hospitalization episodes were observed with 123,544 days of hospitalization. Of these, 8752 (17.3%) episodes were overnight hospitalizations, accounting for 81,718 days of hospitalization (66.1% of all hospitalized days). The observed hospitalizations incurred a total cost of €78,759,300, with an annualized per-patient cost of €31,176 [€30,116, €32,274] per patient-year; overnight hospitalizations incurred a total cost of €52,095,225 (66.1% of total hospitalization cost), with an annualized per-patient cost of €36,313 [€34,557, €38,158] per patient-year for those who had overnight hospitalizations.

In total, 188 patients (4.4%) had cardiovascular hospitalization(s), with 254 episodes (0.5% of all episodes) and 1555 days (1.3% of all hospitalized days) of cardiovascular hospitalization; 177 of these episodes (69.7% of cardiovascular hospitalization episodes and 2.0% of all overnight episodes) were overnight hospitalizations, accounting for 1478 days of hospitalization (95.0% of all the days of cardiovascular hospitalization and 1.8% of all the days of overnight hospitalization). Those who had cardiovascular hospitalizations generally had more cardiovascular risk factors, such as hypertension, diabetes mellitus, and dyslipidaemia, and used more cardiovascular or antidiabetic medications; a higher proportion of these patients

had lung cancer than those who did not have any cardiovascular hospitalization (**Table 10.1**). For those who had cardiovascular hospitalizations, the IR of cardiovascular hospitalization was estimated to be 5.6 [4.6, 6.9] episodes per 100 person-years, with an annualized LOS of 52.9 [39.8, 70.3] days per 100 person-years (**Table 10.2**). Overall, the observed cardiovascular hospitalizations incurred a total cost of €991,313 (1.3% of total hospitalization cost), with an annualized per-patient cost of €1614 [€92, €28,257] per patient-year for those with cardiovascular hospitalizations; overnight cardiovascular hospitalizations incurred a total cost of €942,225 (1.2% of total hospitalization cost), with an annualized per-patient cost of €9195 [€6700, €12,620] per person-year for those with overnight cardiovascular hospitalizations.

During the first year of follow-up, higher rates of cardiovascular admissions were observed for those who had cardiovascular hospitalizations, with an estimated 27.7 [0.8, 923.0] episodes per 100 person-years and 253.1 [14.4, 4432.5] days of hospitalization per 100 person-years; similar trends were observed for overnight cardiovascular hospitalizations (**Table 10.3**). Similar to the overall analysis, cardiovascular hospitalizations accounted for 0.5% of all hospitalization episodes (199 of 39,623 episodes) and 1.3% of all days of hospitalization (1152 of 99,795 days) during the first year of follow-up; overnight cardiovascular hospitalizations accounted for 69.7% of all cardiovascular hospitalization episodes (140 of 199 episodes), 1.9% of all overnight hospitalization episodes (140 of 67364 episodes), 94.9% of all days of cardiovascular hospitalization (1093 of 1152 days), and 1.6% of all days of overnight hospitalization (1093 of 67,364 days) during the first year of follow-up.

Sensitivity analysis of only patients with at least one year of follow-up included 2116 patients. In agreement with the early clustering of attendances as aforementioned, lower IR of hospitalization and annualized LOS were observed for all types of hospitalizations (**Supplementary Table 10.5**) than the main analyses above. Notwithstanding this, the IR of cardiovascular hospitalizations remained lower than the overall IR of all hospitalizations.

Table 10.2 Incidence rates of hospitalization throughout the study period.

	Proportion of patients with event (N, %)	Incidence rate [95% CI], episodes per 100 person-years	Annualized LOS [95% CI], days per 100 person-years
All admissions	4143 (95.8)	1166.6 [1132.0, 1202.3]	4557.0 [4381.9, 4739.0]
All overnight admissions [1]	2931 (67.8)	309.6 [292.9, 327.3]	4608.2 [4338.6, 4894.6]
Cardiovascular admissions [1]	188 (4.4)	5.6 [4.6, 6.9]	52.9 [39.8, 70.3]
Overnight cardiovascular admissions [1]	142 (3.3)	4.0 [3.1, 5.0]	742.1 [430.3, 1279.7]

[1] Estimates calculated for patients with event using zero-inflated negative binomial regression

CI, confidence interval. LOS, length of stay.

Table 10.3 Incidence rates of hospitalization within the first year of follow-up.

	Proportion of patients with event (N, %)	Incidence rate [95% CI], episodes per 100 person-years	Annualized LOS [95% CI], days per 100 person-years
All admissions	4142 (95.8)	1388.6 [1358.3, 1419.6]	4890.4 [4724.1, 5062.6]
All overnight admissions [1]	2693 (62.3)	341.0 [312.0, 372.6]	5696.2 [5420.7, 5985.6]
Cardiovascular admissions [1]	149 (3.5)	27.7 [0.8, 923.0]	253.1 [14.4, 4432.5]
Overnight cardiovascular admissions [1]	112 (2.6)	5.0 [4.0, 6.3]	1442.4 [1051.0, 1979.6]

[1] Estimates calculated for patients with event using zero-inflated negative binomial regression

CI, confidence interval. LOS, length of stay.

10.4. Discussion

Using data from a population-based database in Hong Kong, we described the burden of cardiovascular outcomes, hospitalization, and costs amongst Asian users of ICI. The IR of MACE was low, and cardiovascular hospitalizations and costs contributed to only a small proportion of all hospitalizations and related costs. Importantly, the IR of MACE and cardiovascular hospitalization were both higher during the first year of follow-up, and the most occurrences of MACE were within the first year of follow-up.

Our findings suggested that ICI-related cardiotoxicity is uncommon among Asian users of ICI. Cardiovascular hospitalizations accounted for only 0.5% of all hospitalization episodes, contrasting published governmental figures in 2019, when hospitalizations and deaths from cardiovascular causes accounted for 7.6% of such events.(234) This was in agreement with the general consensus that ICI-related cardiotoxicity is uncommon: a recent meta-analysis of 51 trials found an incidence of 3.1%-5.8% amongst patients using ICI.(286) Meanwhile, another meta-analysis of 63 trials found even lower incidence for MI (0.74 per 100 patients), HF (0.87 per 100 patients), and stroke (0.88 per 100 patients),(287) comparable to the rates we observed. In addition, previous studies observed that most ICI-related cardiotoxic events occurred shortly after initiation of ICI, (288,289) which was echoed by our finding that 77.6% of MACE occurred within the first year after initiating ICI. These findings should aid clinicians during their discussion of therapeutic options with patients eligible for ICI, allowing clinicians to better inform patients of the risks involved and thereby facilitate shared decision-making. Furthermore, the finding that the majority of MACE among patients treated with ICI occur within the first year of ICI initiation underscores the importance of close cardiology follow-up as well as clinician- and patient-level education regarding symptoms that would be suggested of MACE. Indeed, these findings highlight the importance of synergy between oncology and cardiology care providers.

The low frequency of ICI-related cardiotoxicity does not undermine its clinical importance. Studies have observed mortality rates between 27%-53% amongst patients with ICI-related cardiotoxicity, making it one of the deadliest ICI-related side effects.(288–291) This has fueled ample research of ICI-related cardiotoxicity, with some exploring therapeutic options which, given the inflammatory nature of the condition, have mostly revolved around glucocorticoids and immunosuppressants, in addition to cessation of ICI.(57,289,292,293)

The rarity of ICI-related cardiotoxicity, however, did mean that it is methodologically and statistically difficult to identify its risk factors – knowing the risk factors is crucial for effectively managing ICI users as it allows better stratification of patients at high risk of ICI-related cardiotoxicity, to whom resources may be better allocated for closer monitoring and better optimization of cardiovascular conditions. A case series by Mahmood and colleagues suggested that pre-existing cardiovascular conditions may predispose to ICI-related cardiotoxicity,(294) while a pharmacovigilance study observed that most patients who had ICI-related cardiotoxicity did not have pre-existing cardiovascular conditions.(290) Jain and colleagues attempted to identify risk factors for adverse cardiovascular outcomes in ICI

users,(295) with the type of ICI used, specific types of cancer, and other autoimmunity-related conditions such as thyroiditis, instead of pre-existing cardiovascular conditions, being associated with adverse cardiovascular outcomes.(295) These results nonetheless remain to be validated in other cohorts, underscoring the need to evaluate data from diverse and global patient populations. Brumberger and colleagues also attempted to elucidate the risk factors using multivariable logistic regression, and identified female gender, African American race, and smoking as risk factors for ICI-related cardiotoxicity.(291) Nonetheless, they considered a small number of cardiovascular risk factors, which limited the relevance of the results. Our findings appeared to support the observation by Mahmood and colleagues, with those who had MACE having more cardiovascular risk factors and used more cardiovascular and antidiabetic medications at baseline. Nonetheless, the low event rate precluded any clinically meaningful multivariable regression analysis. Overall, the risk factors for ICI-related cardiotoxicity remains a critical gap in the literature that urgently requires further investigations. In the broader sense, other tools of risk stratification, which may include risk scores or novel biomarkers,(296) warrant further exploration and investigation as well.

To the best of our knowledge, this was one of the first studies to specifically quantify the risk of cardiovascular outcomes and the IR and cost of hospitalization amongst Asian ICI users. With the emerging evidence of racial and ethnic disparity in ICI-related adverse events,(297,298) race / ethnicity-specific quantification of the risk of ICI-related cardiotoxicity and cardiovascular hospitalization is much needed. Although Li and colleagues previously described the incidence of ICI-related adverse events in Chinese patients, cardiovascular events were not reported specifically, and the sample size (1063 patients) limited the generalizability of their findings.(284) Having used data from a large, representative, population-based database in Hong Kong, our cohort essentially included all patients that were treated with ICI in Hong Kong. Our findings thus closely reflected real-world practice and may be more generalizable to other regions in Asia. Further studies from other regions of Asia are required to validate our findings, and comparison against findings from other regions may allow better understanding of the determinants underlying the racial and ethnic disparities in ICI-related cardiotoxicity.

10.4.1. Limitations

This study has several limitations. First, cancer staging was not available, which limited the interpretation and applicability of our findings. Nonetheless, ICI are generally used for advanced disease, and given that this study set out to describe the overall epidemiology of MACE and hospitalizations amongst users of ICI, our findings remain valid and clinically relevant. Second, all diagnoses and outcomes were defined using ICD codes and could not be individually adjudicated. Nonetheless, all data were input by the treating clinicians independent of the authors, and none of the authors had the authority to influence data input. CDARS have also been shown to have good coding accuracy and data completeness.(232)

10.5. Conclusion

Amongst Asian users of ICI, MACE was uncommon, and a small proportion of hospitalizations and related costs was attributable to cardiovascular causes. Most of the MACE and cardiovascular hospitalizations occurred during the first year after initiating ICI. Further studies on risk stratification and race / ethnicity-specific investigation of ICI-related cardiotoxicity are warranted.

11. Chapter 11: Association between immune checkpoint inhibitors and myocardial infarction in Asians: a population-based self-controlled case series

This chapter is based on the following publication: **Chan JSK**, Tang P, Lee TTL, Chou OHI, Lee YHA, Li G, Leung FP, Wong WT, Liu T, Tse G. Association between immune checkpoint inhibitors and myocardial infarction in Asians: a population-based self-controlled case series. *Cancer Med.* 2023; 12(8): 9541-9546. doi: 10.1002/cam4.5729

11.1. Introduction

Immune checkpoint inhibitors (ICIs) have become a common treatment for many types of cancer. A previous study suggested that ICIs may be associated with atherosclerosis and myocardial infarction (MI)(42). However, unlike ICI-related myocarditis which was relatively well-characterized(299), evidence for ICI-related MI had remained scarce, especially in Asians. With evidence demonstrating racial disparities in the presence and severity of coronary atherosclerosis(300), as well as the incidence and outcome ICI-related adverse events(297), associations between ICIs and MI in Asians warrant further investigations. This study thus explored such associations in Asians.

11.2. Methods

11.2.1. Source of data

This study was approved by The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee and adhered with the Declaration of Helsinki. Patient consent was waived as deidentified data were used. Data were extracted from the Clinical Data Analysis and Reporting System, a prospective, population-based database of patients attending public healthcare facilities in Hong Kong with linked mortality data. This system has been used in research with demonstrable data accuracy and completeness(121,201,232). All underlying data is available on reasonable request to the corresponding author.

11.2.2. Study design

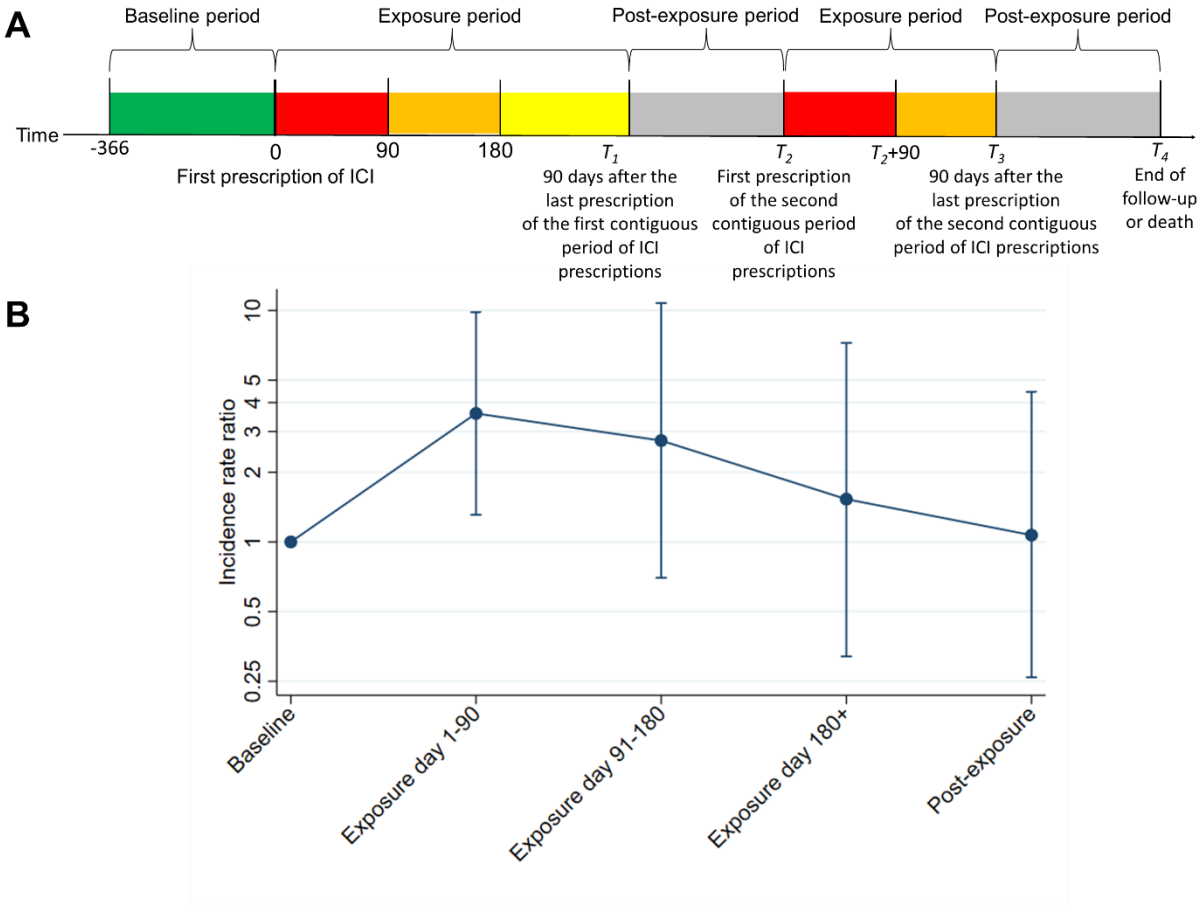
This is a self-controlled case series (SCCS). SCCS is a type of case-only study in which only patients experiencing an outcome of interest are analyzed. It was chosen because, in an observational setting, it is difficult to identify appropriate control groups to be compared against patients receiving ICIs without incurring significant bias by indication, which arises when clinical differences between exposure groups drive both the exposure and the outcome. Bias by indication is notoriously difficult to address, and statistical adjustments are often inadequate(301). In SCCS, rather than using between-individual analyses as in cohort studies, within-individual comparisons of the incidence rate of events before and after exposure are performed. As each patient is compared with his/herself, all measured and unmeasured time-invariant confounders are controlled for(301). The paired nature of the analysis used in SCCS

also helps maintaining statistical power, thus allowing SCCS to be used reliably for relatively rare outcomes(302).

11.2.3. Eligibility criteria and definitions of outcomes and study sub-periods

Patients with cancer receiving any ICI (programmed cell death protein-1 inhibitors [PD1i], PD ligand-1 inhibitors [PDL1i], or cytotoxic T-lymphocyte associated protein-4 inhibitors [CTLA4i]) in Hong Kong between 1/1/2014-31/12/2020 were identified. Those without MI (identified using International Classification of Diseases, Ninth revision [ICD-9] codes [410-411.0 and 412]) within 1/1/2013-31/12/2021 were only analysed for the crude cohort-level incidence rates (IRs), but not the SCCS analysis. The baseline period was defined as the year before the first ICI prescription. The exposure periods included contiguous ICI prescriptions (i.e. inter-prescription gaps <60 days) and the ensuing 90 days, beyond which cardiac immune-related adverse events were rare(303). Post-exposure periods encompassed periods not described above, until death or end of follow-up (31/12/2021), whichever earlier. MI episodes over contiguous days were treated as singular events. Cardiovascular mortality within 30 days post-event were deemed MI-related(304). ICD codes used to identify cancer, cardiovascular mortality, and cardiovascular risk factors have been described elsewhere(121). The study design is summarized in **Figure 11.1A**.

Figure 11.1 (A) Diagram illustrating the study design. Each analysed sub-period of exposure is coded in a different colour (red/orange/yellow). The second contiguous period of immune checkpoint inhibitor (ICI) prescriptions was shorter than 180 days, hence the truncation of the 90-180 days sub-period of exposure (orange). (B) Incidence rate ratios for each sub-period of exposure and the post-exposure period, compared to baseline.



11.2.4. Statistical analysis

Crude cohort-level IRs (IRs) pre- and post-ICI initiation were calculated amongst all identified ICI users. SCCS analyses were performed on the final cohort using fixed-effects conditional Poisson regression, with durations of the above sub-periods as the exposure variable. Summary statistics were IR ratios (IRRs) and 95% confidence intervals.

To account for the small but potentially important possibility of delayed cardiac events, an *a priori* sensitivity analysis was performed with the exposure period extended to 180 days after the last prescription within a contiguous prescription period. Additionally, as mortality associated with MI may skew estimates, another *a priori* sensitivity analysis was performed with exclusion of patients who had MI-related mortality.

Furthermore, to minimize heterogeneity in the ICI used, a post-hoc analysis was performed, restricting the analysis to those who only received PD1i. Due to small sample sizes, this analysis could not be performed for PDL1i nor CTLA4i.

Two-sided $p<0.05$ were considered significant. All analyses were performed on Stata v16.1 (StataCorp LLC, USA).

11.3. Results

Altogether, 3684 ICI users were identified (median follow-up 442 [interquartile range 145-989] days; median exposure 164 [91-315] days), of whom 24 had MI during the study period (20 PD1i users, one PDL1i user, and three PD1i+CTLA4i users; median follow-up 436 [156-888] days; median exposure 175.5 [115-412] days). Lung cancer occurred in nine, liver cancer in four, renal cancer in three, and other cancers in eight patients. Baseline demographic and cardiovascular risk factors are summarized in **Table 11.1**. Eight had MI during baseline (one PD1i user, three PD1i+CTLA4i users, and one PDL1i user), 12 during exposure (11 PD1i users, and one PD1i+CTLA4i user), and four during post-exposure (all PD1i users). Three had MI-related death: two during exposure and one during post-exposure. Crude cohort-level MI IRs during the baseline, exposure, and post-exposure periods were 2.2, 4.8, and 1.0 per 1000-person-years, respectively.

Table 11.1 Summary of baseline demographics and cardiovascular risk factors of the included patients.

Age, years	70 [60-77] †
Male sex, N (%)	17 (70.8)
Hypertension, N (%)	16 (66.7)
Diabetes mellitus, N (%)	9 (37.5)
Hyperlipidaemia, N (%)	16 (66.7)
Ischaemic heart disease, N (%)	11 (45.8)
Heart failure, N (%)	6 (25.0)
Chronic kidney disease, N (%)	1 (4.2)
Atrial fibrillation, N (%)	2 (8.3)
Stroke, N (%)	3 (12.5)

† Median and interquartile range

Compared to baseline, the incidence of MI was significantly higher in the first 90 days of exposure (IRR 3.59 [95% confidence interval 1.31-9.83], p=0.013; **Figure 11.1B**), but not days 91-180 (IRR 2.74 [0.70-10.76], p=0.148) or days ≥181 (IRR 1.53 [0.32-7.24], p=0.591) of exposure, nor the post-exposure period (IRR 1.07 [0.26-4.45], p=0.923).

Consistently, in the sensitivity analysis with extended exposure period, the incidence of MI was significantly higher within the first 90 days of exposure (IRR 3.53 [1.29-9.67], p=0.014), but not days 91-180 (IRR 2.01 [0.52-7.75], p=0.309) or days ≥181 (IRR 1.13 [0.25-5.01], p=0.884) of exposure, nor the post-exposure period (IRR 1.94 [0.39-9.60], p=0.418). The sensitivity analysis excluding the three patients who had MI-related mortality also showed similar results, with a significantly higher MI incidence within the first 90 days of exposure (IRR 3.00 [1.05-8.59], p=0.041), but not days 91-180 (IRR 1.61 [0.33-7.75], p=0.556) or days ≥181 (IRR 0.83 [0.15-5.01], p=0.838) of exposure, nor the post-exposure period (IRR 0.89 [0.22-3.59], p=0.868).

In the post-hoc analysis of the 20 patients who only received PD1i, similar results were observed, with the incidence of MI being significantly higher within the first 90 days of exposure (IRR 5.21 [1.60, 17.06], p=0.006), but not days 91-180 (IRR 3.60 [0.86, 15.08], p=0.079) or days ≥181 (IRR 1.39 [0.33, 5.82], p=0.651) of exposure, nor the post-exposure period (IRR 0.87 [0.23, 3.24], p=0.837).

11.4. Discussion

This was the first SCCS exploring associations between ICIs and MI in Asians. The incidence of MI increased significantly within 90 days of ICI initiation but did not persist beyond this time period. Mechanistically, the early spike in MI incidence observed in this study agreed with previous animal studies in which short-term ICI administration induced atherosclerotic plaque inflammation and progression(305). Specifically, accelerated atherosclerosis, vasculitis, and focal myocarditis mediated by ICI-induced immune activation and inflammation have been proposed as likely mechanisms underlying ICI-related MI, although other contributors such as sociodemographic factors and comorbidities may be at play too(306). In the present cohort, cardiovascular risk factors were common which may have amplified the effects of ICI-induced acceleration in atherosclerotic progression. Furthermore, we confirmed and extended previous clinical findings reporting increased MI incidence after ICI use(42), with the low IR of MI also comparable with prior observations(42,121,303). In particular, while previous clinical studies focused on the first event and neglected recurrent events(42), we provided novel evidence for the timing of spikes in the incidence of MI, echoing previous findings that most ICI-related cardiovascular events occur early(303). Importantly, the post-exposure MI incidence was not significantly different from baseline. This bridges an important gap in the literature, as previous investigations had not reported temporal variations in the risk of MI after ICI, and, as chronic immune-related adverse events become an increasing concern, it was unclear how long the cardiovascular risks associated with ICI use would persist(307).

Using population-based data, our findings were representative and likely generalizable to other Asian/Chinese cohorts. Clinically, these findings highlighted the importance of cardiac monitoring within the first 90 days of ICI use, which, according to the 2022 European Society of Cardiology guidelines, should be multidisciplinary(13). The post-exposure normalization of MI incidence may reassure clinicians and patients over potential concerns for sustained increases in MI incidence, facilitating shared decision-making. Moving forward, these novel

data on the timing of MI incidence spiking should prompt further, larger investigations of the timing of cardiovascular risks to allow more granular recommendations for the scheduling of cardiac monitoring and follow-up, as the current recommendations in this regard have inadequate levels of evidence (mostly level C only, i.e. from "consensus of opinion of the experts and/or small studies, retrospective studies, registries")(13). Furthermore, as it has been suggested that different classes of ICI may be associated with different cardiovascular risks(281), further studies should delineate class-/agent-specific associations with MI, as we did with patients who received only PD1i. Predictors and prognosticators of ICI-related MI also warrant further investigations, as well as relevant treatments and prophylactic cardioprotective strategies – in particular, statins have been explored for the latter and have shown promising results, slowing atherosclerotic progression in ICI users and thus having the potential to prevent ICI-related MI(306,308).

Nonetheless, this study was not devoid of limitations. It was limited by potential time-varying confounders, event-dependence of risks, and the presence of event-related censoring. We attempted to mitigate event-related censoring using a sensitivity analysis which excluded patients who had MI-related mortality. This yielded consistent results, reinforcing our findings' validity. Also, data for MI subtypes were not available, and outcome adjudication was not possible due to the nature of the database. Nonetheless, this database has been demonstrated to have good data accuracy and completeness(232), and the small number of events observed was unlikely to have allowed further meaningful analysis of different MI subtypes. Overall, further studies are required to confirm our findings, as well as evaluating the generalizability of our findings to different populations.

11.5. Conclusion

ICIs associated with increased MI incidence in Asian Chinese patients during the first 90 days of use, but not later.

12. Chapter 12: Temporal trends in guideline-recommended cardiometabolic testing completeness before initiating immune checkpoint inhibitors: a cohort study

This chapter is based on the following publication: **Chan JSK**, Chou OHI, Lee TTL, Lee YHA, Chan RNC, Dee EC, Ng K, Liu T, Tse G. Temporal trends in guideline-recommended cardiometabolic testing completeness before initiating immune checkpoint inhibitors: a cohort study. *J Intern Med.* 2024; 295(3): 375-378. doi: 10.1111/joim.13754

12.1. Introduction

Immune checkpoint inhibitors (ICIs) are increasingly utilized, but are associated with cardiotoxicity(43,121,306). The cardiovascular needs of ICI users was addressed by the European Society of Cardiology's (ESC) 2022 Cardio-Oncology Guidelines(13), with cardiometabolic testing recommended before initiating ICIs ("pre-ICI"), including glycaemic (HbA1c or fasting glucose), lipid, renal and natriuretic peptide testing, electrocardiogram, and echocardiography(13). However, current practices of pre-ICI cardiometabolic testing are undescribed, and ensuring testing completeness may improve cardiovascular outcomes(309). We thus examined trends in pre-ICI cardiometabolic testing completeness and explored whether such trends influenced cardiovascular outcomes.

12.2. Methods

This study was approved by an institutional review board and conducted in accordance with the Declaration of Helsinki. As deidentified data were used, individual consent requirement was waived.

12.2.1. Source of data

Data were obtained from the Clinical Data Analysis and Reporting System (CDARS), a population-based electronic medical records database in Hong Kong that prospectively records diagnostic, procedural, and prescription data of patients attending public hospitals/clinics in Hong Kong which serve an estimated 90% of the population(199). Details of CDARS have been covered elsewhere(310). Diagnoses were encoded by *International Classification of Diseases, Ninth Revision* (ICD-9) codes (**Supplementary Table 12.1**), as ICD-10 has not been implemented in CDARS to date. Mortality data were obtained from the linked Hong Kong Death Registry, which is a governmental registry linked to legal records and which contains the death records of all Hong Kong citizens. Mortality causes were encoded by ICD-9/10 codes (**Supplementary Table 12.2**). Both databases have been used extensively for research in both cardiovascular and non-cardiovascular fields(60,200,201,225,226,270). Previous studies have validated CDARS' diagnostic coding for a range of cardiovascular conditions such as myocardial infarction, stroke, heart failure, and atrial fibrillation, demonstrating that the coded diagnoses had good positive predictive values (85.4%, 91.1%, 76.0%, and 95%, respectively)(225,311,312), with another study demonstrating near-perfect (>99% accuracy) records of demographics and drug prescriptions(313). Meanwhile, the encoded mortality

causes have been used in official governmental publications, in addition to numerous peer-reviewed publications(314).

12.2.2. Patient population

This cohort study included all patients with cancer who were initiated on immune checkpoint inhibitor(s) between 1 Jan 2013 and 31 Dec 2021, without any exclusion criteria.

12.2.3. Exposures, key measures/outcomes, and follow-up

Patients were grouped by the year of ICI initiation (2013-2017, 2018-2019, and 2020-2021) which constituted the exposure in this study. ICIs included programmed cell death protein 1 (PD-1) inhibitors, programmed cell death-ligand 1 (PD-L1) inhibitors, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors. As per the European Society of Cardiology's cardio-oncology guideline, cardiometabolic workup prior to initiation of cancer therapy (including ICI) should include glycaemic workup (HbA1c and/or fasting glucose), electrocardiogram, transthoracic echocardiography, and testing for cardiac troponin, natriuretic peptides, and renal function / estimated glomerular filtration rate (eGFR)(13). However, natriuretic peptide testing is not available in public hospitals/clinics in Hong Kong, and data for electrocardiogram and echocardiography were unavailable. Therefore, the occurrence and timing of any glycaemic workup, and testing for total cholesterol, HDL-C, cardiac troponin, and eGFR (including creatinine-only testing) within five years before ICI initiation were recorded. As cardiac troponin testing may have been performed for patients with clinical suspicion of myocardial ischaemia instead of being part of cardiometabolic workup, measurements within seven days of any diagnosis/hospitalization for myocardial infarction were excluded. Completeness of cardiometabolic workup at 90/180 days was quantified by the total number of the above tests performed within 90 and 180 days before ICI initiation, respectively. The proportion of patients with each component of cardiometabolic workup was also reported, which is an adaptation of secondary domain 2.1 in the recommended "quality indicators for the prevention and management of cancer therapy-related cardiovascular toxicity in cancer treatment" as published by the European Society of Cardiology(309).

All patients were followed up from ICI initiation for up to two years, until 31/12/2021, or until death, whichever occurred earlier. Follow-up was limited to two years as patients initiated on ICI in 2020-2021 could only have up to two years' follow-up. Any occurrence and timing of major adverse cardiovascular event (MACE; the first hospitalization/diagnosis of non-fatal myocardial infarction, non-fatal stroke, heart failure, or cardiovascular mortality) and non-cardiovascular mortality during follow-up were recorded. All outcomes were ascertained using ICD codes (**Supplementary Tables 12.1** and **12.2**). Owing to the nature of the data source, there was no loss to follow-up.

12.2.4. Other variables collected

The following variables were collected at baseline (ICI initiation): age, sex, race, type of cancer, cardiovascular comorbidities (hypertension, heart failure, myocardial infarction, stroke, ischaemic heart disease, atrial fibrillation, ventricular arrhythmia or cardiac arrest, valvular heart disease, chronic obstructive pulmonary disease, and peripheral arterial disease), diabetes mellitus, dyslipidaemia, chronic kidney disease, and prescription of non-ICI medications (angiotensin-converting enzyme inhibitors / angiotensin receptor blockers, metformin, sulfonylureas, insulins, dipeptidyl peptidase-4 inhibitors, beta-blockers, statins, dihydropyridine calcium channel blockers, and chemotherapeutic agents). All prescription records were automatically recorded as part of the electronic medical records within CDARS. All diagnoses were ascertained using ICD-9 codes as listed in **Supplementary Table 12.1**; ICD-10 codes were not used as they have not been implemented in CDARS to date. Data on the diagnosis of diabetes mellitus was additionally supplemented by the prescription of any antidiabetic medication and HbA1c measurements taken prior to ICI initiation, with any HbA1c >6.5% being considered to be diagnostic(315). Data on the diagnosis of dyslipidaemia was additionally supplemented by the prescription of any lipid-lowering medication. Data on the diagnosis of hypertension was additionally supplemented by the prescription of any antihypertensive medication. Owing to the nature of the variables collected and our data sources, there were no missing values for any of the variables.

12.2.5. Statistical analysis

As the main analysis, completeness of cardiometabolic workup at 90/180 days were compared between groups (i.e. patients initiated on ICI in different years) using Poisson regression, with risk ratios (signifying the comparative 'risk' of having more complete cardiometabolic workup) as summary statistics. Both univariable and multivariable regressions were performed, with the latter adjusting for all above-listed covariates (in subsection *Other variables collected*); covariates were selected *a priori* based on clinical and epidemiological knowledge. Five *a priori* subgroup analyses were performed for this main analysis, with stratification for sex, age groups (<60 years, 60-70 years, and >70 years), the presence of any major cardiovascular condition (ischaemic heart disease, myocardial infarction, stroke, peripheral arterial disease, heart failure, ventricular arrhythmia or cardiac arrest, valvular heart disease, and atrial fibrillation), the presence of hypertension, the presence of diabetes mellitus, and the presence of dyslipidaemia.

In a secondary analysis, multivariable binary logistic regression adjusting for all above-listed covariates was used to further compare the odds of having undergone each component of cardiometabolic workup within 90/180 days before ICI initiation between groups, with odds ratios as summary statistics. The respective proportions of patients who underwent each component of cardiometabolic workup were calculated with logit-transformed 95% confidence intervals. Trends in these proportions over time were tested using a non-parametric test developed by Cuzick(205).

To explore whether any differences in the completeness of cardiometabolic workup translated to differences in cardiovascular outcomes, Fine-Gray competing risk regressions were used in an exploratory analysis to compare the cumulative incidence of MACE between groups, with non-cardiovascular mortality as the competing event, and with sub-hazard ratios as summary statistics. This analysis was performed at both one-year and two-year follow-up for more granular analyses. Both univariable and multivariable regressions were performed, with the latter adjusting for all above-listed covariates. Moreover, in an effort to explore whether differences in the completeness of cardiometabolic workup over the years influenced cardiovascular outcomes, further adjustments were performed for the number of workup components tested within 180 days before ICI initiation (as a surrogate of cardiometabolic workup completeness). If such influence was present, the between-year sub-hazard ratios should be substantially modified by adjustments for cardiometabolic workup completeness. The cumulative incidence of MACE was visualized using the Aalen-Johansen estimator, which was chosen over the Kaplan-Meier estimator as the latter gives biased estimates in the presence of competing risks(120,239). Lastly, an *a priori* sensitivity analysis was performed in which the Pepe and Mori test, which does not assume proportional hazards, was used to compare the cumulative incidence of MACE between patients who were initiated on ICI in different years.

All p-values were two-sided, with $p<0.05$ considered statistically significant. Continuous variables were described as medians with interquartile ranges, whilst categorical variables were described as counts with percentages. All analyses were performed using Stata/IC version 16.1 (StataCorp LLC, College Station, Texas, United States of America).

12.3. Results

Altogether, 4324 patients were analyzed (baseline characteristics in **Table 12.1**). Patients initiated on ICI more recently had more complete cardiometabolic testing within both 90 (2020-2021 vs 2013-2017: adjusted risk ratio [aRR] 1.10[95% confidence interval: 1.03-1.18], p=0.005) and 180 (aRR 1.09[1.03-1.16], p=0.005) days pre-ICI (**Table 12.2**). Subgrouping mostly produced directionally consistent estimates with overlapping confidence intervals (**Tables 12.3-12.4)**.

Table 12.1 Baseline characteristics of included patients.

	All patients	2013-2017	2018-2019	2020-2021
Number of patients, N	4324	937	1551	1836
Median follow-up duration, years [interquartile range]	0.9 [0.4-2.0]	2.0 [2.0-2.0]	1.1 [0.3-2.0]	0.7 [0.3-1.2]
Type(s) of immune checkpoint inhibitor				
Anti-PD-1 only, N (%)	3329 (77.0)	855 (91.3)	1181 (76.1)	1293 (70.4)
Anti-PD-L1 only, N (%)	819 (18.9)	41 (4.4)	294 (19.0)	484 (26.4)
Anti-CTLA4 only, N (%)	6 (0.1)	3 (0.3)	3 (0.2)	0 (0)
Anti-PD-1 and anti-CTLA4 only, N (%)	170 (3.9)	38 (4.1)	73 (4.7)	59 (3.2)
Type of cancer (numbers include potential overlaps)				
Lung cancer, N (%)	2005 (46.4)	330 (35.2)	728 (46.9)	947 (51.6)
Head and neck cancer, N (%)	210 (4.9)	48 (5.1)	84 (5.4)	78 (4.3)
Nasopharyngeal cancer, N (%)	76 (1.8)	17 (1.8)	30 (1.9)	29 (1.6)
Breast cancer, N (%)	138 (3.2)	45 (4.8)	43 (2.8)	50 (2.7)
Colorectal cancer, N (%)	102 (2.4)	29 (3.1)	34 (2.2)	39 (2.1)
Liver cancer, N (%)	540 (12.5)	136 (14.5)	214 (13.8)	190 (10.4)
Stomach cancer, N (%)	97 (2.2)	25 (2.7)	36 (2.3)	36 (2.0)
Melanoma, N (%)	109 (2.5)	22 (2.4)	44 (2.8)	43 (2.3)
Renal cell carcinoma, N (%)	182 (4.2)	39 (4.2)	72 (4.6)	71 (3.9)
Esophageal cancer, N (%)	46 (1.1)	8 (0.9)	15 (1.0)	23 (1.3)
Cervical cancer, N (%)	26 (0.6)	3 (0.3)	6 (0.4)	17 (0.9)
Lymphoma, N (%)	181 (4.2)	63 (6.7)	59 (3.8)	59 (3.2)
Leukaemia, N (%)	43 (1.0)	26 (2.8)	10 (0.6)	7 (0.4)
Plasma cell dyscrasia, N (%)	8 (0.2)	6 (0.6)	2 (0.1)	0 (0)
Other malignancies, N (%)	805 (18.6)	190 (20.3)	271 (17.5)	344 (18.7)
Demographics				
Male, N (%)	2905 (67.2)	596 (63.6)	1056 (68.1)	1253 (68.3)
Age, years (median [interquartile range])	63.5 [55.4-70.7]	60.9 [50.6-68.4]	63.1 [54.9-70.7]	64.9 [58.2-71.6]
Race, N (%)				
East Asian	4101 (94.8)	862 (92.0)	1471 (94.8)	1768 (96.3)
Caucasian	27 (0.6)	4 (0.4)	14 (0.9)	9 (0.5)

	All patients	2013-2017	2018-2019	2020-2021
South Asian	15 (0.4)	5 (0.5)	3 (0.2)	7 (0.4)
Others / unknown	181 (4.2)	66 (7.0)	63 (4.1)	52 (2.8)
Comorbid conditions				
Hypertension, N (%)	1993 (46.1)	399 (42.6)	700 (45.1)	894 (48.7)
Ischaemic heart disease, N (%)	201 (4.7)	24 (2.6)	61 (3.9)	116 (6.3)
Myocardial infarction, N (%)	46 (1.1)	6 (0.6)	11 (0.7)	29 (1.6)
Heart failure, N (%)	52 (1.2)	8 (0.9)	16 (1.0)	28 (1.5)
Atrial fibrillation, N (%)	97 (2.2)	15 (1.6)	32 (2.1)	50 (2.7)
Ventricular arrhythmia or cardiac arrest, N (%)	9 (0.2)	0 (0)	4 (0.3)	5 (0.3)
Valvular heart disease, N (%)	20 (0.5)	1 (0.1)	12 (0.8)	7 (0.4)
Diabetes mellitus, N (%)	949 (22.0)	168 (17.9)	339 (21.9)	442 (24.1)
Dyslipidaemia, N (%)	1227 (28.4)	202 (21.6)	437 (28.2)	588 (32.0)
Chronic kidney disease, N (%)	39 (0.9)	10 (1.1)	11 (0.7)	18 (1.0)
Chronic obstructive pulmonary disease, N (%)	116 (2.7)	10 (1.1)	36 (2.3)	70 (3.8)
Stroke, N (%)	76 (1.8)	15 (1.6)	24 (1.6)	37 (2.0)
Peripheral arterial disease, N (%)	7 (0.2)	1 (0.1)	3 (0.2)	3 (0.2)
Prescription of non-immune checkpoint inhibitor medications				
ACEI/ARB, N (%)	984 (22.8)	175 (18.7)	349 (22.5)	460 (25.1)
Metformin, N (%)	594 (13.7)	101 (10.8)	209 (13.5)	284 (15.5)
Sulfonylurea, N (%)	380 (8.8)	68 (7.3)	135 (8.7)	177 (9.6)
Insulin, N (%)	370 (8.6)	62 (6.6)	114 (7.4)	194 (10.6)
DPP4 inhibitor, N (%)	185 (4.3)	31 (3.3)	64 (4.1)	90 (4.9)
Beta-blocker, N (%)	974 (22.5)	188 (20.1)	338 (21.8)	448 (24.4)
Statin, N (%)	1144 (26.5)	192 (20.5)	417 (26.9)	535 (29.1)
Dihydropyridine CCB, N (%)	1576 (36.5)	311 (33.2)	555 (35.8)	710 (38.7)
Other anti-cancer therapeutic agents, N (%)	2567 (59.4)	590 (63.0)	902 (58.2)	1075 (58.6)
HER-2 receptor antagonist	36 (0.8)	16 (1.7)	12 (0.8)	8 (0.4)
Anthracyclines	280 (6.5)	105 (11.2)	88 (5.7)	87 (4.7)
5-Fluorouracil	168 (3.9)	52 (5.6)	58 (3.7)	58 (3.2)
Platinum compounds	2377 (55.0)	540 (57.6)	846 (54.6)	991 (54.0)
Taxanes	777 (18.0)	185 (19.7)	259 (16.7)	333 (18.1)

	All patients	2013-2017	2018-2019	2020-2021
Antifolates	1135 (26.3)	238 (25.4)	423 (27.3)	474 (25.8)

ACEI, angiotensin-converting enzyme inhibitor. ARB, angiotensin receptor blocker. CCB, calcium channel blocker. CTLA4, cytotoxic T-lymphocyte associated protein 4. DPP4, dipeptidyl peptidase 4. PD-1, programmed cell death protein 1. PD-L1, programmed cell death ligand 1.

Table 12.2 Comparison of the completeness of cardiometabolic tests and the odds of having undergone each component of the cardiometabolic tests of interest within 90 or 180 days before immune checkpoint inhibitor (ICI) initiation throughout the study period.

Workup / measure	Timepoint	Summary statistic	Year of ICI initiation		
			2013-2017 (N=937)	2018-2019 (N=1551)	2020-2021 (N=1836)
Number of cardiometabolic tests done	90 days	Unadjusted RR	1 (reference)	1.11 [1.04, 1.18], p=0.003	1.17 [1.10, 1.25], p<0.001
		Adjusted RR	1 (reference)	1.06 [0.99, 1.13], p=0.092	1.10 [1.03, 1.18], p=0.005
	180 days	Unadjusted RR	1 (reference)	1.14 [1.08, 1.22], p<0.001	1.20 [1.13, 1.27], p<0.001
		Adjusted RR	1 (reference)	1.08 [1.01, 1.15], p=0.017	1.09 [1.03, 1.16], p=0.005
Glycaemic	90 days	Adjusted OR	1 (reference)	1.12 [0.91, 1.37], p=0.274	1.46 [1.20, 1.78], p<0.001
	180 days		1 (reference)	1.22 [1.01, 1.47], p=0.043	1.42 [1.17, 1.71], p<0.001
Total cholesterol	90 days	Adjusted OR	1 (reference)	1.37 [1.05, 1.79], p=0.021	1.56 [1.20, 2.03], p=0.001
	180 days		1 (reference)	1.44 [1.14, 1.81], p=0.002	1.54 [1.23, 1.94], p<0.001
HDL-C	90 days	Adjusted OR	1 (reference)	1.34 [1.02, 1.76], p=0.037	1.55 [1.18, 2.02], p=0.001
	180 days		1 (reference)	1.41 [1.12, 1.78], p=0.004	1.55 [1.23, 1.95], p<0.001
Troponin	90 days	Adjusted OR	1 (reference)	1.33 [0.90, 1.97], p=0.151	0.67 [0.43, 1.02], p=0.062
	180 days		1 (reference)	1.13 [0.81, 1.57], p=0.470	0.58 [0.41, 0.84], p=0.003
eGFR	90 days	Adjusted OR	1 (reference)	0.32 [0.06, 1.74], p=0.188	0.79 [0.12, 5.08], p=0.807
	180 days		Model convergence not achieved		

CI, confidence interval. eGFR, estimated glomerular filtration rate. HDL-C, high density lipoprotein cholesterol. OR, odds ratio. RR, risk ratio.

Table 12.3 Results from subgroup analysis for having more complete cardiometabolic tests within 90 days before immune checkpoint inhibitor (ICI) initiation. Adjusted risk ratios and 95% confidence intervals are displayed.

Subgroup		Year of ICI initiation		
		2013-2017 (N=937)	2018-2019 (N=1551)	2020-2021 (N=1836)
Sex	Male (N=2905)	1 (reference)	1.08 [0.99, 1.17], p=0.069	1.12 [1.04, 1.22], p=0.005
	Female (N=1419)	1 (reference)	1.02 [0.91, 1.15], p=0.741	1.04 [0.92, 1.17], p=0.528
Age (years)	<60 (N=1620)	1 (reference)	1.03 [0.93, 1.15], p=0.535	1.11 [0.99, 1.24], p=0.066
	60-70 (N=1524)	1 (reference)	1.07 [0.95, 1.20], p=0.255	1.13 [1.01, 1.26], p=0.037
	>70 (N=1180)	1 (reference)	1.07 [0.93, 1.23], p=0.328	1.05 [0.92, 1.20], p=0.506
Major cardiovascular condition(s)	Present (N=246)	1 (reference)	1.10 [0.82, 1.47], p=0.522	1.01 [0.76, 1.35], p=0.933
	Absent (N=4078)	1 (reference)	1.06 [0.99, 1.13], p=0.120	1.11 [1.03, 1.18], p=0.004
Hypertension	Present (N=1993)	1 (reference)	1.06 [0.96, 1.17], p=0.250	1.10 [1.00, 1.21], p=0.044
	Absent (N=2331)	1 (reference)	1.07 [0.97, 1.17], p=0.183	1.11 [1.01, 1.22], p=0.035
Diabetes mellitus	Present (N=949)	1 (reference)	1.14 [0.99, 1.31], p=0.065	1.15 [1.01, 1.32], p=0.038
	Absent (N=3375)	1 (reference)	1.04 [0.96, 1.12], p=0.355	1.09 [1.00, 1.17], p=0.038
Dyslipidaemia	Present (N=1227)	1 (reference)	1.05 [0.92, 1.19], p=0.465	1.05 [0.93, 1.18], p=0.461
	Absent (N=3097)	1 (reference)	1.05 [0.97, 1.14], p=0.210	1.12 [1.03, 1.21], p=0.007

Table 12.4 Results from subgroup analysis for having more complete cardiometabolic tests within 180 days before immune checkpoint inhibitor (ICI) initiation. Adjusted risk ratios and 95% confidence intervals are displayed.

Subgroup		Year of ICI initiation		
		2013-2017 (N=937)	2018-2019 (N=1551)	2020-2021 (N=1836)
Sex	Male (N=2905)	1 (reference)	1.10 [1.02, 1.19], p=0.012	1.10 [1.02, 1.18], p=0.018
	Female (N=1419)	1 (reference)	1.03 [0.92, 1.15], p=0.589	1.09 [0.98, 1.21], p=0.123
Age (years)	<60 (N=1620)	1 (reference)	1.04 [0.94, 1.15], p=0.497	1.09 [0.98, 1.21], p=0.104
	60-70 (N=1524)	1 (reference)	1.08 [0.97, 1.20], p=0.150	1.10 [1.00, 1.22], p=0.060
	>70 (N=1180)	1 (reference)	1.14 [1.01, 1.29], p=0.037	1.10 [0.98, 1.25], p=0.114
Major cardiovascular condition(s)	Present (N=246)	1 (reference)	1.15 [0.89, 1.49], p=0.287	0.97 [0.75, 1.25], p=0.789
	Absent (N=4078)	1 (reference)	1.08 [1.01, 1.15], p=0.025	1.11 [1.04, 1.18], p=0.002
Hypertension	Present (N=1993)	1 (reference)	1.09 [1.00, 1.19], p=0.052	1.11 [1.02, 1.21], p=0.020
	Absent (N=2331)	1 (reference)	1.08 [0.99, 1.18], p=0.088	1.10 [1.01, 1.20], p=0.038
Diabetes mellitus	Present (N=949)	1 (reference)	1.10 [0.97, 1.24], p=0.127	1.05 [0.94, 1.19], p=0.384
	Absent (N=3375)	1 (reference)	1.07 [0.99, 1.15], p=0.077	1.11 [1.03, 1.20], p=0.004
Dyslipidaemia	Present (N=1227)	1 (reference)	1.06 [0.95, 1.18], p=0.296	1.02 [0.92, 1.14], p=0.662
	Absent (N=3097)	1 (reference)	1.08 [1.00, 1.16], p=0.051	1.14 [1.05, 1.23], p=0.001

All tests' completeness improved, except cardiac troponin which decreased slightly, and estimated glomerular filtration rate which remained high (**Figure 12.1, Table 12.5**). Multivariable logistic regression confirmed such findings (**Table 12.2**). Nonetheless, testing completeness remained poor overall (**Figure 12.1, Table 12.5**). **Supplementary Figures 12.1-12.2** showed the number of tests within 90/180 days pre-ICI. **Supplementary Figures 12.3-12.7** showed the time between the most recent pre-ICI tests and ICI initiation.

Figure 12.1 Respective proportions of patients who underwent the cardiometabolic tests of interest within (A) 90 and (B) 180 days before initiating immune checkpoint inhibitor(s) (ICIs) throughout the study period. Bars indicate 95% confidence intervals. eGFR, estimated glomerular filtration rate. HDL-C, high density lipoprotein cholesterol.

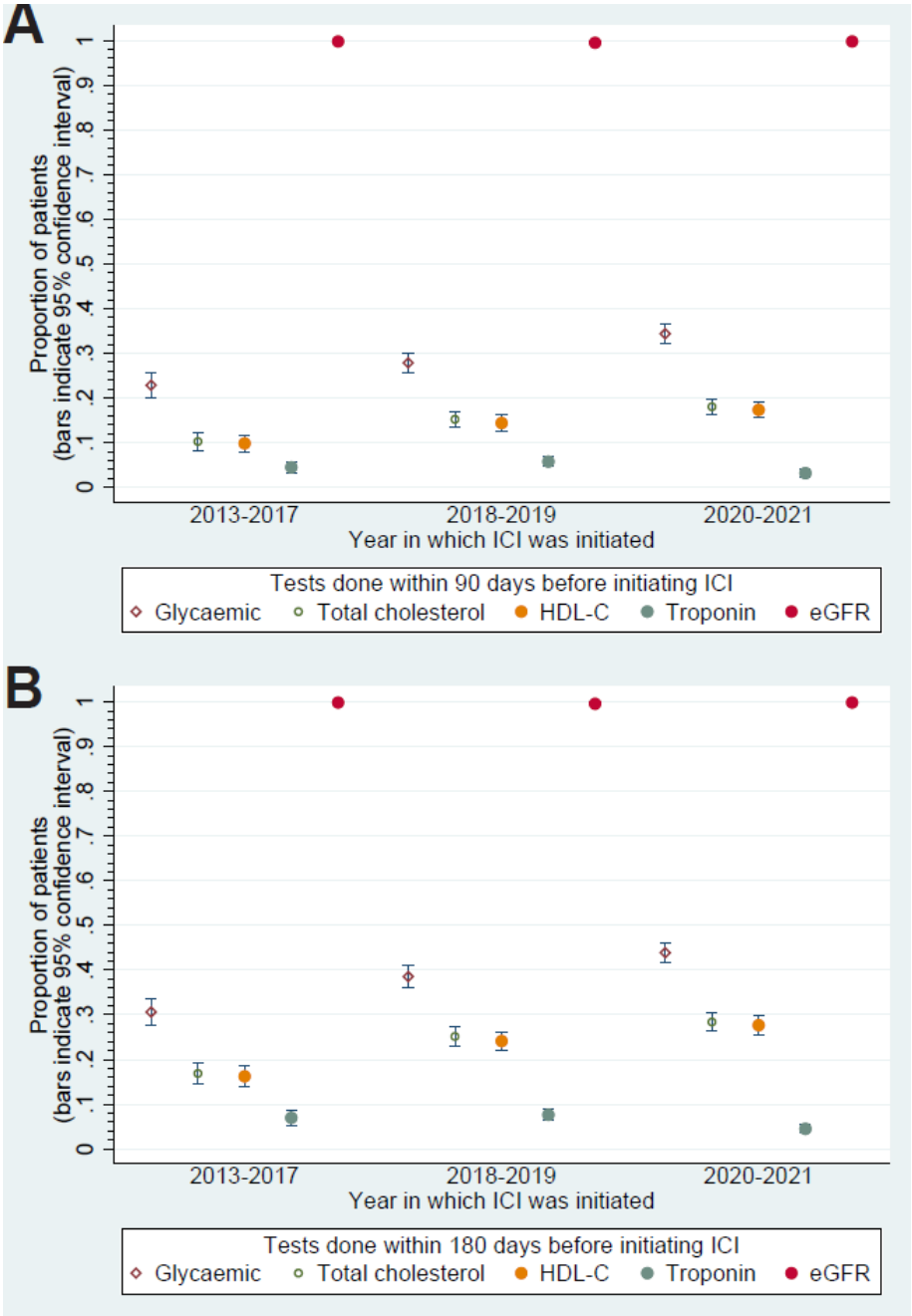


Table 12.5 Respective proportions (in percentage) of patients who underwent the cardiometabolic tests of interest within 180 and 90 days before initiating immune checkpoint inhibitor(s) (ICIs) throughout the study period. Numbers in brackets are 95% confidence intervals.

Test	Timepoint	Year of ICI initiation			p_{trend}
		2013-2017 (N=937)	2018-2019 (N=1551)	2020-2021 (N=1836)	
Glycaemic	180 days	30.6 [27.8, 33.7]	38.6 [36.2, 41.0]	43.9 [41.6, 46.2]	<0.001
	90 days	22.8 [20.3, 25.6]	27.9 [25.7, 30.1]	34.4 [32.2, 36.6]	<0.001
Total cholesterol	180 days	16.9 [14.6, 19.4]	25.1 [23.0, 27.4]	28.4 [26.4, 30.5]	<0.001
	90 days	10.2 [8.5, 12.4]	15.2 [13.5, 17.1]	18.0 [16.4, 19.9]	<0.001
HDL-C	180 days	16.2 [14.0, 18.7]	24.1 [22.0, 26.3]	27.7 [25.7, 29.8]	<0.001
	90 days	9.8 [8.1, 11.9]	14.4 [12.7, 16.2]	17.3 [15.7, 19.1]	<0.001
Troponin	180 days	6.9 [5.5, 8.8]	7.6 [6.4, 9.0]	4.5 [3.6, 5.5]	0.002
	90 days	4.5 [3.3, 6.0]	5.7 [4.7, 7.0]	3.2 [2.4, 4.1]	0.025
eGFR	180 days	99.9 [99.2, 100.0]	99.6 [99.1, 99.8]	99.9 [99.6, 100.0]	0.707
	90 days	99.8 [99.2, 99.9]	99.5 [99.0, 99.7]	99.8 [99.4, 99.9]	0.753

eGFR, estimated glomerular filtration rate. HDL-C, high density lipoprotein cholesterol.

Over a 0.9-year median follow-up [interquartile range: 0.4-2 years], 130 patients (3.0%) had MACE; 2185 had non-cardiovascular mortality (50.5%). Unadjusted Fine-Gray regression found no significant differences in MACE cumulative incidence between years of ICI initiation (**Figure 12.2, Table 12.6**). Although adjusted analysis found those initiated on ICI more recently having lower two-year MACE cumulative incidence (possibly due to shorter follow-up in these patients), no significant one-year differences were observed. Additional adjustment for 180-day testing completeness did not meaningfully modify these associations (**Table 12.6**). Sensitivity analysis produced similar results as unadjusted regression (**Table 12.7**).

Figure 12.2 Aalen-Johansen cumulative incidence curve of major adverse cardiovascular events with up to two years of follow-up, stratified by the year of immune checkpoint inhibitor initiation.

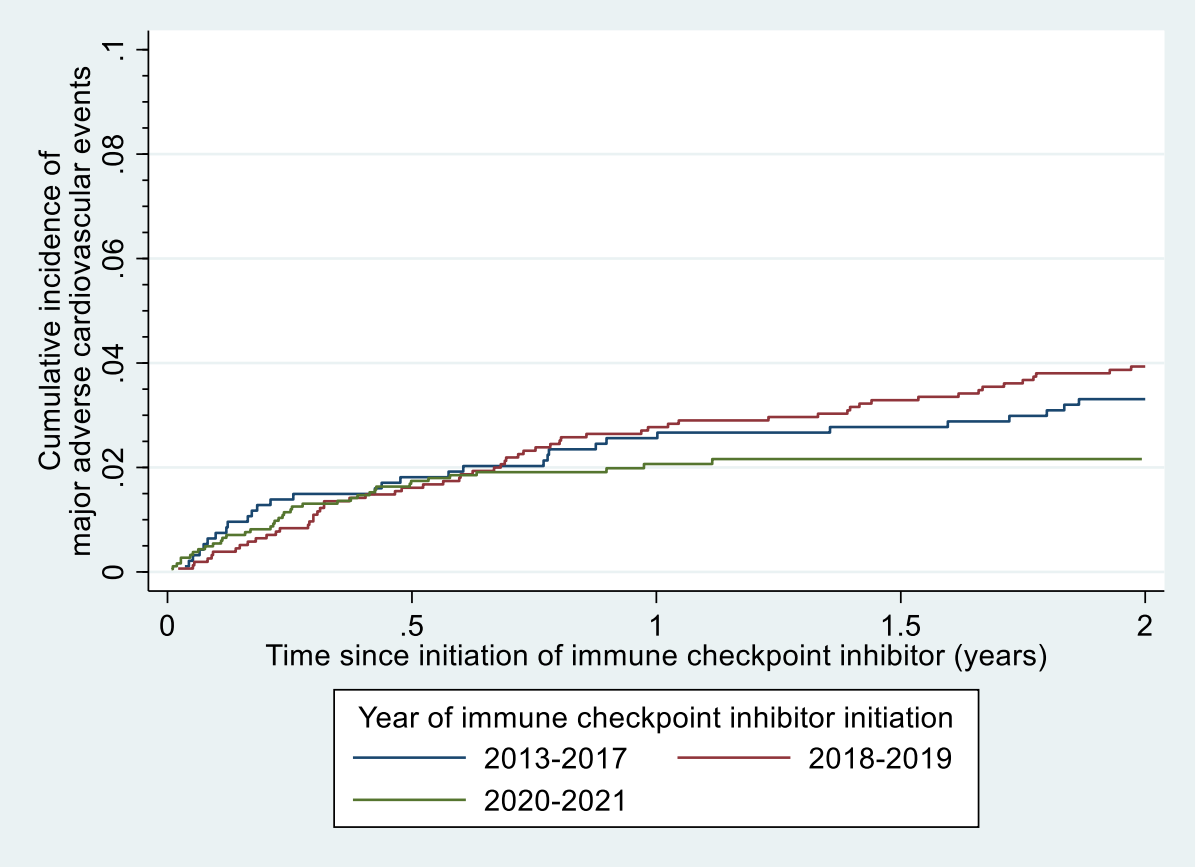


Table 12.6 Results of Fine-Gray competing risk regression exploring differences in the one- and two-year cumulative incidences of major adverse cardiovascular events across different years of immune checkpoint inhibitor (ICI) initiation. Subhazard ratios (SHRs) and the corresponding 95% confidence intervals are displayed.

		Year of ICI initiation		
		2013-2017	2018-2019	2020-2021
1-year	Unadjusted	1 (reference)	1.09 [0.66, 1.79], p=0.744	0.81 [0.49, 1.35], p=0.423
	Adjusted	1 (reference)	1.00 [0.59, 1.67], p=0.989	0.69 [0.40, 1.20], p=0.185
	Further adjusted for the number of cardiometabolic tests performed within 180 days before ICI initiation[1]	1 (reference)	0.99 [0.59, 1.66], p=0.970	0.69 [0.40, 1.19], p=0.182
2-year	Unadjusted	1 (reference)	1.23 [0.80, 1.89], p=0.352	0.73 [0.45, 1.16], p=0.181
	Adjusted	1 (reference)	1.03 [0.66, 1.61], p=0.892	0.58 [0.35, 0.96], p=0.036
	Further adjusted for the number of cardiometabolic tests performed within 180 days before ICI initiation[2]	1 (reference)	1.02 [0.65, 1.59], p=0.938	0.58 [0.35, 0.96], p=0.034

[1] SHR for the number of cardiometabolic tests performed within 180 days before ICI initiation: 1.04 [0.88, 1.22], p=0.663

[2] SHR for the number of cardiometabolic tests performed within 180 days before ICI initiation: 1.07 [0.93, 1.23], p=0.355

Table 12.7 Results of the Pepe and Mori tests comparing the cumulative incidence of one- and two-year cumulative incidences of major adverse cardiovascular events between patients initiated on immune checkpoint inhibitors (ICIs) in different years.

Year of ICI initiation	2018-2019	2020-2021
2013-2017	1-year: p=0.741 2-year: p=0.851	1-year: p=0.653 2-year: p=0.529
2018-2019		1-year: p=0.958 2-year: p=0.542

12.4. Discussion

This was one of the first studies examining cardiometabolic testing completeness in patients with cancer receiving ICIs. Improving testing completeness likely reflected increasing awareness of the cardiometabolic impacts of ICI and other cancer therapies, with similar observations for other therapies(122). Nonetheless, most tests were still only performed for selected patients, and the degree of improvements were likely insufficient to influence outcomes. Cardiometabolic testing completeness remains a potential opportunity for bettering cardiovascular outcomes in these patients, possibly with dedicated cardio-oncology services(316).

Using population-based data, our findings were representative and generalizable to many Asian metropolitans. Whilst data for some cardiometabolic testing components were unavailable, most were included, and echocardiography was only recommended for patients at high cardiovascular risks(13). Some cardiovascular variables/risk factors were unavailable, e.g. blood pressure, but numerous covariates were considered and should cover most confounders. Furthermore, individual outcome adjudication was impossible, and misdiagnosis/miscoding of ICI-related cardiovascular sequelae was possible. Lastly, Hong Kong's healthcare system is heavily subsidized. Our findings may have limited applicability to countries/regions with different medical financing systems(317).

12.5. Conclusion

Although cardiometabolic testing completeness in patients with cancer being initiated on ICI was improving, completeness remained poor. Such improvements probably did not meaningfully influence cardiovascular outcomes.

13. Chapter 13: Critical analysis and discussion

Chapters 2-12 of this thesis explored different cancer factors, patient factors, and social factors and their associations with cardiovascular health and/or outcomes in cancer survivors / patients with cancer using various methodologies.

13.1. Social factors: social determinants of health

Chapters 2-4 focused on social factors. Chapter 2 demonstrated, in a cross-sectional study, that worse SDOH was independently associated with worse cardiovascular health amongst prevalent American cancer survivors,(318) whilst chapter 4 extended this association to cardiovascular mortality in a prospective cohort study.(319) Chapter 3 explored psychological distress as a cardiovascular health determinant in greater detail, further showing that psychological distress was independently associated with all of the components of cardiovascular health except obesity.(147) Both chapters 2 and 3 found the associations to be significantly stronger in younger and female cancer survivors. The former finding was possibly because ageing had a much stronger impact on cardiovascular health in older individuals. The latter was possibly due to a combination of social factors (e.g. sexism(157)) and biological factors (e.g. lower vascular reactivity, effects of sex hormones, and more adverse effects of stress on endothelial function in females).(162) Although further mechanistic studies are needed to confirm these postulations, the subgroup analysis results identified young, female cancer survivors as the ones who may require and, by extension, benefit the most from social / psychological support, which would justify policies and social interventions specifically targeting these cancer survivors.

Both chapters 2 and 4 found economic stability, food insecurity, neighborhood, physical environment and social cohesion (NPESC), and psychological distress to be domains of SDOH which were particularly associated with worse cardiovascular health or higher risk of cardiovascular mortality. These were consistent with previous reports of similar associations in both non-cancer cohorts(106,157,320–323) and cancer survivors,(108–110,324–326) and were mechanistically plausible. Cancer can cause economic instability by increasing medical expenses and reducing one's physical ability to work. In turn, economic instability adversely impacts cardiovascular health and outcomes in multiple ways, including but not limited to preventing access to preventive cardiovascular care and cardio-oncology services, psychological distress, food insecurity, poorer living conditions, and having less time for exercising.(123) Food insecurity is likely a result of economic instability, and impacts cardiovascular health and outcomes by means of nutritional imbalances or deficiencies and increased intake of unhealthy food. NPESC, which concerns the natural, built, and social environment of one's neighbourhood, is often related to one's economic status and impacts health by affecting lifestyle risk factors (such as levels of physical activity, drinking, and smoking) and psychosocial stress.(327) More recent studies have also pointed to pollution levels, especially air pollution levels, as a mediator of the health effects of NPESC. A cohort study using data of over 5.5 million individuals from the United States' Surveillance, Epidemiology, and End Results Program found that every 10 $\mu g/m^3$ increase in the county-level long-term average fine particulate matter ($PM_{2.5}$) exposure was associated with a 32%

increase (95% confidence interval: 26%-39%) in the risk of cardiovascular mortality.(324) Such association is supported by previous studies showing that air pollution exposure increases systemic inflammation and oxidative stress, which are associated with the development of both cancer and cardiovascular diseases.(112)

Chapter 3 further explored the association between psychological distress and cardiovascular health in cancer survivors, with significant associations for all components of cardiovascular health except obesity. Psychological distress was specifically chosen amongst all the domains of SDOH as it appeared to be less discussed and explored. The observed associations had plausible underlying mechanisms both socially and biologically. Cancer may cause psychological distress due to the daunting and often life-changing nature of a cancer diagnosis, increased financial burden from cancer therapies and reduced ability to work, reduced quality of life due to cancer and/or cancer therapies, and, after remission, the fear for relapse. Some cancer therapies, such as chemotherapy, are also known to directly cause neurological changes in the brain which can lead to increased negative emotions.(328) On the other hand, psychological distress adversely impacts cardiovascular health by means of adverse associations with behavioural risk factors, as well as biological changes such as autonomic activation, increased cortisol secretion, and endothelial dysfunction.(175,176) Although the cross-sectional nature of the studies in chapters 2 and 3 predisposed to the possibility of reverse causation, results from chapter 4 strongly suggested that this did not drive the associations found in chapters 2 and 3, and that their directionality were likely correctly postulated. Interestingly, the association between psychological distress and cardiovascular health was weaker in cancer survivors than in the general population (i.e. participants in the National Health Interview Survey who did not have any history of cancer). This difference was possibly due to there being other factors that have greater impact on cardiovascular health in cancer survivors, such as cancer therapies and cancer diagnosis per se. Again, further studies are needed to confirm this postulation.

It is important to note that chapters 2-4 have a number of limitations. First, as aforementioned, chapters 2 and 3 were both cross-sectional studies, meaning that it was impossible to discern the directionality of associations, and that reverse causation was possible. This was partially mitigated by chapter 4 which consistently showed independent associations between SDOH and the risk of cardiovascular mortality in a longitudinal / cohort study, although differences in outcomes meant that the reverse causation cannot be ruled out in chapters 2 and 3. Second, all three chapters relied on data from NHIS which were self-reported, with the exception for mortality data (used in chapter 4 only) which were linked to the official National Death Index. Further disease-specific data, such as cancer staging and cancer therapies, were also unavailable. Unfortunately, due to the anonymous nature of NHIS data, it has not been possible for the NHIS diagnostic data to be validated against medical records, nor was it possible to extract linked diagnostic or prescription data, even though NHIS has been used extensively in cardiovascular and oncology research. These were the main reasons that findings from chapters 2-4 cannot be considered definitive. Third, in chapter 4, competing risks due to non-cancer and non-cardiovascular mortality could not be account for using Fine-Gray sub-distribution regression. This was purely due to software limitations, as there is no readily available

implementation of such analyses with survey-specific statistics in Stata and R. To this end, chapter 4 handled competing risks using the cause-specific hazards approach, which is the only choice available and has been used by other teams, including members of the National Center for Health Statistics of the United States.(189–191) Further developments in medical statistics and integration of relevant models into readily available statistical packages are needed before this issue can be overcome. Fourth, a large number of participants were excluded due to missing data in chapters 2-4. Nonetheless, missingness was largely due to random sampling of subsets for different questions in the NHIS, which meant that this was unlikely to substantially impact the representativeness of the findings. Fifth, all three chapters used the prevalent case design, i.e. including participants with prevalent cancer or history of cancer. As cancer and its treatments are likely to affect SDOH, changes in SDOH since the time of initial cancer diagnosis could not be ascertained and may bias the findings. Future studies using new case design, i.e. including patients and recording SDOH data at the point of cancer diagnosis, are required. Lastly, the observational nature of these studies precluded inference of causality, and the possibility of residual and unobserved confounding cannot be excluded.

13.1.1. Social factors: gaps, challenges, and future directions

Moving forward, there remain many gaps in the SDOH literature that need to be bridged. First, there is no standard definition of SDOH. The definition of SDOH used in chapters 2 and 4 was based on research done by the Kaiser Family Foundation,(134) which has also been used by others in previous works.(133,135) This differed slightly from the definition given by Healthy People 2030(102) – although both are relatively similar to the older Dahlgren-Whitehead model(329) and rather different from the framework set in 2008 by the World Health Organization, a multi-tiered system which is far more complex and less workable than the former definitions from an epidemiological research point of view.(330) This lack of standardized definition makes it difficult for researchers to build on one another's works, as well as increasing the difficulty for clinicians and non-expert readers to understand and act on these research findings. However, arriving at a standard definition of SDOH is not easy, if not impossible. As a socially based measure, SDOH inevitably varies between geographical regions and cultures, and is likely to change over time. For instance, whilst availability of health insurance may be an important SDOH in countries without universal healthcare such as the United States, it is unlikely to be as important in countries or regions with universal healthcare such as Hong Kong. Regarding temporal changes in SDOH definition, a case in point would be the relevance of access to internet booking of doctor appointments – this would not have been nearly as relevant 30 years ago as it is now. Additionally, even within the same region and culture, the importances of individual domains of social factors are most likely different between people, and it may be difficult to arrive at a representative and widely accepted definition that includes all domains of importance. Notwithstanding these challenges, future multinational research exploring the subjective and objective importance of different social factors in different regions will be helpful in bettering understanding of SDOH overall. Both qualitative and quantitative studies would be valuable in such efforts. Qualitative studies, which often involve structured interviews of subjects with open questions, can help identify factors that people from different cultural and sociodemographic backgrounds consider to be important in terms of quality of life, psychological well-being, and beyond. Meanwhile, quantitative studies, such as the ones included in this thesis, involve quantitative descriptions

and analysis of associations and effects, and are important in demonstrating the representativeness of proposed SDOH components (e.g. by means of large-scale surveys), as well as the effects of proposed SDOH components on key outcomes as validation (e.g. by means of large prospective cohort studies). Ultimately, it will likely require efforts from major, reputable, international organizations such as the World Health Organization to devise and set out universal definitions, possibly with separate factors with global and specific regional importance.

Second, which is related to the first point above, it is unclear how SDOH should be quantified. Whilst a large part of this is certainly due to the aforementioned problem with definitions, it remains a significant problem even within the context of specific sets of definitions. In most prior health-related research, domains of SDOH have been studied separately.(104–110) Although the concept of using a composite score to quantify SDOH in a single metric can be found in earlier work such as one by Röbl *et al* in 2013,(331) Figueroa *et al* first coined the term "polysocial risk score" in 2020,(143) with He *et al* and Javed *et al* subsequently publishing two of the first studies deriving outcome-specific (type 2 diabetes mellitus and atherosclerotic cardiovascular disease, respectively) polysocial risk scores in 2021.(138,332) This sort of composite score is potentially more attractive to clinicians as it condenses a person's SDOH into a single number, which can then be actioned upon depending on the predicted risk of an outcome – an algorithmic approach that is commonplace, or even standard, in many branches of medicine. Although these scores were statistical derived and validated with rigorous weighting for each SDOH domain, they were specific for their respective outcome and differed from each other significantly due to differences in outcomes, data source, SDOH definition, study design, and statistical models used. Meanwhile, chapters 2 and 4 also attempted to capture SDOH using a single, composite score, with each domain of SDOH comprising different numbers of one-point questions, which were then summed to derive the composite SDOH score. This was the most straightforward way of deriving a composite SDOH score. Although it neglected interactions between different domains of SDOH and the different importance of each SDOH domain, with the number of questions in each domain being directly proportional to the domain's influence on the composite score, it was arguably the only option available for the given scenario. Given that weightings and interactions are necessarily outcome- and context-dependent, models developed in prior studies for different outcomes in completely different populations cannot be used in chapters 2 and 4. Probably for similar reasons, the simple additive approach used in chapters 2 and 4 has also been used by other teams for similar purposes in different disease areas.(135,168,333–335) Whilst it was theoretically possible to statistically derive a polysocial risk score with weighted variables and interaction terms, the above already illustrates that such disease- and outcome-dependent approach is inviable, especially if such risk scores were to be proposed for widespread clinical usage, since it will be impossible to derive a separate model for each outcome of interest for each disease in each demographic / population of substantial significance. There is thus a need for future efforts to explore means to construct polysocial risk scores that are more widely applicable to different people with different diseases and from different regions – this certainly goes hand in hand with resolving the aforementioned issue with definitions. As such, the aforementioned approach of using qualitative studies to identify factors of specific importance

to certain subsets of individuals may be valuable in ensuring the construct validity of a polysocial risk score.

Third, there is a global lack of SDOH data for research usage. This is a particularly serious problem outside of North America and Oceania – as of March 2023, The Global Determinants of Health Dataset Aggregator identified 26 datasets with SDOH from North America, 15 from Oceania, 12 from Africa and Asia each, nine from Europe, and six from South America.(336) It is important to note that of these datasets, only one of the six datasets from Southa America (17%) had health outcomes available, contrasting North America and Oceania, for which 13 of 26 (50%) and 13 of 15 (87%) had such outcomes available, respectively. This imbalance in data availability possibility stemmed from a later recognition of SDOH in research in some regions, and more importantly, a lack of available funding and research infrastructure in certain regions. Such imbalance makes it difficult to understand the impact of SDOH thoroughly outside of North America and Oceania, and this underrepresentation of other regions may skew perception of the impact and actionability of different domains of SDOH. Future prospective studies with longitudinal follow-up for health outcomes in regions outside of North America and Oceania will be critically important. Collection of relevant variables and explorations have also been planned in my future studies with local institutions in Hong Kong concerning urological cancers and potentially other areas of interest in cardiology and cardio-oncology. Ideally, future SDOH-focused registries should be set up with recording of both SDOH data and medical data – both diagnostic and therapeutic data, as well as linkage to governmental death registries for death records and causes of death (as is the case for the Hong Kong data source used in chapters 5-11). The availability of such datasets will most likely boost research in SDOH, as well as allowing external validation of polysocial risk scores to ensure their content validity – something which has been extremely difficult due to the lack of viable datasets. Whilst a population-based registry of such sort may be difficult, utilizing complex survey designs may overcome this problem and generate a nationally or regionally representative dataset with reasonable amounts of resources. Examples of such surveys already exist in the NHIS, the data source for chapters 2-4 – in fact, a combination or linked dataset of the NHIS and the National Health and Nutrition Examination Survey, both of which are already linked to the national death index and multiple administrative healthcare databases, would be rather similar to what was suggested above. Unfortunately, this is not possible as of the time of writing, and efforts to build such registries remain to be undertaken.

13.2. Cancer factors and patient factors

Chapters 5-11 explored the cardiovascular burden of patients receiving specific cancer therapies, or cancer or patient factors which may be determinants of these patients' cardiovascular health or outcomes. These chapters made use of population-based electronic medical records data from Hong Kong and focused on patients with prostate cancer undergoing androgen deprivation therapy (ADT; chapters 5-9) or patients with cancer receiving immune checkpoint inhibitors (ICIs; chapter 10-12), both of whom are known to have significantly elevated cardiovascular risks due to the respective medications.

13.2.1. Androgen deprivation therapy

ADT is a cornerstone of prostate cancer treatment with proven oncological efficacy, and has been recommended by international societal guidelines.(194,240) The cardiovascular effects of ADT were primarily exerted through disruptions of the hypothalamic-pituitary-gonadal axis, with the loss of male sex hormones – which have protective effects on cardiovascular and metabolic functions – resulting in increased risks of diabetes, dyslipidaemia, and adverse cardiovascular events.(40,195) Whilst these cardiovascular events were mostly thought to be atherosclerotic in nature, with most studies therefore focusing on myocardial infarction and ischaemic stroke, emerging evidence has increasingly established that ADT increases the risk of heart failure as well.(337) Although this may be mediated by the atherosclerotic effects of ADT, it may also be a consequence of insulin resistance, which is both an established consequence of ADT(338,339) and a proven pathophysiological cause of heart failure.(340,341) Although many comparative studies have been performed to delineate the cardiovascular effects of ADT, very few have quantified the burden of cardiovascular events in patients receiving these medications, especially over long follow-up periods in non-Caucasian cohorts. This was the purpose of chapters 5 and 6, quantifying the cardiovascular burden in terms of the cumulative incidence of major adverse cardiovascular events (MACE), total and emergency cause-specific hospitalizations, and cause-specific mortality.(120,122) In addition to numerically estimating these burden, these studies also observed a relatively constant incidence rate of MACE and cardiovascular mortality, contrasting cancer mortality which plateaued around after 15 years. These suggested that the elevation in cardiovascular risk – though not demonstrable by chapters 5 and 6, this has been shown by prior studies – persists after the initiation of ADT, although this needs verification by large comparative studies with long-term follow-up. Clinically, these results may be useful for urologists and oncologists for discussing the pros and cons of ADT and other treatment options with patients with prostate cancer. This is possibly limited by the lack of control groups in these two chapters. However, given the well-established clinical indications of ADT, it would have been very difficult to identify appropriate and clinically meaningful patients as controls without incurring any bias by indication. It could be argued that alternative reporting metrics, such as standardized mortality rates, could have made interpretation easier. However, given that a diagnosis of cancer per se is associated with increased cardiovascular risks, and that patients with prostate cancer tend to be of substantially older age than the general population, standardization using age distributions in the general population would not have been particularly helpful. Meanwhile, the results supported the practice recommended by the European Society of Cardiology's (ESC) 2022 cardio-oncology guidelines, i.e. recommending indefinite annual cardiovascular risk assessment in patients receiving potentially cardiotoxic medications.(13)

As conceded by the said guidelines, however, long-term cardiovascular monitoring still requires further research, as the effectiveness of such practice remains to be proven. Whilst randomised controlled trials may be difficult to conduct due to ethical issues and the long follow-up required, it would be helpful to compare large prospective cohorts of patients with prostate cancer receiving ADT and long-term cardiovascular monitoring against historical data or similar patients elsewhere without long-term cardiovascular monitoring. This would not only allow examination of whether cases are detected and interventions given earlier, but also whether unnecessary follow-up investigations and treatments occurred due to false-positive

results, thereby allowing decision analyses and cost-effective analyses – both of which would inform whether these monitoring recommendations are justified. Nonetheless, for these studies to be effective in shaping practice and guidelines, concerted efforts by researchers worldwide in tackling this question using consensually defined measures and outcomes will facilitate systematic analysis of findings. This may require consensus documents or recommendation statements from internationally reputable professional societies of the relevant disciplines, potentially a collaboration of cardiovascular, oncological, and urological societies.

Chapters 7-9 explored patient or cancer factors that were associated with the risk of adverse cardiovascular events. Chapter 7 explored the associations between major cardiovascular comorbidities – which are patient factors – and the risk of adverse cardiovascular events.(342) This study was conducted in view of the lack of evidence pertaining to the prognosticators of cardiovascular events in patients with prostate cancer receiving ADT. The results showed, first, that the presence of any cardiovascular comorbidity was associated with the presence of other comorbidities, and, second and more crucially, the number of cardiovascular comorbidities present may be prognostically more important than the type of comorbidities present. Whilst these findings are not meant for guiding clinical practice directly, and so no evaluation / validation of model performance was performed, they provide important food for thought in future studies of cardiovascular risk stratification tool in these patients – an area in which research is sorely needed, as the currently recommended scores (e.g. SCORE2) have not been validated in patients receiving cancer therapies.(13) Many common cardiovascular risk stratification tools, such as PREVENT and SCORE2, consider a number of cardiovascular risk factors to compute an estimate of cardiovascular risk by means of sophisticated equations based on survival models.(244,343) This is also true for a number of risk scores more specific to cardiovascular medicine, such as the EuroSCORE II, the GARFIELD-AF score, and the SEX-SHOCK score.(344–346) These scores cannot be calculated manually, which arguably makes these scores less accessible and user-friendly in daily clinical practice, contrasting simpler integer-based scores such as HAS-BLED, qSOFA, and CHA_2DS_2-VASc which have remained widely used by physicians globally for their brevity and recommended by societal guidelines for their thorough validation.(347–349) The findings of chapter 7 suggested the possibility of considering the number of cardiovascular comorbidities as a candidate predictor in future risk stratification tools, in order to simplify the resultant model and facilitating clinical use. More broadly speaking, these findings hopefully raise clinicians' awareness of the influence of cardiovascular comorbidities on adverse cardiovascular events, potentially encouraging further research in this area.

However, large prospective cohorts will be required for the derivation of any risk stratification tool – regardless of the tool targeting specific subsets of patients with cancer or cancer survivors in general – with external validation in other cohorts. Contemporary cardiovascular risk scores such as SCORE2 may be referenced for their rigorous statistical methods. Particularly, the approach used by SCORE2 to handle the different baseline risk level of different geographical regions, i.e. by incorporating a "regional risk level" variable which changes the baseline risk of the estimation equation,(350) may be a viable solution to the issue of heterogeneity in cancer therapy-related cardiotoxicity between different classes of cancer therapies. In addition, recent

times have seen an increasing use of machine learning techniques in cardio-oncology.(351) With their ability to find obscure patterns in large amounts of data and handle high-level interactions, machine learning techniques may improve the performance of cardiovascular risk scores in patients with cancer. That said, the selection of predictor variables still requires clinical and biological plausibility, meaning that a purely data-driven approach to risk score derivation may not be ideal. Machine learning also commonly produces "black box" models, meaning that the constituent equations and coefficients are not explicitly known, which severely hampers efforts to externally validate such models. Additionally, as discussed above, sophisticated equations may not be as pragmatic to clinicians, which further suggests that models derived purely from machine learning may be realistically suboptimal. Overall, any cardiovascular risk stratification tool for patients with cancer will need to balance model performance, generalizability, and operational simplicity and approachability for it to be clinically useful.

Chapter 8 explored visit-to-visit variability in glycated haemoglobin (HbA1c; VVHV), which is a patient factor, as a potential marker of cardiovascular risk in ADT users.(352) Most studies had only studied point measurements of glycaemic control; VVHV might offer another means of evaluating glycaemic control with consideration of longitudinal changes, which is of interest in these patients due to the known metabolic effects of ADT.(195) The study showed an increase in VVHV after ADT initiation, with higher post-initiation VVHV being associated with higher risks of MACE. The subgroup findings – which showed that baseline use of antidiabetic medications reduced changes in VVHV – may suggest that it is a treatable target. This is consistent with a *post hoc* analysis of the EMPA-REG OUTCOME trial, which found that empagliflozin significantly reduced VVHV.(353) However, the same study found that the cardiovascular benefits of empagliflozin in these patients were not mediated by reductions in VVHV, meaning that VVHV may be a marker of glycaemic control but not a treatment target per se.(353) Also importantly, the mechanisms and determinants of VVHV have remained unclear despite studies in numerous other conditions.(249–253) These uncertainties warrant further mechanistic and clinical studies.

Aside from highlighting the relevance of serial glycaemic monitoring using HbA1c – as recommended by the ESC(13) – the findings may suggest that serial measurement of other cardiometabolic markers should be explored as prognosticators too, e.g. troponin and lipids, the latter of which has been studied extensively in other conditions and shown to be associated with the risk of multiple adverse cardiovascular outcomes.(354–356) That said, there remains no standard measure of variability, with the coefficient of variation, standard deviation, and average real variability having been used in different studies.(249–253,352,354–356) A prognostically powerful, computationally simple, and interpretatively intuitive measure of variability will be ideal for clinical use, but it remains to be identified and validated. Meanwhile, as mentioned above, empagliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i), has been shown to reduce VVHV.(353) The same class of medications have been shown to be associated with reductions in the risk of cardiovascular events in patients with prostate cancer and diabetes mellitus.(357,358) Whilst SGLT2i is not routinely recommended for patients with prostate cancer at the moment, this may suggest VVHV as a marker of response to

cardioprotective or cardiometabolic treatments, especially in patients with diabetes mellitus, or as a marker of residual cardiovascular risk despite such treatments. If true, this may allow more personalized and effective titration of cardiometabolic medications. That said, the above hypothesis needs to be proven using high quality data, preferably from prospective cohorts to ensure freedom from bias by indication and information bias.

Chapter 9 compared the cardiovascular risks associated with gonadotropin-releasing hormone (GnRH) agonists and antagonists, which is an example of cancer factors that influence cardiovascular outcomes.(359) GnRH agonists were postulated to be associated with higher cardiovascular risks mainly due to initial increases in androgen levels, as well as activation of GnRH receptors on CD3-positive T cells in atherosclerotic plaques which heightens inflammation and hence the risk of plaque progression or rupture and cardiovascular events.(360,361) Initial clinical evidence from oncological trials supported this, but the first trial designed specifically to investigate this issue, the PRONOUNCE trial, was underpowered after it was terminated due to slow enrolment and lower-than-expected event rates, with the published analyses showing no significant differences in MACE between degarelix (a GnRH antagonist) and leuprolide (a GnRH agonist).(95) The study observed no significant differences between degarelix and GnRH agonists in the short-term – which was consistent with PRONOUNCE(95) – but significantly higher cardiovascular risks with GnRH agonists in the long-term. Specifically, these differences were observed in those with known cardiovascular risk factors, but not in those without. Previous observational studies had also observed higher cardiovascular risks in GnRH agonist users,(362) contrasting a meta-analysis of oncological trial data which has found the opposite.(363) This was usually attributed to bias by indication, i.e. GnRH antagonists being preferentially given to those with higher cardiovascular risk in real-world practice. Although this remains a strong possibility here, it was largely mitigated by the use of inverse probability treatment weighting which balanced numerous baseline characteristics between the treatment arms (degarelix and GnRH agonists), including many cardiovascular comorbidities and risk factors.

Chapter 9 also highlighted the need to study the long-term effects of these medications. It was noteworthy that previous trials, including PRONOUNCE, were mostly limited to one year of follow-up, meaning that the long-term cardiovascular effects of these medications remain largely unexplored in trials.(363) Although an increase in long-term cardiovascular risk despite contrasting short-term observational data and neutral short-term trial results may appear somewhat unintuitive, one must bear in mind that our current understanding of the pathophysiological basis of the cardiovascular effects of GnRH agonists and antagonists is patchy at best. Aside from GnRH agonists and antagonists, other agents used for pharmacological ADT – which are often lumped together in the cardio-oncology, oncology and urology literature – have also been observed to have different cardiovascular effects, even those within the same class (e.g. enzalutamide and abiraterone, both androgen receptor signalling inhibitors(56)). Overall, this points to the need for more granular understanding of the cardiovascular effects of individual agents within each class of cardiotoxic cancer therapy.

13.2.2. Immune checkpoint inhibitors

The adverse cardiovascular effects of ICIs result from immune activations and heightened inflammatory processes.(364) The most lethal and thus most studied event is myocarditis, but emerging evidence suggests that ICIs accelerate atherosclerosis and thus potentially increase longer-term cardiovascular risks, with likely mechanisms including T cell activation and inhibition of atherosclerotic downregulators such as PD-1, PD-L1 and CTLA4 which are direct targets of ICIs.(365–367) Similar to chapter 5, chapter 10 quantified the burden of MACE in patients with cancer receiving ICIs,(121) observing that over three-fourths of MACE occurred within one year of initiating ICIs, with the cumulative incidence curve tapering at approximately the two-year mark. Similarly, the cardiovascular hospitalization rate was also highest within the first year. These finding highlighted that, despite the above postulation of longer-term cardiovascular effects, there only appeared to be a short-term spike in cardiovascular burden. Chapter 11 further extended this investigation of the temporality of cardiovascular effects, focusing on myocardial infarction(51) – whilst Drobni *et al* had shown that ICI use increases the risk of MI, that study gave little information about the timing of MI and whether the effects were acute or chronic in nature.(42) Making use of a self-controlled case series design to overcome the issue that is the lack of a control group, Chapter 11 found the risk of MI to be significantly increased only in the 90 days after initiation, but not later, with the point estimate of incidence rate ratio declining to almost 1.0 in the post-exposure period. Although the study was limited by a small sample size, the point estimates and confidence intervals strongly suggested that a clinically meaningful increase in the risk of MI was unlikely at least after ICI exposure. Overall, the findings from chapters 10 and 11 provided insights into when patients are at the most risk of cardiovascular events and, thus, are in the greatest need for relevant monitoring.

The 2022 ESC guidelines recommended cardiovascular monitoring after ICI initiation by means of electrocardiogram and troponin levels every cycle for the first four cycles, and then the same with routine cardiometabolic assessment every three cycles thereafter.(13) Whilst our results largely supported this schedule, this schedule of cardiovascular monitoring remains to be validated for efficacy and cost-effectiveness. These modalities of cardiovascular monitoring are also unlikely to be effective for other events such as heart failure and pericarditis. Although it may be argued that these conditions are largely diagnosed based on clinical history, patients receiving ICI often suffer from multiple comorbid conditions with longstanding physical illnesses, such that new symptoms of these cardiovascular conditions may go unnoticed or dismissed easily by both the patient and treating physician. This means that cardiovascular monitoring for these conditions may be helpful, but this requires further work on the temporality of these conditions, as well as studies of the best modalities for monitoring these conditions cost-effectively.

Meanwhile, the logical follow-up questions to our finding that ICI increases the risk of MI, and more broadly to the well-known observation of ICI-related myocarditis, is how to identify patients at high risk of these acute adverse cardiovascular events, and how to prevent these events. Some studies have already tried to explore risk factors of ICI-related myocarditis, but efforts thus far have largely been hampered by the rarity of these events. Thus far, combination

ICI therapy appears to be the only risk factor consistently demonstrated to be associated with particularly high risks of myocarditis,(286,368) a findings which others have extended to cardiovascular adverse events in general.(295) Indeed, studying cardiovascular adverse events as a composite outcome can increase statistical power and provide a broader view of the cardiovascular risks associated with ICI use, but disaggregating these events may have its merits in allowing characterization of conditions with different underlying pathophysiology and, in the case of myocarditis, substantially different outcomes. Realistically, the former is well-suited for retrospective analysis of electronic medical records data, as was done in chapter 10, where the lower data granularity is of relatively low importance. To study risk factors for disaggregated outcomes such as myocarditis, large prospective cohorts with detailed clinical, biochemical and even histopathological / postmortem examinations are needed, which, given the rarity of such events, will require international registries. Meanwhile, prevention of these events will likely require understanding their risk factors, as well as the pathophysiological nature of these events. Whilst ICI-related myocarditis is known to be immune-mediated, it is less clear-cut for MI occurring in patients receiving ICI. Whilst immune-mediated accelerated atherosclerotic progression has been a strong contender for being a mediator of MI in these patients,(42,369) others have suggested vasculitis and coronary artery vasospasm as possible causes of MI in these patients.(370–372) These would imply different agents as potentially protective against MI in these patients. For instance, plaque-stabilizing agents such as statins may be effective if accelerated atherosclerosis is indeed the predominant pathophysiological pathway, while dihydropyridine calcium channel blockers may be effective if vasospasm plays a key role. Nonetheless, the low incidence rates of these events imply that routine prescription of any cardioprotective agent may not be beneficial or cost-effective, which again emphasizes the need to identify patients at high risk of these events. Although the 2022 ESC guidelines recommended the HFA-ICOS risk stratification tool, the relevant supporting evidence levels were relatively low, representing a persistent need for further studies.(13,71) As aforementioned, international registries may enable derivation and validation of better risk stratification tools for patients receiving ICI, which have the potential to be the stepping stone for further studies – trials even – of cardioprotective agents for these patients.

13.2.3. Limitations of chapters 5-11 and broader relevance

Chapters 5-11 shared the same source of data and thus shared a number of major limitations. First, there was no data on cancer staging and histology, which may have biased findings especially in comparative studies such as chapter 9. Second, data for some important cardiovascular risk factors, such as smoking status and body-mass index were not available. To minimize this limitation, an extensive list of cardiometabolic comorbidities and medications were included as covariates in adjusted analyses to remove confounding effects as much as possible. Third, it was not possible to adjudicate the recorded diagnoses and outcomes, and coding error was possible. Nonetheless, the data source had been used extensively in prior studies,(373) with some studies having validated specific diagnostic codes and outcomes, including cardiovascular ones.(225,236,311) All data were also extracted from electronic medical records automatically recorded from input by the patients' treating clinical teams, with access restrictions and anonymization rendering it impossible for users of the data source to alter the data individually. Fourth, for non-descriptive studies (chapters 7-9 and 11), the

observational nature precluded the inference of causality, and residual or unobserved confounding remains a potential issue.

Aside from the treatment-specific implications mentioned above, chapters 5-11 highlighted angles in which future studies can tackle gaps in the cardio-oncology literature. For instance, thorough descriptive studies are valuable in bettering understanding of the natural history and health burden of patients at risk of cardio-oncology issues. Though not specifically explored in this thesis, descriptive studies will be especially valuable for patients with cancer who have cardiovascular comorbidities, as they are commonly excluded from oncological trials.(374) Such studies have the potential of bettering understanding of the temporal progression of comorbidities and frailty in these patients, which are complex and may inform further studies of interventions and strategies aimed at slowing such progression. Besides, the exploration of VVHV in chapter 8 highlighted the potential utility of more novel cardiometabolic metrics – derived from measurements readily available from routine follow-up – in cardiovascular risk stratification of patients with cancer. However, there is often a lack of thorough understanding of the determinants of these novel cardiometabolic metrices, as well as the mediating pathways of their associations with outcomes. These need to be clarified before these metrices can be interpreted meaningfully with physiological implications and thus used clinically. A good example is visit-to-visit lipid variability (VVLV), which is conceptually similar to VVHV but concerns lipids instead of HbA1c. Despite extensive studies demonstrating strong associations between VVLV and adverse cardiovascular outcomes,(356,375–378) amongst other outcomes such as cancer,(379) VVLV has not seen any meaningful clinical use, largely due to uncertainties over its physiological meaning and implications, as well as whether it is a treatable target. To this end, I recently led a study using prospective data from the United States' Multi-Ethnic Study of Atherosclerosis and demonstrated that the aforementioned prognostic associations observed for VVLV may not be explained entirely by the atherogenic properties of lipids, and may be related to inflammation.(380) Whilst the results were by no means conclusive and only provided limited mechanistic insights into the implications of VVLV, I believe this was a step in the right direction. Further studies similarly aimed at understanding the mechanistic underpinnings of VVHV and other novel cardiometabolic metrices in both cancer survivors and other populations are warranted.

Meanwhile, the comparison between GnRH agonists and antagonists in chapter 9 highlighted the need to better understand intra-class differences in adverse event profiles, which has been suggested to be applicable to ICIs,(281) tyrosine kinase inhibitors,(381) and anthracyclines(382) as well. These medications are often lumped together in cardio-oncology studies with the presumption of a homogeneous class effect. Larger registries are likely required to overcome this issue though, as often there is insufficient sample sizes when splitting a cohort by the specific agents used, as was the case in chapters 10-11. Furthermore, chapter 11 illustrated the potential of novel study designs in cardio-oncology research, as they often offer unique advantages over more traditional / conventional designs (e.g. cohort studies, case-control studies). For instance, self-controlled case series, as used in chapter 11, only require patients who developed the outcome of interest, increasing efficiency and reducing the time, effort and resources required for building a large cohort. The self-controlled nature also meant

that time-invariant confounders were inherently eliminated.(383) Such design is useful in cases where a clinically meaningful and fair control group is difficult to identify, or where bias by indications is difficult to overcome in a cohort design – a common scenario in cardio-oncology research.

13.3. Holistic research in cardio-oncology

Although this critical analysis and discussion has addressed social factors and cancer and patient factors separately, there is no doubt that these factors are intertwined, influencing each other and impacting cardiovascular health and outcomes in complex manners. As a field, it will be important for studies in cardio-oncology to address all these factors comprehensively and systematically. For instance, beyond conducting association studies to identify risk factors and determinants of cardiovascular health and outcomes, future studies should move on to investigating whether these risk factors are true treatment targets, meaning that they are modifiable, and that modifications translate into benefits in terms of health measures or clinical outcomes. This will initially require large prospective cohort studies with sufficiently granular data, before eventually involving well-designed RCTs that are inclusive and representative of the relevant clinical populations – inclusivity and representation have been identified as key problems in cardio-oncology RCTs in the US.(374) Regardless of study design though, there remains a need for prospective cardio-oncology studies outside of the US,(12) especially ones with longer follow-up periods – the recently initiated Global Cardio Oncology Registry is a good first step in this direction.(384)

Meanwhile, study outcomes should be specified carefully, especially in RCTs and with greater consideration given to clinical relevance. Some of the most prominent cardio-oncology trials, such as the PREVENT and STOP-CA trials,(82,83) used imaging measurements (left ventricular ejection fraction in both of these trials) as the primary outcome. Whilst this ensured statistical power, the detected differences in left ventricular ejection fraction (<10% absolute differences) were of questionable clinical significance, and although a low left ventricular ejection fraction is well-established as a predictor of poorer cardiovascular outcomes, it differs significantly in clinical meaning from more established outcomes such as MACE. On the other hand, symptomatic or quality of life measures are clinically important and warrant studying formally as an outcome in cardio-oncology RCTs. These may include "softer" cardiovascular outcomes, such as cardiovascular hospitalizations, which significantly impact patients' quality of life, and were explored in chapters 6, 7, and 10. However, combining patient-reported metrics with conventional, "hard" events is methodologically challenging, as symptomatic or quality of life measures are typically repeated measures, while MACE and other similar "hard" events are typically time-to-event outcomes. Whilst at least one model has been developed to combine repeated measures and time-to-event outcomes, it assumes that the repeated measures and time-to-event components are equivalent in importance, which is almost never the case in medicine.(385) A potential solution to this issue is the use of the win ratio, a relatively novel analytic technique formally published by Pocock *et al* in 2012 based on the Finkelstein-Schoenfield test, which allows hierarchization of composite endpoints and accommodates different types of outcomes (such as the scenario of repeated measures and time-to-event outcomes above) in the same composite endpoint.(386) The win ratio allows estimation of the

likelihood of the treatment arm "winning", i.e. doing better overall, than the comparator arm, which is a clinically intuitive interpretation. This analytic approach has been adopted by a number of landmark cardiovascular trials, such as ATTR-ACT,(387) ATTRibute-CM,(388) EMPULSE,(389) and TRILUMINATE,(390) and the seminal paper by Pocock *et al* described applications in the observational context as well.(386) Although there are potential issues with refinements being made continually,(391,392) the win ratio approach remains to have immense potential in the cardio-oncology sphere.

Nonetheless, methodological challenges aside, studies on functional, mental and social well-being will benefit from collaborations with allied health professionals, as these areas are out of the scope of expertise of many clinician-scientists in the field of cardio-oncology. Similarly, it will be important to increase patient involvements in cardio-oncology research – this not only empowers patients, but it also allows patients to draw from their lived experience to guide the development of patient-reported outcomes (such as the aforementioned symptomatic and quality-of-life measures). Studies have shown that despite logistical tradeoffs, increased patient engagement was helpful in ensuring the relevance of study outcomes, improving study enrollment and retention, and facilitating dissemination of research findings to the wider patient population,(393–396) with the potential of ultimately increasing the likelihood of making real-life impacts. Overall, patient engagement in cardiovascular studies remains in working progress, and such efforts are certainly warranted in the cardio-oncology sphere.

13.4. Translating research into practice

As important as it is to push the field and make progress in research, it is crucial to translate research into practice. This was part of the aim of chapter 5, where temporal trends in MACE and mortality were examined in patients with prostate cancer receiving ADT,(122) as well as chapter 12, which built on the same theme to examine the temporal trends in the completeness of guideline-recommended cardiometabolic testing prior to ICI initiation in addition to trends in MACE.(188) Concerningly, chapter 5 revealed that although the all-cause mortality rate has been declining, the risk of MACE has increased with time even in competing risk analysis where non-cardiovascular mortality was accounted for as a competing event. Importantly, those who were initiated on ADT more recently had more cardiovascular risk factors or comorbidities. This suggested that the increase in the risk of MACE was unlikely to have been explainable by the improved survival; instead, it was possibly due to a slow shift in the cardiovascular risk profile of patients receiving ADT. Meanwhile, chapter 12 observed that even though the completeness of pre-ICI cardiometabolic testing improved over time, overall completeness of such testing remained poor, and the improvement in completeness did not meaningfully impact the risk of MACE.

Despite the limitations inherent to the source of data (as previously discussed, such as the possibly of miscoding), both chapters highlighted that there remains much to be done to improve cardiovascular health and outcomes in these specific patients with cancer, despite the evident advancements in cardio-oncology in recent years. In the grand scheme of medicine, research is only the first step towards improving health and outcomes, and translating research

into practice requires policymakers to allocate sufficient resources, clinicians (including allied health professionals) to be educated and to implement and advocate for evidence-based practice, administrators to facilitate these changes in practice wherever needed, and patients to be educated and supported physically, mentally, and socioeconomically. Many hurdles need to be overcome to be able to provide holistic and equitable multidisciplinary care to patients with cancer. Moving forward, similar studies will be important for monitoring progress and identifying gaps and opportunities that ought to be addressed. To facilitate reporting and harmonize research findings to improve their comparability and generalizability, the ESC has published a list of quality indicators for the prevention and management of cancer therapy-related cardiovascular toxicity in cancer treatment,(309) while the International Cardio-Oncology Society and the American College of Cardiology have recently called for further work in this area.(397) Future studies should make use of these quality indicators where possible. Of course, aside from monitoring progress, as chapter 12 did, it is equally, if not more important to study ways of implementing guideline-recommended and evidence-based cardio-oncology practice in the real world. Cardio-oncology is one of the fastest-growing fields in cardiovascular medicine,(12) and frequent changes in practice according to the latest guidelines and evidence can be difficult and can sometimes interrupt pre-exiting work flows. Implementation research exploring the barriers for clinicians to follow the latest guidelines and evidence in day-to-day practice and optimizing ways to roll out updated clinical workflows will be important for translating research into practice.

14. Appendices

14.1. Appendices for Chapter 2

14.1.1. Supplementary tables for Chapter 2

Supplementary Table 14.1 Components of the social determinants of health score

Shorter version of survey items	Longer version of survey items	Survey Responses	Analytic recode
ECONOMIC STABILITY			
Employment	What was your employment status as of last week?	Working for pay at a job or business; With a job or business but not at work; Looking for work; Working, but not for pay, at a family-owned job or business; Not working at a job or business and not looking for work	0 = "Employed or Retired"; 1 = "Never or Previously Employed"
Sick Leave	Paid sick leave at current job or most current job	Yes; No	0 = "Yes"; 1 = "No"
Family Income	Ratio of family income to poverty threshold		0 = "Middle/High-income" (≥ 200% of poverty threshold); 1 = "Low-income" (< 200% of poverty threshold)
Any Difficulty Paying Medical Bills	In the past 12 months did you/anyone in the family have problems paying or were unable to pay any medical bills? Include bills for doctors, dentists, hospitals, therapists, medication,	Yes; No	0 = "No"; 1 = "Yes"

	equipment, nursing home or home care.		
Unable to Pay Medical Bills	If previous question = Yes: Do you/Does anyone in your family currently have any medical bills that you are unable to pay at all?	Yes; No	0 = "No"; 1 = "Yes"
Cost-related medication non-adherence (positive if any of the following 3 questions' answer was Yes):			
… Skipped medication doses to save money	During the past 12 months, were any of the following true for you? …You skipped medication doses to save money	Yes; No	0 = "No"; 1 = "Yes"
… Took less medicine to save money	During the past 12 months, were any of the following true for you? …you took less medicine to save money	Yes; No	0 = "No"; 1 = "Yes"
… Delayed filling prescription to save money	During the past 12 months, were any of the following true for you? …You delayed filling a prescription to save money	Yes; No	0 = "No"; 1 = "Yes"
Delayed/Foregone Care due to Cost (positive if any of the following 2 questions' answer was Yes):			
Delayed Care due to Cost	During the past 12 months, has medical care been delayed for because	Yes; No	0 = "No"; 1 = "Yes"

	of worry about the cost? (Do not include dental care)		
Foregone Care due to Cost	During the past 12 months, was there any time when needed medical care, but did not get it because couldn't afford it?	Yes; No	0 = "No"; 1 = "Yes"
High Financial Distress Composite Score (aggregate score from the following 6 questions);			From the aggregate sum of the following 6 items, divided into quartiles:
Worried about …			0 = quartiles 1-3; 1 = quartile 4
… Money for retirement	How worried are you right now about not having enough money for retirement?	Very worried; Moderately worried; Not too worried; Not worried at all	0 = "Not too worried/Not worried at all"; 1 = "Mod/Very worried"
… Medical costs of illness/accident	How worried are you right now about not being able to pay medical costs of a serious illness or accident?	Very worried; Moderately worried; Not too worried; Not worried at all	0 = "Not too worried/Not worried at all"; 1 = "Mod/Very worried"
… Maintaining standard of living	How worried are you right now about not being able to maintain the standard of living you enjoy?	Very worried; Moderately worried; Not too worried; Not worried at all	0 = "Not too worried/Not worried at all"; 1 = "Mod/Very worried"

… Medical costs of healthcare	How worried are you right now about not being able to pay medical costs for normal healthcare?	Very worried; Moderately worried; Not too worried; Not worried at all	0 = "Not too worried/Not worried at all"; 1 = "Mod/Very worried"
… Paying monthly bills	How worried are you right now about not having enough to pay your normal monthly bills?	Very worried; Moderately worried; Not too worried; Not worried at all	0 = "Not too worried/Not worried at all"; 1 = "Mod/Very worried"
… Paying rent/mortgage/housing costs	How worried are you right now about not being able to pay your rent, mortgage, or other housing costs?	Very worried; Moderately worried; Not too worried; Not worried at all	0 = "Not too worried/Not worried at all"; 1 = "Mod/Very worried"
NEIGHBOURHOOD, PHYSICAL ENVIRONMENT AND SOCIAL CONTEXT			
House Tenure	Is this house/apartment owned or being bought, rented, or occupied by some other arrangement by [you/or someone in your family]?	Owned or being bought; Rented; Other arrangement	0 = "Own or being bought"; 1 = "Rent/Other arrangement"
Neighborhood Quality (Help)	How much do you agree or disagree with the following statements about your neighborhood? Would you say… People in this neighborhood help each other out.	Definitely agree; Somewhat agree; Somewhat disagree; Definitely disagree	0 = "Agree (Somewhat/Definitely)"; 1 = "Disagree (Somewhat/Definitely)"

Neighborhood Quality (Trust)	How much do you agree or disagree with the following statements about your neighborhood? Would you say… People in this neighborhood can be trusted.	Definitely agree; Somewhat agree; Somewhat disagree; Definitely disagree	0 = "Agree (Somewhat/Definitely)"; 1 = "Disagree (Somewhat/Definitely)"
Neighborhood Quality (Close Knit)	How much do you agree or disagree with the following statements about your neighborhood? Would you say… This is a close-knit neighborhood.	Definitely agree; Somewhat agree; Somewhat disagree; Definitely disagree	0 = "Agree (Somewhat/Definitely)"; 1 = "Disagree (Somewhat/Definitely)"
Neighborhood Quality (Accountability)	How much do you agree or disagree with the following statements about your neighborhood? Would you say… There are people I can count on in this neighborhood.	Definitely agree; Somewhat agree; Somewhat disagree; Definitely disagree	0 = "Agree (Somewhat/Definitely)"; 1 = "Disagree (Somewhat/Definitely)"
COMMUNITY AND SOCIAL CONTEXT			
Kessler K6 Scale for High Psychological Distress (derived from the following 6 questions):			From the aggregate sum of the following 6 items: 0 = "No psychological distress" (sum ≤ 12); 1 = "Psychological distress" (sum ≥ 13)

… Feeling sad	During the past 30 days, how often did you feel …so sad that nothing could cheer you up?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	0 = "None of the time"; 1 = "A little of the time"; 2 = "Some of the time"; 3 = "Most of the time"; 4 = "All of the time"
… Nervous	During the past 30 days, how often did you feel … nervous?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	0 = "None of the time"; 1 = "A little of the time"; 2 = "Some of the time"; 3 = "Most of the time"; 4 = "All of the time"
… Restless/fidgety	During the past 30 days, how often did you feel … restless or fidgety?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	0 = "None of the time"; 1 = "A little of the time"; 2 = "Some of the time"; 3 = "Most of the time"; 4 = "All of the time"
… Restless/fidgety	During the past 30 days, how often did you feel … restless or fidgety?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	0 = "None of the time"; 1 = "A little of the time"; 2 = "Some of the time"; 3 = "Most of the time"; 4 = "All of the time"

… Hopeless	During the past 30 days, how often did you feel … hopeless?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	0 = "None of the time"; 1 = "A little of the time"; 2 = "Some of the time"; 3 = "Most of the time"; 4 = "All of the time"
… Everything was an effort	During the past 30 days, how often did you feel … that everything was an effort?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	0 = "None of the time"; 1 = "A little of the time"; 2 = "Some of the time"; 3 = "Most of the time"; 4 = "All of the time"
… Worthless	During the past 30 days, how often did you feel … worthless?	All of the time; Most of the time; Some of the time; A little of the time; None of the time	0 = "None of the time"; 1 = "A little of the time"; 2 = "Some of the time"; 3 = "Most of the time"; 4 = "All of the time"
FOOD			
Food Insecurity (based on US Dept. of Agriculture Standardized Questionnaire)			From the aggregate sum of the following 10 items: 0 = "Food Secure" (sum ≤ 2); 1 = "Food Insecure" (sum ≥ 3)

… Worried food would run out before got money to buy more	[fill 2: I/We] worried whether [fill 3: my/our] food would run out before [fill 4: I/we] got money to buy more. Was that often true, sometimes true, or never true for [fill 1: you/your family] in the last 30 days?	Often true; Sometimes true; Never true	0 = "Never true"; 1 = "Sometimes true/Often true"
… Food did not last before had money to get more	The food that [fill 1: I/we] bought just didn't last, and [fill 1: I/we] didn't have money to get more. Was that often true, sometimes true, or never true for [fill 2: you/your family] in the last 30 days?	Often true; Sometimes true; Never true	0 = "Never true"; 1 = "Sometimes true/Often true"
… Could not afford to eat balanced meals	[fill 1: I/We] couldn't afford to eat balanced meals. Was that often true, sometimes true, or never true for [fill 2: you/your family] in the last 30 days?	Often true; Sometimes true; Never true	0 = "Never true"; 1 = "Sometimes true/Often true"
… Cut size or skipped meals because not enough money	In the last 30 days, did [fill 1: you/you or other adults in your family] ever cut the size of your meals or skip meals because there wasn't enough money for food?	Yes; No	0 = "No"; 1 = "Yes"
… If above question = Yes: How many days in past month?	In the last 30 days, how many days did this happen?	01-30 days (continuous response)	0 = if < 3 days; 1 = if ≥ 3 days

… Eat less than felt should because not enough money	In the last 30 days, did you ever eat less than you felt you should because there wasn't enough money for food?	Yes; No	0 = "No"; 1 = "Yes"
… Hungry but did not eat because not enough money	In the last 30 days, were you ever hungry but didn't eat because there wasn't enough money for food?	Yes; No	0 = "No"; 1 = "Yes"
… Lose weight because not enough money for food	In the last 30 days, did you lose weight because there wasn't enough money for food?	Yes; No	0 = "No"; 1 = "Yes"
… Not eat for a whole day because not enough money for food	In the last 30 days, did [fill 1: you/you or other adults in your family] ever not eat for a whole day because there wasn't enough money for food?	Yes; No	0 = "No"; 1 = "Yes"
… If above question = Yes: How many days in past month?	In the last 30 days, how many days did this happen?	01-30 days (continuous response)	0 = if < 3 days; 1 = if ≥ 3 days
EDUCATION			
English Language	How well do you speak English?	Very well; Well; Not well; Not at all	0 = "Well/Very Well"; 1 = "Not well/Not at all"
Education Attainment	What is the HIGHEST level of school completed or the highest degree received?	Never attended/kindergarten only; 1st grade; 2nd grade; 3rd grade; 4th grade; 5th grade; 6th grade; 7th grade; 8th grade; 9th grade; 10th grade; 11th grade; 12th grade; GED or equivalent; High school graduate; Some college, no degree; Associate degree: occupational, technical, or vocational program;	0 = "≥ Some college"; 1 = "≤ High School"

		Associate degree: academic program; Bachelor's degree; Master's degree; Professional school degree; Doctoral degree	
Health Information Technology use: Looked up health info on internet	DURING THE PAST 12 MONTHS, have you ever used computers for any of the following …Look up health information on the Internet	Yes; No	0 = "No"; 1 = "Yes"
Health Information Technology use: Filled a prescription online	DURING THE PAST 12 MONTHS, have you ever used computers for any of the following …Fill a prescription	Yes; No	0 = "No"; 1 = "Yes"
Health Information Technology use: Scheduled a healthcare appointment online	DURING THE PAST 12 MONTHS, have you ever used computers for any of the following …Schedule an appointment with a health care provider	Yes; No	0 = "No"; 1 = "Yes"
Health Information Technology use: Communicated with healthcare provider online	DURING THE PAST 12 MONTHS, have you ever used computers for any of the following …Communicate with a health care provider by email	Yes; No	0 = "No"; 1 = "Yes"
Health Information Technology use: Used	DURING THE PAST 12 MONTHS, have you ever used computers for any	Yes; No	0 = "No"; 1 = "Yes"

internet chat rooms to learn about health topics	of the following …Use online chat groups to learn about health topics		
HEALTHCARE SYSTEM			
Insurance Status	Multiple questions	Uninsured; Private; Medicaid; Medicare; Other	0 = "Uninsured"; 1 = "Insured"
Usual Source of Care	Is there a place that you USUALLY go to when you are sick or need advice about your health?	Yes; There is no place; There is more than one place	0 = "Usual source of care"; 1 = "No usual source of care"
Trouble finding a doctor/provider, past 12m	DURING THE PAST 12 MONTHS, did you have any trouble finding a general doctor or provider who would see you?	Yes; No	0 = "No"; 1 = "Yes"
MD's office not accept you as new patient, past 12m	DURING THE PAST 12 MONTHS, were you told by a doctor's office or clinic that they would not accept you as a new patient?	Yes; No	0 = "No"; 1 = "Yes"
MD's office not accept your insurance, past 12m	DURING THE PAST 12 MONTHS, were you told by a doctor's office or clinic that they did not accept your health care coverage?	Yes; No	0 = "No"; 1 = "Yes"
Delayed Medical Care: Couldn't get through on phone	There are many reasons people delay getting medical care. Have you delayed getting care for any of the following reasons in the PAST 12	Yes; No	0 = "No"; 1 = "Yes"

	MONTHS? ..... You couldn't get through on the telephone		
Delayed Medical Care: Couldn't get appt soon enough	There are many reasons people delay getting medical care. Have you delayed getting care for any of the following reasons in the PAST 12 MONTHS? ..... You couldn't get an appointment soon enough	Yes; No	0 = "No"; 1 = "Yes"
Delayed Medical Care: Wait too long at MD's office	There are many reasons people delay getting medical care. Have you delayed getting care for any of the following reasons in the PAST 12 MONTHS? ..... Once you get there, you have to wait too long to see the doctor	Yes; No	0 = "No"; 1 = "Yes"
Delayed Medical Care: Not open when you could go	There are many reasons people delay getting medical care. Have you delayed getting care for any of the following reasons in the PAST 12 MONTHS? ..... The clinic/doctor's office wasn't open when you could get there	Yes; No	0 = "No"; 1 = "Yes"
Delayed Medical Care: No transportation	There are many reasons people delay getting medical care. Have you delayed getting care for any of the following reasons in the PAST 12	Yes; No	0 = "No"; 1 = "Yes"

	MONTHS? ..... You didn't have transportation		
Quality of Care (Satisfaction)	In general, how satisfied are you with the healthcare you received in the past 12 months?	Very satisfied; Somewhat satisfied; Somewhat dissatisfied; Very dissatisfied; You haven't had health care in the past 12 months	0 = "Somewhat/Very Satisfied"; 1 = "Somewhat/Very Dissatisfied or No healthcare in past year"

Supplementary Table 14.2 Unweighted proportion of the included subjects having each component and sub-item of the social determinants of health (SDOH) score.

Components and sub-items of the SDOH score	N (%)
Economic stability	
Never / previously employed	95 (1.2)
No paid sick leave	3116 (37.8)
Low family income	2050 (24.8)
Difficulty paying medical bills	973 (11.8)
Unable to pay medical bills	462 (5.6)
Cost-related medication non-adherence	672 (8.1)
Foregone / delayed medical care due to cost	680 (8.2)
Worried about money for retirement	2932 (35.5)
Worried about medical costs of illness / accident	2691 (32.6)
Worried about maintaining standard of living	2556 (31.0)
Worried about medical costs of normal healthcare	1732 (21.0)
Worried about paying monthly bills	1714 (20.8)
Worried about paying rent / mortgage / housing costs	1213 (14.7)
Neighborhood, physical environment, and social cohesion	
Housing was rental / from other arrangement	1683 (20.4)
People in neighborhood did not help each other	1155 (14.0)
There were not people that can be counted on in neighborhood	988 (12.0)
People neighborhood could not be trusted	904 (11.0)
Neighborhood was not close-knit	2656 (32.2)
Community and social context	
Psychological distress	383 (4.6)
Food	
Food insecurity	570 (6.9)
Education	
Could not speak English language well / at all	127 (1.5)
Did not look up health information on internet in the past 12 months	4157 (50.4)
Did not fill a prescription on the internet in the past 12 months	1104 (13.4)
Did not schedule medical appointment on the internet in the past 12 months	861 (10.4)
Did not communicate with healthcare provider by email in the past 12 months	1315 (15.9)
Did not use chat groups to learn about health topics in the past 12 months	327 (4.0)
Less than high school education	2859 (34.6)
Healthcare system	
Uninsured	168 (2.0)
No usual source of care	191 (2.3)
Trouble finding a doctor / healthcare provider	263 (3.2)
Not accepted by doctor's office as new patient	249 (3.0)
Insurance not accepted by doctor's office	301 (3.7)
Delayed medical care due to not being able to get through on the phone	242 (2.9)
Delayed medical care due to not being able to get an appointment soon enough	638 (7.7)
Delayed medical care due to waiting too long at the doctor's office	412 (5.0)
Delayed medical care due to the doctor's office not being open when there was time to visit	219 (2.7)
Delayed medical care due to a lack of transportation	185 (2.2)
Dissatisfied with the quality of care / no healthcare in the past year	415 (5.0)

Supplementary Table 14.3 Demographics and components of cardiovascular health in included and excluded subjects. All percentages were unweighted. The non-missing percentages used the sample size of the population without missing data as the denominator, while the missing percentages used the sample size of all excluded subjects as the denominator.

	Included	Excluded
Sample size	8254	8332
Weighted sample size	10,887,989	10,651,338
Demographics		
Age in years, N (%)		
18-45	581 (7.0)	923 (11.1)
46-64	2524 (30.6)	2771 (33.3)
65 or above	5149 (62.4)	4638 (55.4)
Male, N (%)	3755 (45.5)	3124 (37.5)
Race, N (%)		
White	7405 (89.7)	7217 (86.8)
Black / African American	526 (6.4)	709 (8.5)
American Indian / Alaskan native	39 (0.5)	60 (0.7)
Asian	154 (1.9)	185 (2.2)
Multiple race	130 (1.6)	142 (1.7)
Missing	0 (0)	19 (0.2)
Sexual orientation, N (%)		
Heterosexual	7995 (96.9)	7644 (97.0)
Missing	0 (0)	452 (5.4)
Type of cancer		
Breast, N (%)	1502 (18.2)	1613 (19.4)
Prostate, N (%)	1094 (13.3)	885 (10.6)
Lung, N (%)	274 (3.3)	288 (3.5)
Colorectal, N (%)	531 (6.4)	558 (6.7)
Skin (melanoma), N (%)	646 (7.8)	581 (7.0)
Other types, N (%)	2687 (32.6)	3097 (37.2)
Unknown, N (%)	2097 (25.4)	1841 (22.1)
Cardiovascular risk factors		
Hypertension, N (%)	4883 (59.2)	4391 (52.8)
Missing	0 (0)	19 (0.2)
Diabetes mellitus, N (%)	1955 (23.7)	1680 (20.2)
Missing	0 (0)	7 (0.1)
Hypercholesterolemia, N (%)	4411 (53.4)	2873 (34.7)
Missing	0 (0)	63 (0.8)
Smoking, N (%)	4313 (52.3)	4163 (50.5)
Missing	0 (0)	92 (1.1)
Physical inactivity, N (%)	5204 (63.1)	4745 (66.7)
Missing	0 (0)	1218 (14.6)
Inadequate sleep, N (%)	1239 (15.0)	1480 (19.0)
Missing	0 (0)	534 (6.4)
Obesity, N (%)	2702 (32.7)	2811 (33.7)
Missing	0 (0)	0 (0)
Excessive alcohol use, N (%)	458 (8.9)	427 (9.4)
Missing	3091 (37.5)	3775 (45.3)

Supplementary Table 14.4 Proportions of the included and excluded subjects having each component and sub-item of the social determinants of health (SDOH) score. All percentages were unweighted. The non-missing percentages used the sample size of the population without missing data as the denominator, while the missing percentages used the sample size of all excluded subjects as the denominator.

Components and sub-items of the SDOH score	Included, N (%)	Excluded, N (%)	
		Present	Missing
Sample size	8254	8332	
Economic stability			
Never / previously employed	95 (1.2)	169 (2.0)	5 (0.1)
No paid sick leave	3116 (37.8)	3212 (36.9)	787 (9.5)
Low family income	2050 (24.8)	2655 (36.9)	1127 (13.5)
Difficulty paying medical bills	973 (11.8)	1345 (16.2)	23 (0.3)
Unable to pay medical bills	462 (5.6)	716 (8.6)	32 (0.4)
Cost-related medication non-adherence	672 (8.1)	700 (11.3)	2156 (25.9)
Foregone / delayed medical care due to cost	680 (8.2)	991 (11.9)	0 (0)
Worried about money for retirement	2932 (35.5)	3273 (41.4)	432 (5.2)
Worried about medical costs of illness / accident	2691 (32.6)	3010 (38.1)	427 (5.1)
Worried about maintaining standard of living	2556 (31.0)	2977 (37.7)	431 (5.2)
Worried about medical costs of normal healthcare	1732 (21.0)	2128 (26.9)	422 (5.1)
Worried about paying monthly bills	1714 (20.8)	2240 (28.3)	420 (5.0)
Worried about paying rent / mortgage / housing costs	1213 (14.7)	1690 (21.4)	425 (5.1)
Neighborhood, physical environment, and social cohesion			
Housing was rental / from other arrangement	1683 (20.4)	2453 (29.5)	27 (0.3)
People in neighborhood did not help each other	1155 (14.0)	1307 (17.3)	785 (9.4)
There were not people that can be counted on in neighborhood	988 (12.0)	1237 (16.2)	712 (8.6)
People neighborhood could not be trusted	904 (11.0)	1148 (15.4)	869 (10.4)
Neighborhood was not close-knit	2656 (32.2)	2681 (35.3)	732 (8.8)
Community and social context			
Psychological distress	383 (4.6)	433 (5.6)	561 (6.7)
Food			
Food insecurity	570 (6.9)	575 (8.1)	1227 (14.7)

Education			
Could not speak English language well / at all	127 (1.5)	232 (3.4)	1457 (17.5)
Did not look up health information on internet in the past 12 months	4157 (50.4)	3268 (40.4)	251 (3.0)
Did not fill a prescription on the internet in the past 12 months	1104 (13.4)	589 (7.3)	245 (2.9)
Did not schedule medical appointment on the internet in the past 12 months	861 (10.4)	507 (6.3)	248 (3.0)
Did not communicate with healthcare provider by email in the past 12 months	1315 (15.9)	749 (9.3)	245 (2.9)
Did not use chat groups to learn about health topics in the past 12 months	327 (4.0)	234 (2.9)	246 (3.0)
Less than high school education	2859 (34.6)	3537 (42.7)	57 (0.7)
Healthcare system			
Uninsured	168 (2.0)	420 (5.1)	21 (0.3)
No usual source of care	191 (2.3)	447 (5.5)	136 (1.6)
Trouble finding a doctor / healthcare provider	263 (3.2)	281 (3.4)	147 (1.8)
Not accepted by doctor’s office as new patient	249 (3.0)	259 (3.2)	153 (1.8)
Insurance not accepted by doctor’s office	301 (3.7)	361 (4.4)	159 (1.9)
Delayed medical care due to not being able to get through on the phone	242 (2.9)	226 (2.8)	159 (1.9)
Delayed medical care due to not being able to get an appointment soon enough	638 (7.7)	560 (6.9)	164 (2.0)
Delayed medical care due to waiting too long at the doctor’s office	412 (5.0)	389 (4.8)	167 (2.0)
Delayed medical care due to the doctor’s office not being open when there was time to visit	219 (2.7)	257 (3.2)	165 (2.0)
Delayed medical care due to a lack of transportation	185 (2.2)	293 (3.6)	164 (2.0)
Dissatisfied with the quality of care / no healthcare in the past year	415 (5.0)	784 (9.8)	365 (4.4)

Supplementary Table 14.5 Subgroup analyses for the primary outcome (Cardiovascular Health score). Adjusted risk ratios are displayed with 95% confidence intervals.

		N (weighted population)	SDOH score Quartile 1	Quartile 2	Quartile 3	Quartile 4	$p_{interaction}$
Age							
	18-45	581 (901913.4)	1 (reference)	0.76 [0.55-1.04], p=0.087	1.39 [1.04-1.86], p=0.028	1.57 [1.22-2.03], p<0.001	Age 18-45 vs 46-64: 0.69
	46-64	2524 (3,798,639)	1 (reference)	1.06 [0.95-1.17], p=0.30	1.14 [1.04-1.25], p=0.006	1.37 [1.26-1.49], p<0.001	Age 46-64 vs ≥65: 0.003
	≥65	5149 (6,187,436)	1 (reference)	1.04 [1.00-1.08], p=0.070	1.12 [1.07-1.17], p<0.001	1.19 [1.14-1.25], p<0.001	Age ≥65 vs 18-45: 0.026
Sex							
	Male	3755 (5,245,061)	1 (reference)	1.03 [0.98-1.09], p=0.21	1.09 [1.04-1.15], p=0.001	1.22 [1.15-1.29], p<0.001	0.001
	Female	4499 (5,642,928)	1 (reference)	1.04 [0.98-1.11], p=0.18	1.18 [1.12-1.25], p<0.001	1.38 [1.31-1.46], p<0.001	
Race							
	White	7405 (9,870,601)	1 (reference)	1.04 [1.00-1.08], p=0.075	1.15 [1.10-1.20], p<0.001	1.32 [1.27-1.38], p<0.001	0.051
	Non-White	849 (1,017,388)	1 (reference)	0.97 [0.87-1.09], p=0.65	1.02 [0.93-1.13], p=0.64	1.17 [1.05-1.29], p=0.004	
Cancer site							
	Breast	1502 (1,856,066)	1 (reference)	1.04 [0.94-1.15], p=0.48	1.15 [1.05-1.27], p=0.002	1.39 [1.26-1.52], p<0.001	
	Prostate	1094 (1,467,371)	1 (reference)	1.10 [1.01-1.20], p=0.022	1.11 [1.01-1.22], p=0.026	1.13 [1.02-1.25], p=0.018	
	Lung	274 (333,667.2)	1 (reference)	1.04 [0.87-1.26], p=0.497	1.23 [1.07-1.41], p=0.005	1.32 [1.14-1.54], p<0.001	
	Colorectal	531 (651,411.2)	1 (reference)	0.94 [0.81-1.10], p=0.43	1.12 [0.98-1.29], p=0.10	1.21 [1.07-1.38], p=0.003	

Skin (Melanoma)	646 (881,493.4)	1 (reference)	1.03 [0.90-1.18], p=0.66	1.15 [1.02-1.30], p=0.026	1.33 [1.18-1.51], p<0.001

Supplementary Table 14.6 Results of sensitivity analyses.

Outcome	N (weighted population)	SDOH score Quartile 1	Quartile 2	Quartile 3	Quartile 4
Using ordinal regression instead (OR [95% CI])					
Primary outcome (CVH)	8254 (10,887,989)	1 (reference)	1.11 [0.97-1.28], p=0.13	1.54 [1.34-1.77], p<0.001	2.57 [2.21-2.98], p<0.001
Restricting to those without any known cardiac condition (RR [95% CI])					
Primary outcome (CVH)	6011 (8,117,645)	1 (reference)	1.06 [1.01-1.11], p=0.028	1.17 [1.12-1.23], p<0.001	1.34 [1.27-1.40], p<0.001
Outcome defined as CVH+ excessive alcohol use (RR [95% CI])					
Alternative outcome (CVH + excessive alcohol use)	5163 (7,074,146)	1 (reference)	1.02 [0.97-1.07], p=0.48	1.12 [1.06-1.18], p<0.001	1.33 [1.27-1.40], p<0.001

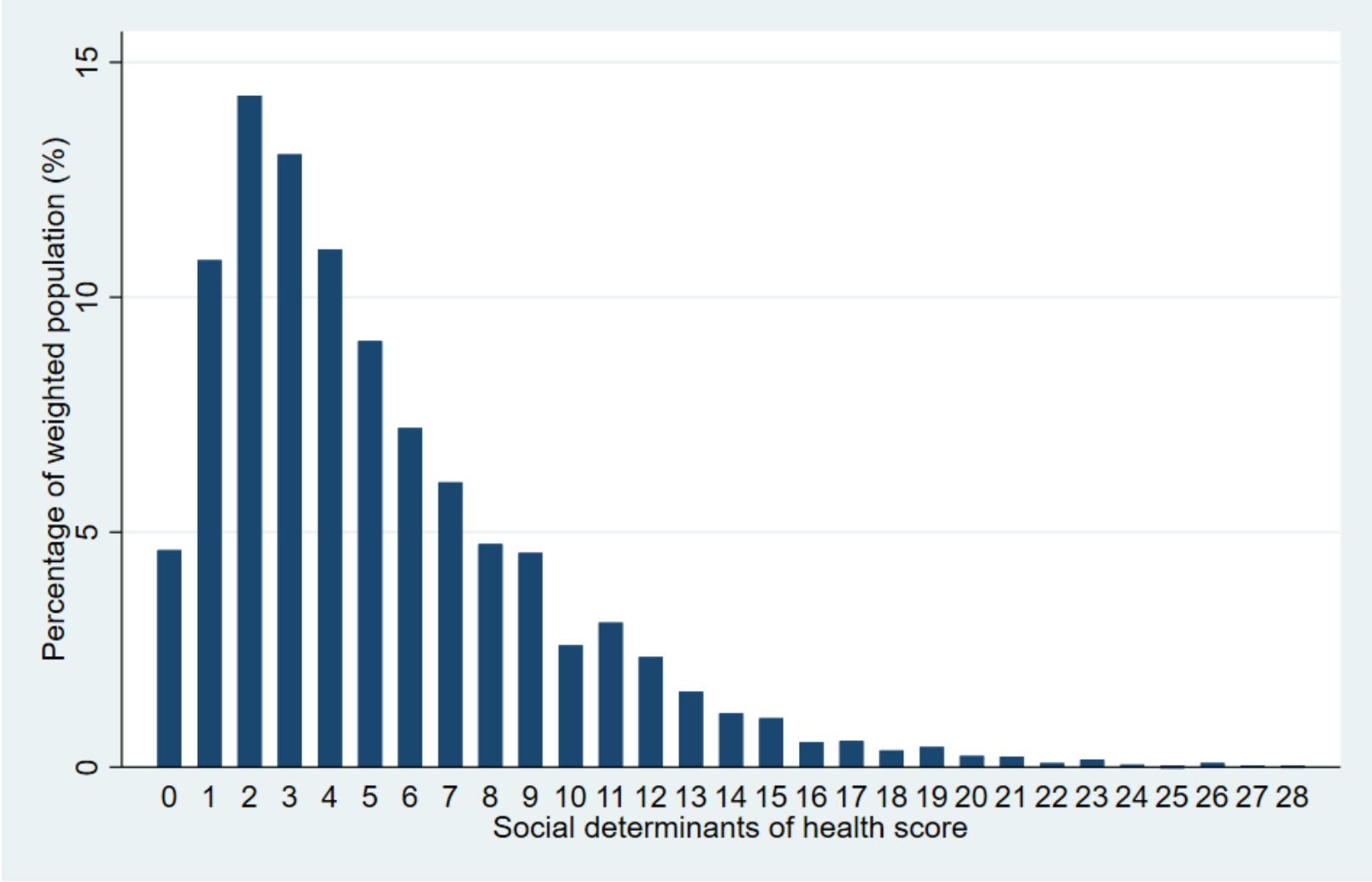
CI, confidence interval. CVH, Cardiovascular Health. OR, odds ratio. RR, risk ratio. SDOH, social determinants of health.

Supplementary Table 14.7 Results of the exploratory analyses exploring associations between the social determinants of health (SDOH) score and self-reported history of cardiometabolic workup within the past year. Adjusted odds ratios are displayed with 95% confidence intervals.

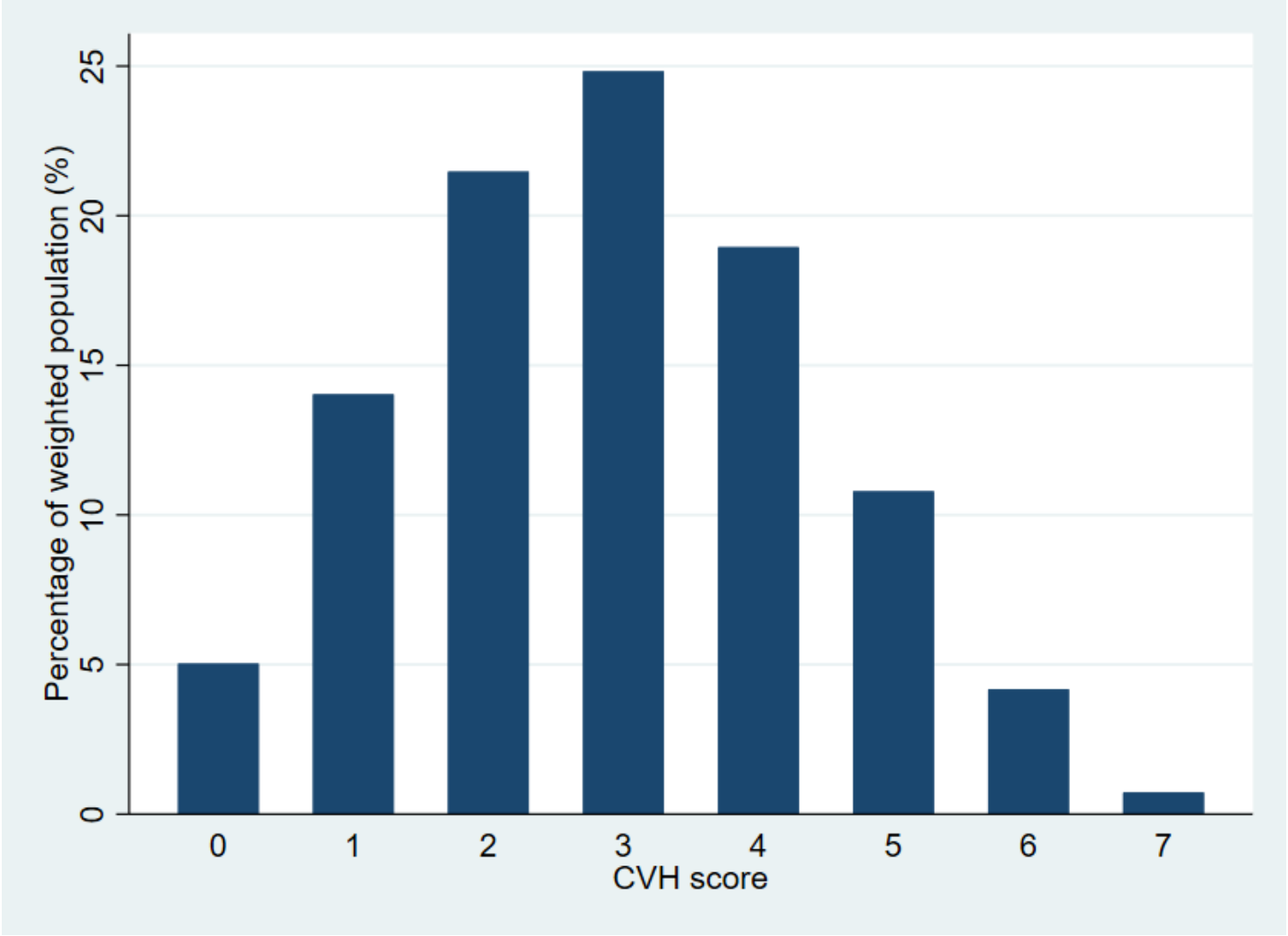
Workup	N (weighted population)	SDOH score			
		Quartile 1	Quartile 2	Quartile 3	Quartile 4
Blood pressure	8250 (10,883,467)	1 (reference)	0.57 [0.32-1.03], p=0.063	1.34 [0.69-2.57], p=0.38	0.89 [0.50-1.58], p=0.70
Fasting glucose	8141 (10,755,332)	1 (reference)	0.91 [0.77-1.08], p=0.29	0.98 [0.82-1.17], p=0.80	1.07 [0.89-1.28], p=0.47
Cholesterol	8182 (10,789,312)	1 (reference)	0.84 [0.62-1.14], p=0.26	0.91 [0.68-1.21], p=0.50	0.94 [0.70-1.26], p=0.69

14.1.2. Supplementary figures for Chapter 2

Supplementary Figure 14.1 Weighted distribution of the social determinants of health score.



Supplementary Figure 14.2 Weighted distribution of the primary outcome (CVH score).



14.2. Appendices for Chapter 3

14.2.1. Supplementary table for Chapter 3

Supplementary Table 14.8 Results of the post hoc exploratory subgroup analyses amongst participants without known cancer.

Subgroup		Adjusted RR [95% CI]	$p_{interaction}$
Age, years old	18-45	1.48 [1.43, 1.54], p<0.001	All pairwise $p_{interaction}$<0.001
	46-64	1.33 [1.29, 1.36], p<0.001	
	≥65	1.24 [1.20, 1.29], p<0.001	
Sex	Male	1.44 [1.39, 1.49], p<0.001	0.901
	Female	1.40 [1.36, 1.43], p<0.001	

CI, confidence interval. RR, risk ratio.

14.3. Appendices for Chapter 4

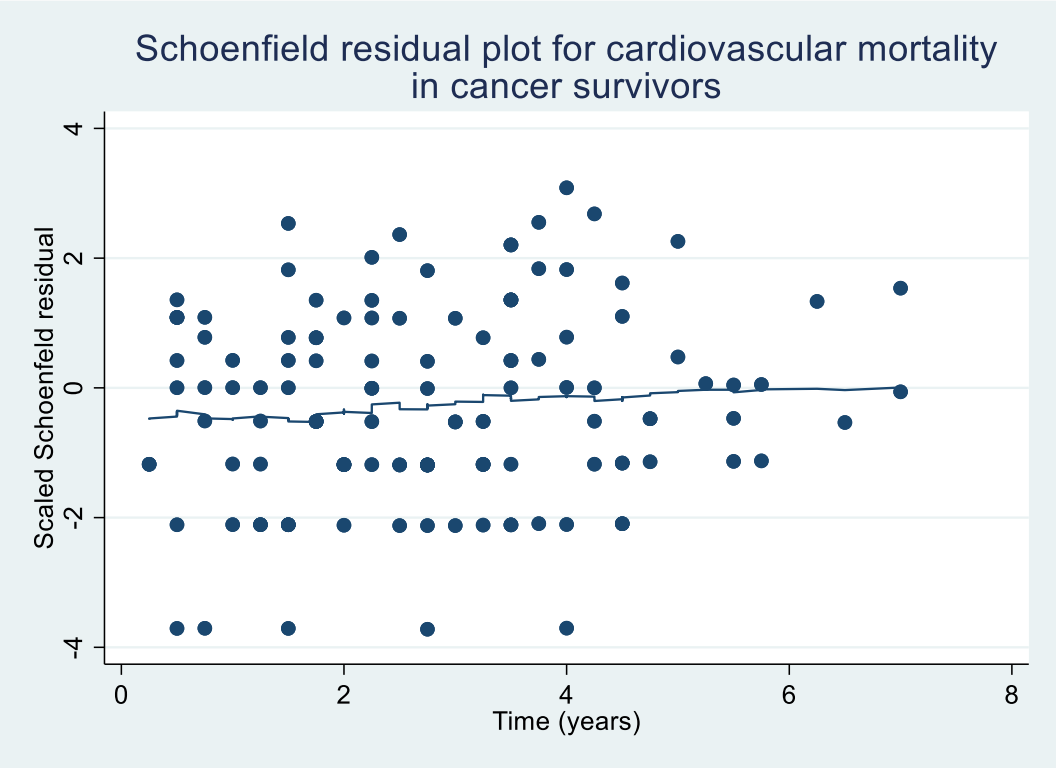
14.3.1. Supplementary table for Chapter 4

Supplementary Table 14.9 Results of the Schoenfield residuals-based test of the proportional hazard assumption for each outcome amongst cancer survivors.

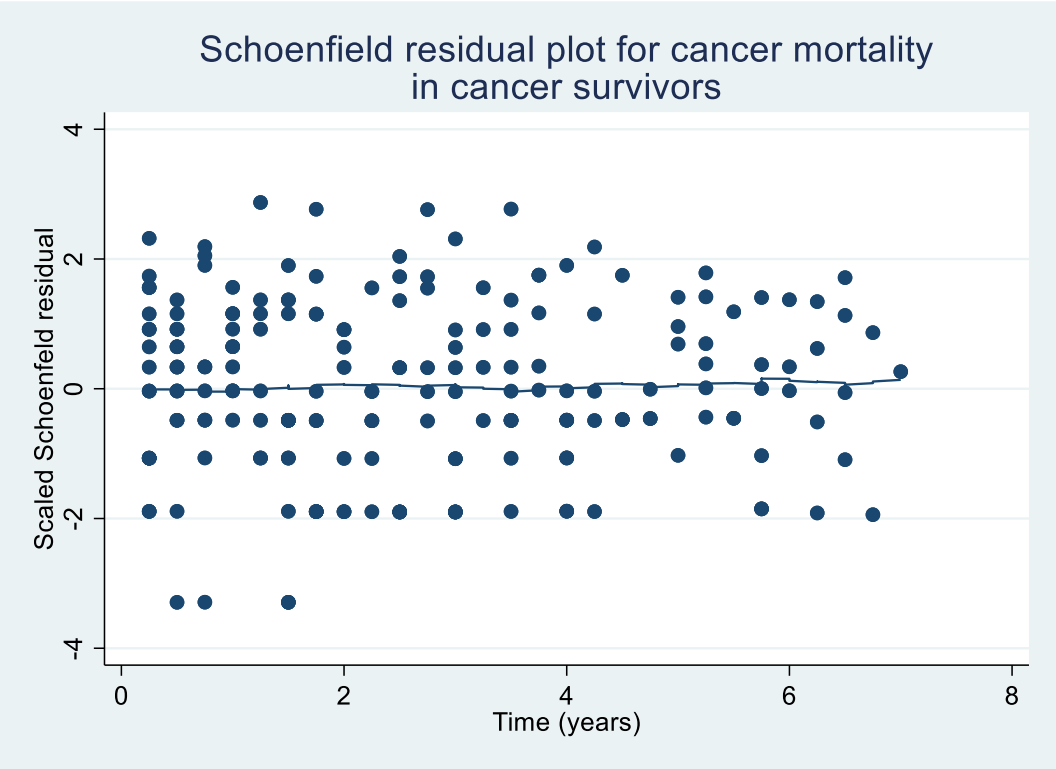
	Cancer survivors			Individuals without cancer		
	ρ	χ^2	p-value	ρ	χ^2	p-value
Cardiovascular mortality	0.123	2.70	0.100	-0.037	1.56	0.211
Cancer mortality	0.002	0.00	0.979	0.011	0.03	0.853
All-cause mortality	0.032	0.78	0.378	-0.005	0.06	0.805

14.3.2. Supplementary figures for Chapter 4

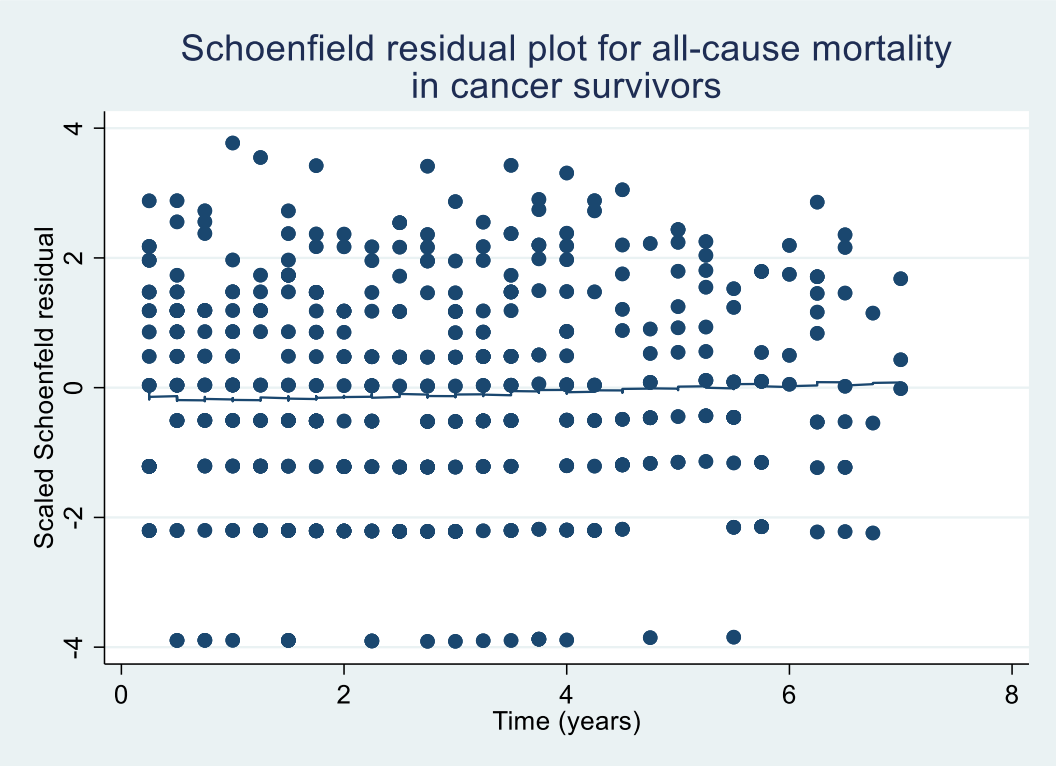
Supplementary Figure 14.3 Schoenfield residual-time plot for cardiovascular mortality amongst cancer survivors.



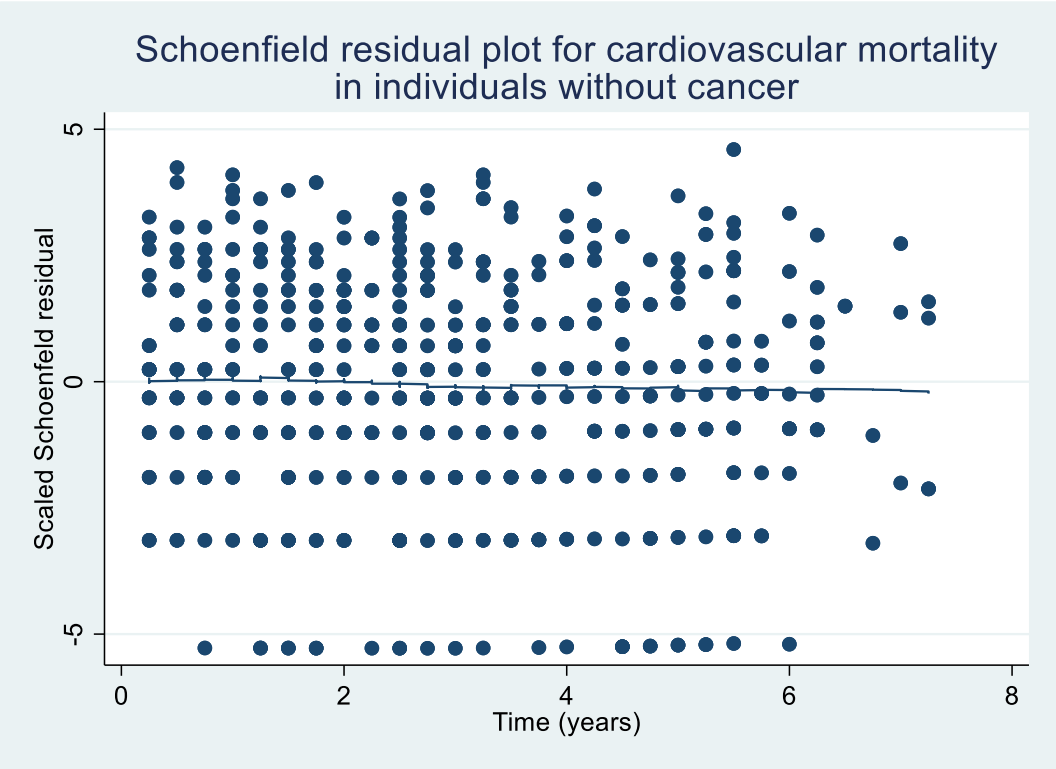
Supplementary Figure 14.4 Schoenfield residual-time plot for cancer mortality amongst cancer survivors.



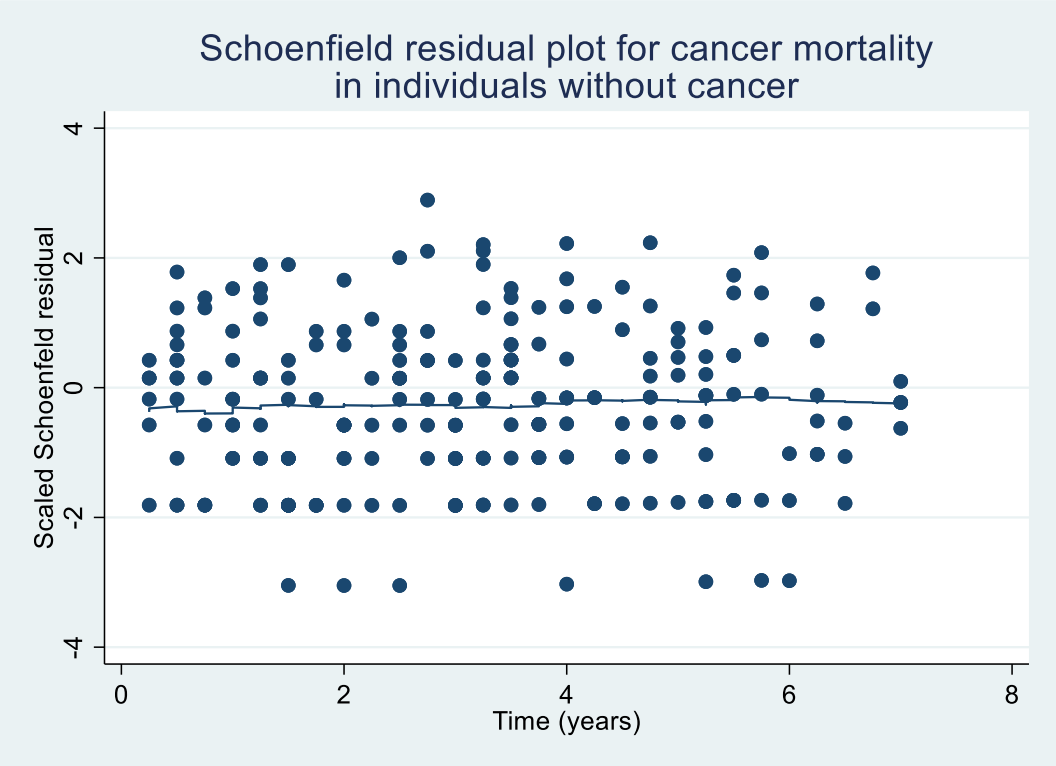
Supplementary Figure 14.5 Schoenfield residual-time plot for all-cause mortality amongst cancer survivors.



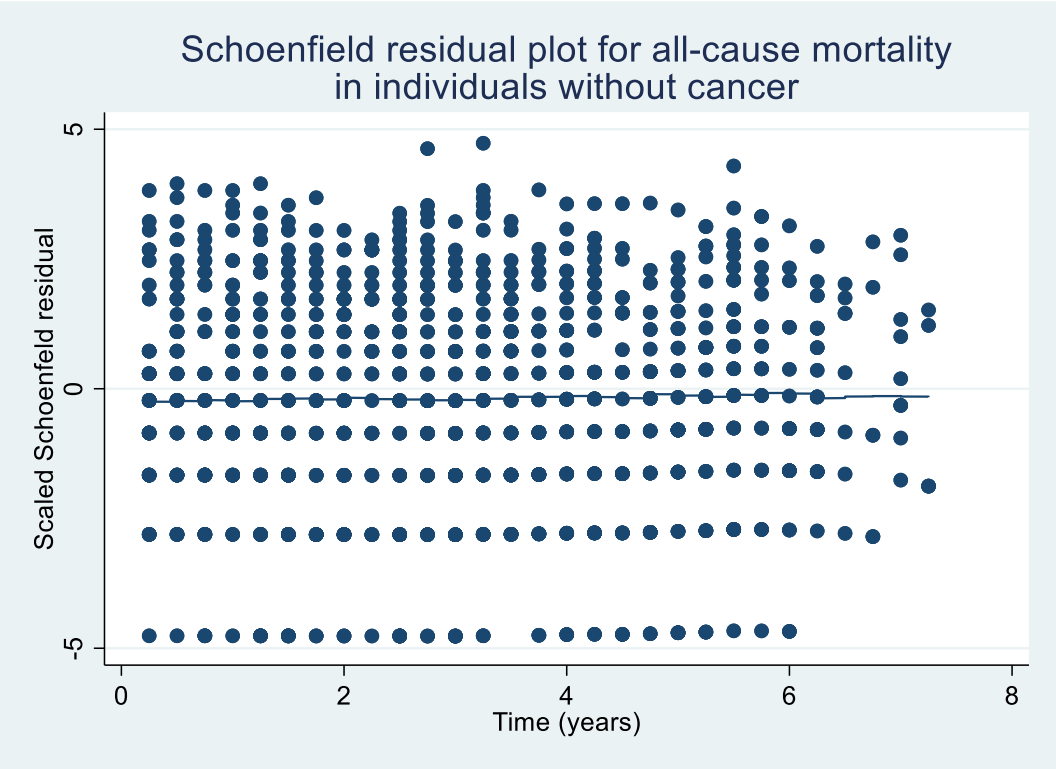
Supplementary Figure 14.6 Schoenfield residual-time plot for cardiovascular mortality amongst individuals without cancer.



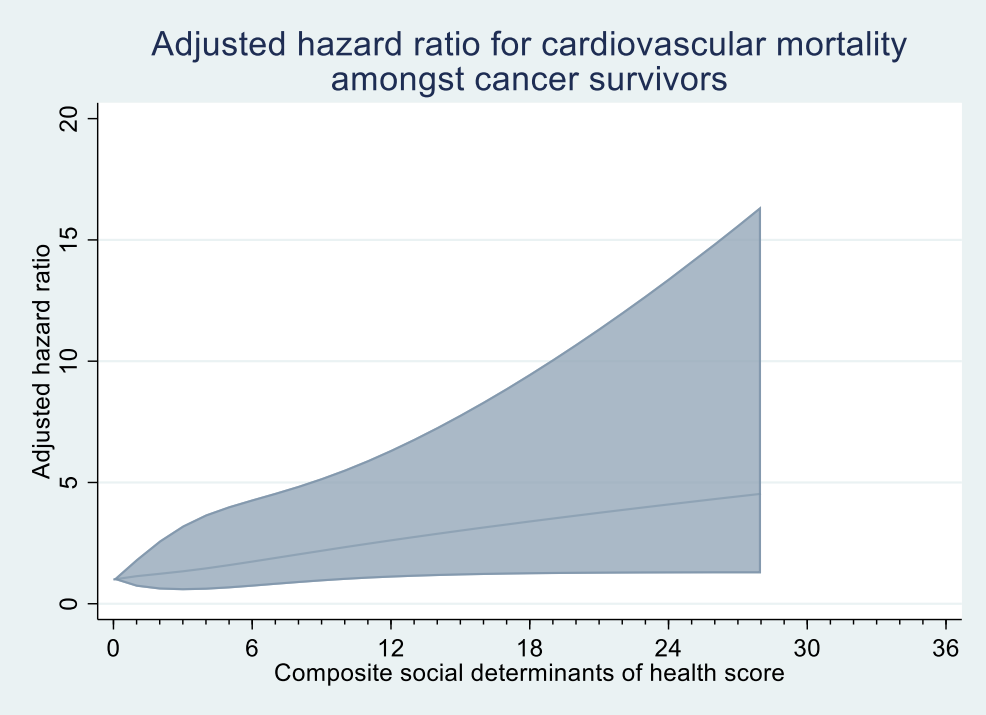
Supplementary Figure 14.7 Schoenfield residual-time plot for cancer mortality amongst individuals without cancer.



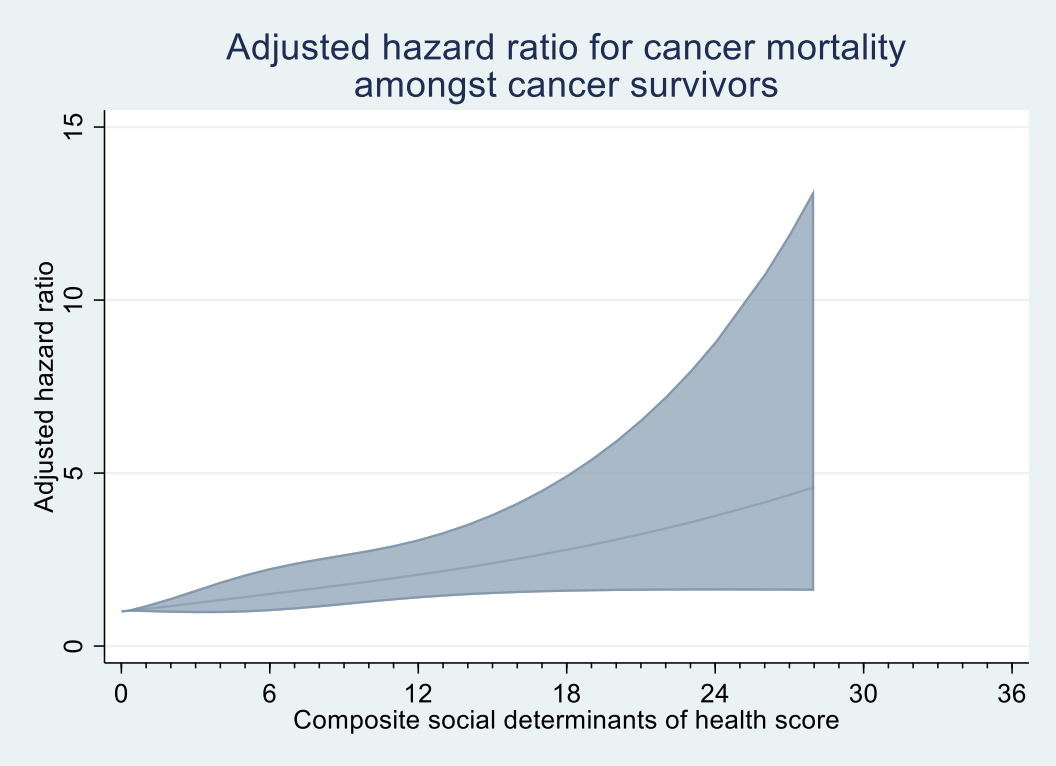
Supplementary Figure 14.8 Schoenfield residual-time plot for all-cause mortality amongst individuals without cancer.



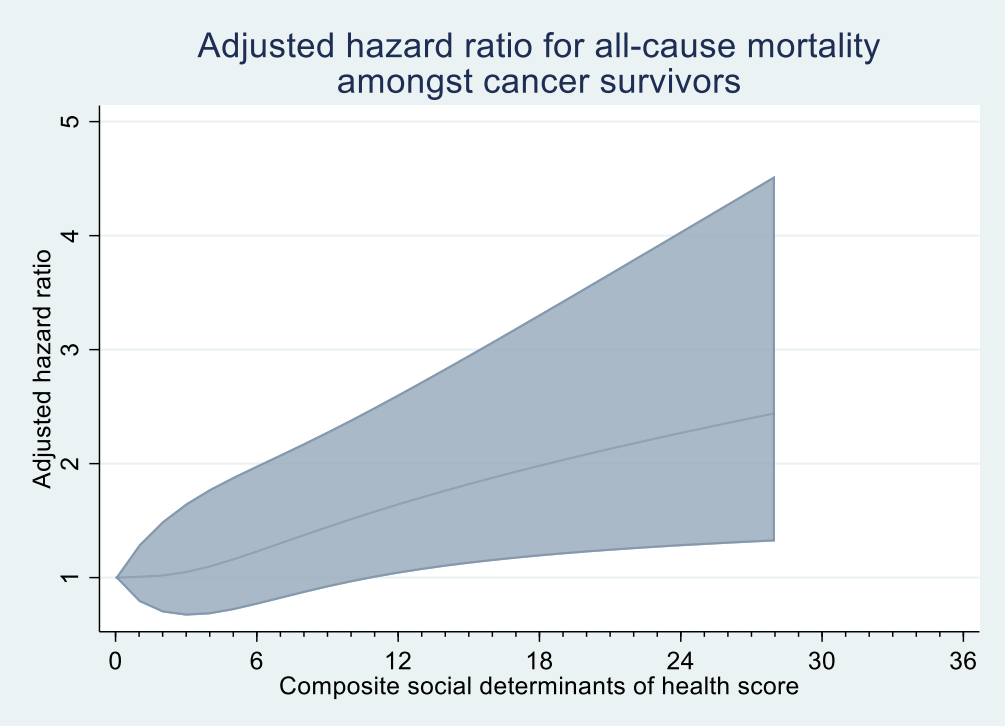
Supplementary Figure 14.9 Restricted cubic spline visualizing the relationship between the composite social determinants of health score and the risk of cardiovascular mortality amongst cancer survivors.



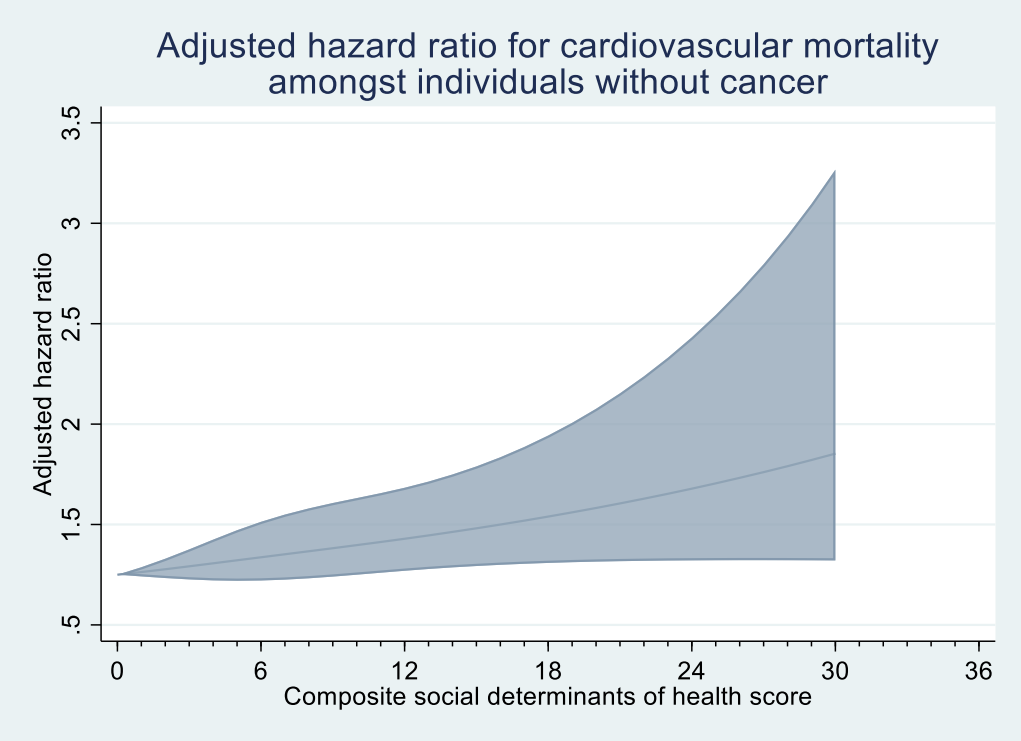
Supplementary Figure 14.10 Restricted cubic spline visualizing the relationship between the composite social determinants of health score and the risk of cancer mortality amongst cancer survivors.



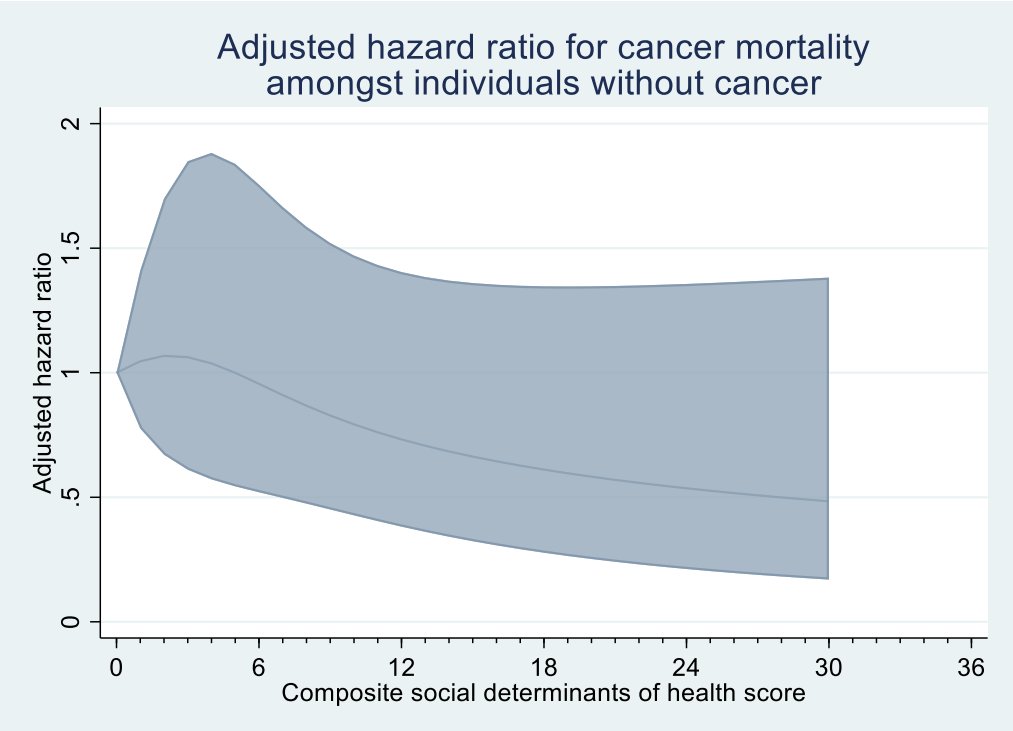
Supplementary Figure 14.11 Restricted cubic spline visualizing the relationship between the composite social determinants of health score and the risk of all-cause mortality amongst cancer survivors.



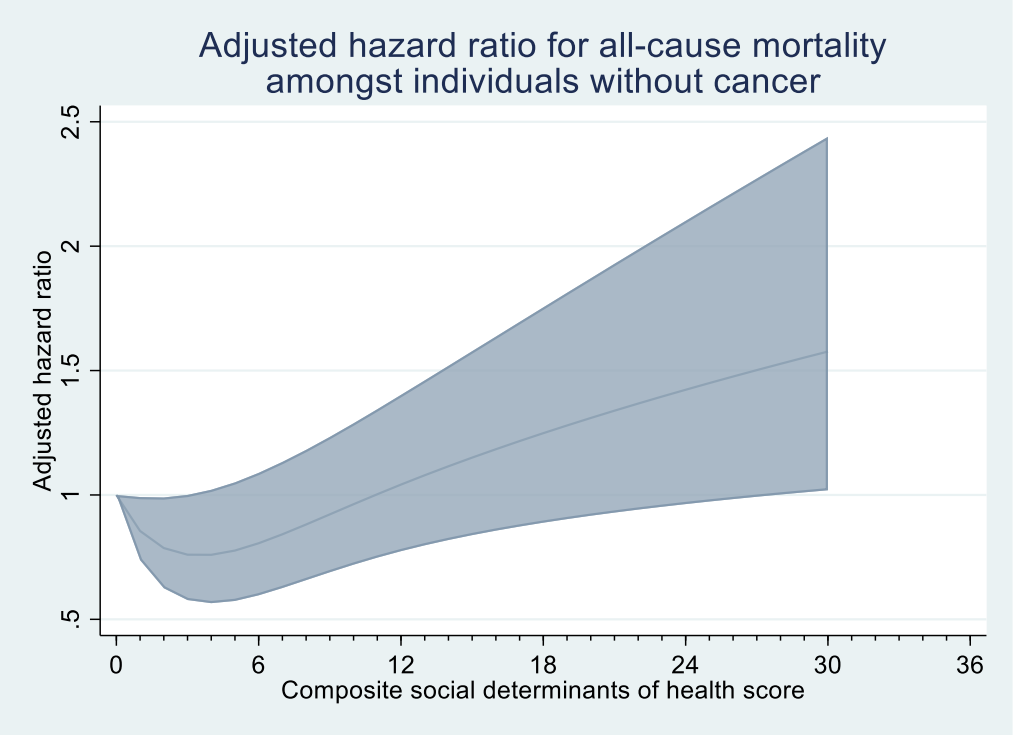
Supplementary Figure 14.12 Restricted cubic spline visualizing the relationship between the composite social determinants of health score and the risk of cardiovascular mortality amongst individuals without cancer.



Supplementary Figure 14.13 Restricted cubic spline visualizing the relationship between the composite social determinants of health score and the risk of cancer mortality amongst individuals without cancer.



Supplementary Figure 14.14 Restricted cubic spline visualizing the relationship between the composite social determinants of health score and the risk of all-cause mortality amongst individuals without cancer.



14.4. Appendices for Chapter 5

14.4.1. Supplementary tables for Chapter 5

Supplementary Table 14.10 International Classification of Diseases, Ninth Revision (ICD-9) codes used to identify outcomes and co-morbidities. All hereby listed codes include the corresponding sub-codes.

Prostate cancer	185													
Heart failure	428													
Myocardial infarction	410													
Diabetes mellitus	250													
Hypertension	401	402	403	404	405	437.2								
Atrial fibrillation	427.31													
Stroke	430	431	432	433	434	435								
Chronic obstructive pulmonary disease	490	491	492	496.0										
Ischaemic heart disease	410	411	412	413	414									
Chronic kidney disease	582	585	586											
Chronic liver disease	456.0	456.1	456.20	456.21	571	572.2	572.3	572.4	572.5	572.6	572.7	572.8		
Anaemia	280	281	282	283	284.0	284.1	284.8	284.9	285					
Dyslipidaemia	272.0	272.1	272.2	272.3	272.4									
Malignancy	140	141	142	143	144	145	146	147	148	149	150	151	152	153
		154	155	156	157	158	159	160	161	162	163	164	165	170
		171	172	173	174	175	179	179	180	181	182	183	184	185
		186	187	188	189	190	191	192	193	194	195	196	197	198

	199	200	201	202	203	204	205	206	207	208	209.0	209.1	209.2
	209.3												

Supplementary Table 14.11 International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes used to identify the cause of death. All hereby listed codes include the corresponding sub-codes.

Type of mortality	ICD codes
Cardiovascular mortality	ICD-9: 390-438 ICD-10: I00-I79

Supplementary Table 14.12 Incidence rates of both outcomes without any restriction on the follow-up duration, stratified by the year of androgen deprivation therapy initiation. Incidence rate ratios displayed were referenced against the 1993-2000 group.

Year of androgen deprivation therapy initiation	Major adverse cardiovascular events [1]		All-cause mortality [2]	
	Incidence rate [3]	Incidence rate ratio	Incidence rate [3]	Incidence rate ratio
1993-2000	4.1 [3.6, 4.6]	1 (reference)	16.2 [15.2, 17.2]	1 (reference)
2001-2007	5.0 [4.7, 5.4]	1.23 [1.06, 1.43], p=0.006	13.6 [13.1, 14.1]	0.84 [0.78, 0.91], p<0.001
2008-2014	5.5 [5.2, 5.9]	1.36 [1.18, 1.57], p<0.001	13.8 [13.3, 14.3]	0.85 [0.80, 0.92], p<0.001
2015-2021	5.7 [5.3, 6.2]	1.41 [1.21, 1.65], p<0.001	15.9 [15.2, 16.6]	0.98 [0.91, 1.06], p=0.660

[1] Log-linear test for trend p<0.001

[2] Log-linear test for trend p=0.168

[3] Per 100 person-year

Supplementary Table 14.13 Restricted mean survival time (in years) for both outcomes, stratified by the year of androgen deprivation therapy initiation. Follow-up duration was restricted to the longest follow-up duration observed in the 2015-2021 group.

Year of androgen deprivation therapy initiation	Major adverse cardiovascular event	All-cause mortality
1993-2000	5.86 [5.73, 6.00]	3.55 [3.40, 3.70]
2001-2007	5.82 [5.74, 5.89]	4.23 [4.14, 4.32]
2008-2014	5.64 [5.58, 5.71]	4.36 [4.29, 4.43]
2015-2021	5.59 [5.51, 5.68]	4.14 [4.06, 4.22]

Supplementary Table 14.14 Competing risk regression for major adverse cardiovascular event using the Fine and Gray sub-distribution model, with non-cardiovascular mortality as the competing event.

Year of androgen deprivation therapy initiation	Sub-hazard ratio [95% confidence interval]	P value
1993-2000	1 (reference)	Not applicable
2001-2007	1.30 [1.09, 1.56]	0.004
2008-2014	1.58 [1.33, 1.88]	<0.001
2015-2021	1.43 [1.19, 1.71]	<0.001

Supplementary Table 14.15 Results of backward stepwise Cox regression identifying the independent risk factors of major adverse cardiovascular event.

	Hazard ratio [95% confidence interval]	P value
Age (per year)	1.05 [1.04, 1.05]	<0.001
Diabetes mellitus	1.41 [1.24, 1.61]	<0.001
Hypertension	1.18 [1.07, 1.30]	0.001
Anaemia	1.36 [1.16, 1.60]	<0.001
Known malignancy	1.46 [1.29, 1.64]	<0.001
Statin use	0.82 [0.72, 0.94]	0.003
Anticoagulant use	1.55 [1.24, 1.93]	<0.001
Metformin use	0.74 [0.63, 0.87]	<0.001
Number of cardiovascular medication (per drug item)	1.17 [1.12, 1.21]	<0.001

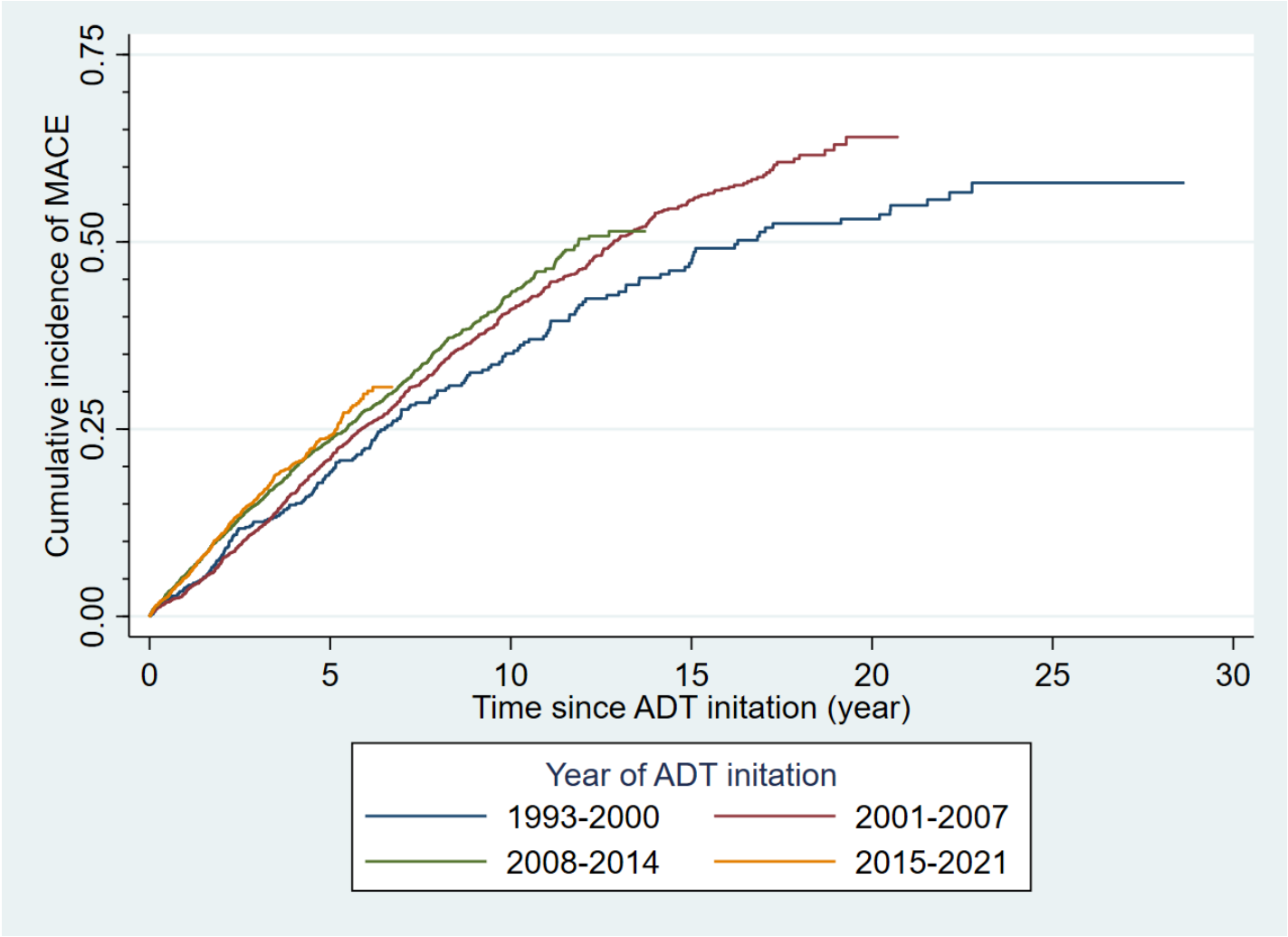
Supplementary Table 14.16 Results of backward stepwise Cox regression identifying the independent risk factors of all-cause mortality.

	Hazard ratio [95% confidence interval]	P value
Age (per year)	1.04 [1.03, 1.04]	<0.001
Medical castration	0.83 [0.79, 0.87]	<0.001
Prior chemotherapy	1.73 [1.20, 2.50]	0.003
Year of androgen deprivation therapy initiation		
2001-2007	0.81 [0.75, 0.88]	<0.001
2008-2014	0.75 [0.70, 0.81]	<0.001
2015-2021	0.86 [0.78, 0.93]	0.001
Diabetes mellitus	1.24 [1.14, 1.36]	<0.001
Insulin use	1.17 [1.06, 1.30]	0.003
Chronic kidney disease	1.12 [1.00, 1.25]	0.056
Anaemia	1.63 [1.51, 1.76]	<0.001
Atrial fibrillation	1.17 [1.06, 1.29]	0.003
Chronic liver disease	1.49 [1.22, 1.82]	<0.001
Chronic obstructive pulmonary disease	1.35 [1.24, 1.45]	<0.001
Prior radiotherapy	1.17 [1.06, 1.31]	0.003
Statin use	0.91 [0.85, 0.98]	0.015
Known malignancy	2.04 [1.93, 2.17]	<0.001
Prior radical prostatectomy	0.92 [0.88, 0.97]	0.001
ACEI/ARB use	0.93 [0.87, 0.99]	0.023
Metformin use	0.60 [0.54, 0.66]	<0.001
Sulphonylurea use	1.13 [1.03, 1.24]	0.013
Number of cardiovascular medication (per drug item)	1.06 [1.03, 1.08]	<0.001

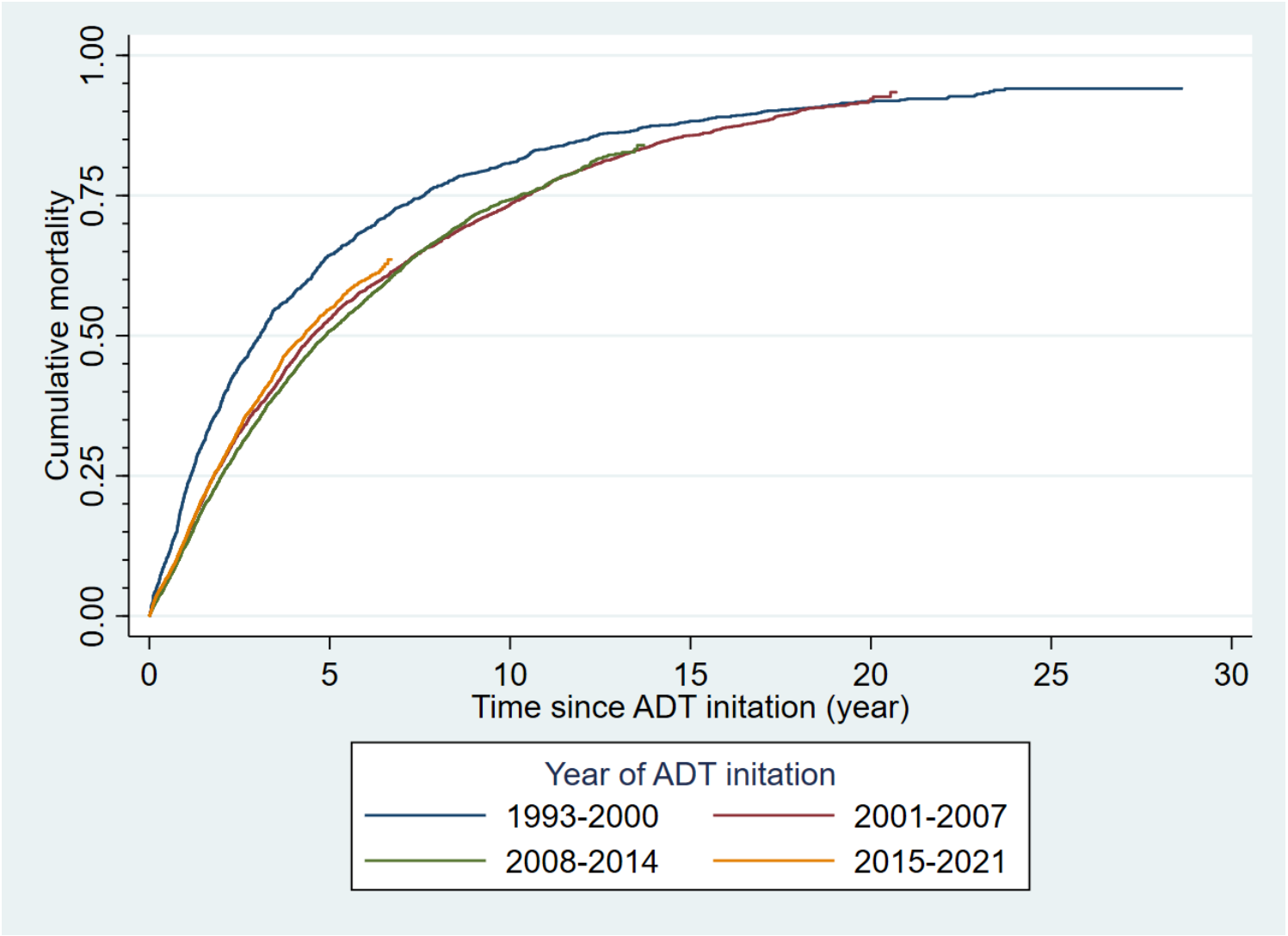
ACEI, angiotensinogen-converting enzyme inhibitor. ARB, angiotensin receptor blocker.

14.4.2. Supplementary figures for Chapter 5

Supplementary Figure 14.15 Kaplan-Meier curve showing the cumulative incidence of major adverse cardiovascular event (MACE) without any restriction on the follow-up duration. ADT, androgen deprivation therapy.



Supplementary Figure 14.16 Kaplan-Meier curve showing the cumulative incidence of all-cause mortality without any restriction on the follow-up duration. ADT, androgen deprivation therapy.



14.5. Appendices for Chapter 6

14.5.1. Supplementary tables for Chapter 6

Supplementary Table 14.17 International Classification of Diseases, Ninth Revision (ICD-9) codes used for identifying outcomes and co-morbidities. All codes include the corresponding sub-codes.

Prostate cancer	185											
Heart failure	428											
Myocardial infarction	410											
Diabetes mellitus	250											
Hypertension	401	402	403	404	405	437.2						
Atrial fibrillation	427.31											
Stroke	430	431	432	433	434	435						
Chronic obstructive pulmonary disease	490	491	492	496.0								
Ischaemic heart disease	410	411	412	413	414							
Chronic kidney disease	582	585	586									
Chronic liver disease	456.0	456.1	456.20	456.21	571	572.2	572.3	572.4	572.5	572.6	572.7	572.8
Anaemia	280	281	282	283	284.0	284.1	284.8	284.9	285			
Dyslipidaemia	272.0	272.1	272.2	272.3	272.4							
Arrhythmia	427											

Supplementary Table 14.18 International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes used for identifying the cause of death. All codes include the corresponding sub-codes.

Cardiovascular mortality	ICD-9: 390-438 ICD-10: I00-I79
Prostate cancer mortality	ICD-9: 185 ICD-10: C61

Supplementary Table 14.19 Number of patients with each type of mortality stratified by the type of androgen deprivation therapy.

		Medical castration (N=6944)	Bilateral orchiectomy (N=5359)	Both medical castration and bilateral orchiectomy (N=1234)
Cardiovascular mortality	Overall, N (%)	311 (4.5)	320 (6.0)	40 (3.2)
	During the first year, N (%)	52 (0.7)	52 (1.0)	7 (0.6)
Prostate cancer mortality	Overall, N (%)	1476 (21.3)	2026 (37.8)	422 (34.2)
	During the first year, N (%)	437 (6.3)	492 (9.2)	61 (4.9)
Mortality from other causes	Overall, N (%)	2092 (30.1)	2076 (38.7)	361 (29.3)
	During the first year, N (%)	451 (6.5)	279 (5.2)	37 (3.0)

Supplementary Table 14.20 Five-year risk (in percentages) of different types of mortality stratified by the type of androgen deprivation therapy. Numbers in brackets are 95% confidence intervals.

	Medical castration (N=6944)	Bilateral orchiectomy (N=5359)	Both medical castration and bilateral orchiectomy (N=1234)
Cardiovascular mortality	3.5 [3.1, 4.0]	3.8 [3.3, 4.4]	2.2 [1.5, 3.2]
Prostate cancer mortality	20.8 [19.7, 21.8]	31.7 [30.4, 32.9]	27.6 [25.1, 30.3]
Mortality from other causes	24.5 [23.4, 25.6]	24.3 [23.2, 25.5]	19.8 [17.5, 22.2]

Supplementary Table 14.21 Number of patients with each type of mortality stratified by ever-prescription of androgen receptor signalling inhibitor(s) (ARSI).

		Never prescribed ARSI (N=8745)	Ever prescribed ARSI (N=4792)
Cardiovascular mortality	Overall, N (%)	520 (6.0)	151 (3.2)
	During the first year, N (%)	98 (1.1)	12 (0.3)
Prostate cancer mortality	Overall, N (%)	2367 (27.1)	1559 (32.5)
	During the first year, N (%)	819 (9.4)	170 (3.6)
Mortality from other causes	Overall, N (%)	3320 (38.0)	1209 (25.2)
	During the first year, N (%)	660 (7.6)	104 (2.2)

Supplementary Table 14.22 Five-year risk (in percentages) of different types of mortality stratified by ever-prescription of androgen receptor signalling inhibitor(s) (ARSI). Numbers in brackets are 95% confidence intervals.

	Never prescribed ARSI (N=8745)	Ever prescribed ARSI (N=4792)
Cardiovascular mortality	4.1 [3.7, 4.5]	2.5 [2.0, 3.0]
Prostate cancer mortality	25.0 [24.1, 25.9]	28.8 [27.4, 30.2]
Mortality from other causes	26.4 [25.4, 27.4]	19.5 [18.3, 20.8]

Supplementary Table 14.23 Incidence rate (IR) and length of stay (LOS) of different types of hospitalizations stratified by the type of androgen deprivation therapy.

		Number of patients with event, N (%)	IR [95% CI], event per 100 person-years	LOS [95% CI], days per 100 person-years
Medical castration	Total number of patients	6944	NA	NA
	Any hospitalizations	6623 (95.4)	362.0 [352.7, 371.5]	2440.7 [2360.6, 2523.5]
	Cardiovascular hospitalizations	1518 (21.9)	13.8 [12.9, 14.8] [1]	132.9 [120.3, 146.7] [1]
	Emergency hospitalizations	5509 (79.3)	127.7 [123.7, 131.8] [1]	1119.1 [1069.9, 1170.6] [1]
	Emergency cardiovascular hospitalizations	1255 (18.1)	8.9 [8.3, 9.5] [1]	80.1 [72.0, 89.2] [1]
BO	Total number of patients	5359	NA	NA
	Any hospitalizations	5261 (98.2)	336.8 [327.6, 346.3]	3036.4 [2934.9, 3141.5]
	Cardiovascular hospitalizations	1277 (23.8)	13.6 [12.6, 14.6] [1]	161.0 [144.0, 180.0] [1]
	Emergency hospitalizations	4848 (90.5)	153.6 [148.8, 158.6] [1]	1384.5 [1334.5, 1436.4] [1]
	Emergency cardiovascular hospitalizations	1103 (20.6)	9.2 [8.5, 9.9] [1]	96.2 [85.6, 108.1] [1]
Both medical castration and BO	Total number of patients	1234	NA	NA
	Any hospitalizations	1234 (100)	376.1 [356.9, 396.3]	2208.5 [2067.3, 2359.5]
	Cardiovascular hospitalizations	260 (21.1)	9.3 [7.9, 10.8] [1]	146.3 [76.5, 280.1] [1]
	Emergency hospitalizations	1106 (89.6)	131.8 [123.4, 140.7] [1]	1065.7 [981.2, 1157.4] [1]
	Emergency cardiovascular hospitalizations	204 (16.5)	5.5 [4.7, 6.5] [1]	114.8 [51.3, 256.5] [1]

BO, bilateral orchiectomy. CI, confidence interval. NA, not applicable.

[1] Estimated for those who had the respective type of hospitalization using zero-inflated negative binomial regression.

Supplementary Table 14.24 Incidence rate (IR) and length of stay (LOS) of different types of hospitalizations stratified by ever-prescription of androgen receptor signalling inhibitor(s) (ARSI).

		Number of patients with event, N (%)	IR [95% CI], event per 100 person-years	LOS [95% CI], days per 100 person-years
Never prescribed ARSI	Total number of patients	8745	NA	NA
	Any hospitalizations	8459 (96.7)	350.3 [342.3, 358.5]	3074.4 [2986.7, 3164.8]
	Cardiovascular hospitalizations	2180 (24.9)	15.6 [14.7, 16.5] [1]	174.5 [160.4, 189.8] [1]
	Emergency hospitalizations	7492 (85.7)	152.8 [148.7, 157.0] [1]	1416.0 [1368.7, 1464.9] [1]
	Emergency cardiovascular hospitalizations	1851 (21.2)	10.3 [9.7, 10.9] [1]	107.9 [98.6, 118.0] [1]
Ever prescribed ARSI	Total number of patients	4792	NA	NA
	Any hospitalizations	4659 (97.2)	359.7 [349.8, 370.0]	1919.8 [1854.3, 1987.5]
	Cardiovascular hospitalizations	875 (18.3)	9.3 [8.6, 10.2] [1]	78.0 [29.6, 205.5] [1]
	Emergency hospitalizations	3971 (82.9)	115.9 [112.1, 119.8] [1]	917.5 [879.2, 957.5] [1]
	Emergency cardiovascular hospitalizations	711 (14.8)	5.9 [5.4, 6.5] [1]	110.5 [75.9, 160.8] [1]

CI, confidence interval. NA, not applicable.

[1] Estimated for those who had the respective type of hospitalization using zero-inflated negative binomial regression.

14.6. Appendices for Chapter 7

14.6.1. Supplementary tables for Chapter 7

Supplementary Table 14.25 International Classification of Diseases, Ninth Revision (ICD-9) codes used for identifying outcomes and co-morbidities. All codes include the corresponding sub-codes.

Prostate cancer	185
Heart failure	428
Myocardial infarction	410
Diabetes mellitus	250
Hypertension	401 402 403 404 405 437.2
Atrial fibrillation	427.31
Ventricular tachycardia or fibrillation	427.1 427.41
Ischaemic stroke	433.01 433.11 433.21 433.31 433.81 433.91 434.01 434.11 434.91 435
Haemorrhagic stroke	430 431 432
Chronic kidney disease	582 585 586
Dyslipidaemia	272.0 272.1 272.2 272.3 272.4

Supplementary Table 14.26 International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes used for identifying the cause of death. All codes include the corresponding sub-codes.

Cardiovascular mortality	ICD-9: 390-438 ICD-10: I00-I79

Supplementary Table 14.27 Number of patients with each combination and number of major cardiovascular comorbidities.

Major cardiovascular comorbidities	Number of patients, N (%)	Number of major cardiovascular comorbidities	Number of patients, N (%)
None	11,159 (82.4)	0	11,159 (82.4)
HF only	357 (2.6)	1	1884 (13.9)
MI only	240 (1.8)		
Stroke only	968 (7.2)		
Arrhythmia only	319 (2.4)		
HF and MI only	73 (0.5)	2	403 (3.0)
HF and stroke only	66 (0.5)		
HF and arrhythmia only	116 (0.9)		
MI and stroke only	30 (0.2)		
MI and arrhythmia only	27 (0.2)		
Stroke and arrhythmia only	91 (0.7)		
HF, MI, and stroke only	12 (0.1)	3	84 (0.6)
HF, MI, and arrhythmia only	30 (0.2)		
HF, stroke, and arrhythmia only	34 (0.3)		
MI, stroke, and arrhythmia only	8 (0.1)		
HF, MI, stroke, and arrhythmia	7 (0.1)	4	7 (0.1)

HF, heart failure. MI, myocardial infarction

Supplementary Table 14.28 Estimated 3-, 5-, and 10-year cumulative incidences of the primary endpoint for the included patients with corresponding 95% confidence intervals, stratified by the number and type of major cardiovascular comorbidity / comorbidities.

Major cardiovascular comorbidities	3-year cumulative incidence, %	5-year cumulative incidence, %	10-year cumulative incidence, %
None of HF/MI/stroke/arrhythmia	11.1 [10.5, 11.7]	15.8 [15.1, 16.5]	23.5 [22.6, 24.4]
HF only	32.5 [27.6, 37.4]	37.0 [31.8, 42.1]	42.4 [36.9, 47.7]
MI only	30.2 [22.7, 34.5]	34.3 [28.0, 40.7]	42.8 [35.8, 49.6]
Stroke only	20.7 [18.2, 23.4]	26.9 [24.0, 29.9]	34.7 [31.3, 38.1]
Arrhythmia only	31.0 [25.8, 36.3]	38.8 [33.1, 44.3]	46.3 [40.1, 52.2]
⩾2 of HF/MI/stroke/arrhythmia	42.2 [37.7, 46.6]	48.4 [43.8, 52.9]	51.3 [46.5, 55.9]

HF, heart failure. MI, myocardial infarction.

Supplementary Table 14.29 Results of subgroup analysis by whether chemotherapy or androgen receptor signaling inhibitors (ARSI) were ever prescribed, as a surrogate for metastatic disease. All values shown are adjusted sub-hazard ratios with corresponding 95% confidence interval.

Major cardiovascular comorbidities	Never prescribed ARSI / chemotherapy (N=8421)	Ever prescribed ARSI / chemotherapy (N=5116)
None of HF/MI/stroke/arrhythmia	1 (reference)	1 (reference)
HF only	1.64 [1.32, 2.05], p<0.001	1.51 [0.98, 2.32], p=0.059
MI only	1.36 [1.02, 1.81], p=0.039	1.54 [1.06, 2.56], p=0.025
Stroke only	0.98 [0.83, 1.17], p=0.851	1.20 [0.93, 1.53], p=0.158
Arrhythmia only	1.55 [1.23, 1.96], p<0.001	1.87 [1.31, 2.66], p<0.001
⩾2 of HF/MI/stroke/arrhythmia	1.90 [1.53, 2.35], p<0.001	1.95 [1.38, 2.78], p<0.001

HF, heart failure. MI, myocardial infarction.

Supplementary Table 14.30 Results of subgroup analysis by the presence of hypertension, diabetes mellitus, or dyslipidaemia. All values shown are adjusted sub-hazard ratios with corresponding 95% confidence intervals.

Major cardiovascular comorbidities	With hypertension / diabetes mellitus / dyslipidaemia (N=5297)	Without hypertension / diabetes mellitus / dyslipidaemia (N=8240)
None of HF/MI/stroke/arrhythmia	1 (reference)	1 (reference)
HF only	1.55 [1.24, 1.93], p<0.001	2.03 [1.41, 2.93], p<0.001
MI only	1.30 [0.99, 1.70], p=0.055	1.70 [1.13, 2.56], p=0.011
Stroke only	1.05 [0.89, 1.24], p=0.568	1.16 [0.90, 1.50], p=0.255
Arrhythmia only	1.65 [1.30, 2.10], p<0.001	1.55 [1.12, 2.13], p=0.008
⩾2 of HF/MI/stroke/arrhythmia	1.96 [1.60, 2.40], p<0.001	2.26 [1.55, 3.28], p<0.001

HF, heart failure. MI, myocardial infarction.

14.7. Appendices for Chapter 8

14.7.1. Supplementary tables for Chapter 8

Supplementary Table 14.31 International Classification of Diseases, Ninth Revision (ICD-9) codes used to identify outcomes and co-morbidities. All hereby listed codes include the corresponding sub-codes.

Prostate cancer	185														
Heart failure	428														
Myocardial infarction	410														
Diabetes mellitus	250														
Hypertension	401	402	403	404	405	437.2									
Atrial fibrillation	427.31														
Stroke	430	431	432	433	434	435									
Chronic obstructive pulmonary disease	490	491	492	496.0											
Ischaemic heart disease	410	411	412	413	414										
Chronic kidney disease	582	585	586												
Chronic liver disease	456.0	456.1	456.20	456.21	571	572.2	572.3	572.4	572.5	572.6	572.7	572.8			
Anaemia	280	281	282	283	284.0	284.1	284.8	284.9	285						
Dyslipidaemia	272.0	272.1	272.2	272.3	272.4										
Malignancy	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154
		155	156	157	158	159	160	161	162	163	164	165	170	171	172
		173	174	175	179	179	180	181	182	183	184	185	186	187	188
		189	190	191	192	193	194	195	196	197	198	199	200	201	202
		203	204	205	206	207	208	209.0	209.1	209.2	209.3				

Supplementary Table 14.32 International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes used to identify the cause of death. All hereby listed codes include the corresponding sub-codes.

Type of mortality	ICD codes
Cardiovascular mortality	ICD-9: 390-438
	ICD-10: I00-I79

Supplementary Table 14.33 Results of univariable Cox regression.

	Hazard ratio [95% confidence interval]	p value
Age (years)	1.05 [1.02, 1.07]	<0.001*
Medical castration	0.62 [0.46, 0.85]	0.003*
Bilateral orchiectomy	1.49 [1.09, 2.04]	0.014*
ADT duration (years)	0.94 [0.90, 0.98]	0.002*
Hypertension	1.34 [0.98, 1.84]	0.070*
Diabetes mellitus	1.35 [0.83, 2.18]	0.224
Dyslipidaemia	1.07 [0.65, 1.75]	0.801
Ischaemic heart disease	1.03 [0.66, 1.61]	0.887
Chronic kidney disease	1.18 [0.48, 2.88]	0.713
Atrial fibrillation	2.36 [1.10, 5.06]	0.027*
Known malignancy	1.15 [0.65, 2.03]	0.627
Prior radiotherapy	1.10 [0.78, 1.56]	0.574
Prior radical prostatectomy	1.04 [0.49, 2.21]	0.927
ACEI/ARB use	0.90 [0.66, 1.23]	0.515
Beta-blocker use	1.23 [0.90, 1.69]	0.185
Metformin use	1.16 [0.83, 1.63]	0.373
Sulphonylurea use	1.02 [0.74, 1.41]	0.893
Insulin use	1.24 [0.81, 1.90]	0.327
Dihydropyridine CCB use	1.12 [0.82, 1.53]	0.485
Antiplatelet use	1.16 [0.83, 1.64]	0.380
Anticoagulant use	0.29 [0.04, 2.09]	0.221
Chemo use	3.14 [0.44, 22.57]	0.255
Steroid use	0.89 [0.57, 1.40]	0.625
Ever used ARSI	0.78 [0.56, 1.08]	0.132
Baseline HbA1c	1.13 [1.01, 1.27]	0.031*

Supplementary Table 14.34 Comparison of changes in visit-to-visit HbA1c variability between patients with and without diabetes mellitus. Medians and interquartile ranges are shown.

	With diabetes mellitus (N=655)	Without diabetes mellitus (N=54)	p value
Per-unit change in CV	0.024 [-0.015-0.073]	0.014 [0.002-0.030]	0.521
Percentage change in CV, %	41.0 [-19.0-146.9]	53.4 [51.2-153.4]	0.355
Per-unit change in ARV, %	0.183 [-0.100-0.526]	0.099 [-0.030-0.255]	0.201
Percentage change in ARV, %	40.0 -180.2-137.0]	58.7 [-22.2-156.4]	0.528

ARV, average real variability. CV, coefficient of variation.

Supplementary Table 14.35 Comparison of changes in visit-to-visit HbA1c variability between patients with and without use of antidiabetic medication(s). Medians and interquartile ranges are shown.

	With use of antidiabetic medication(s) (N=610)	Without use of any antidiabetic medication(s) (N=99)	p value
Per-unit change in CV	0.024 [-0.017-0.073]	0.020 [0.001-0.053]	0.659
Percentage change in CV, %	38.8 [-20.7-137.2]	55.7 [38.1-197.9]	0.025
Per-unit change in ARV, %	0.181 [-0.111-0.520]	0.117 [-0.015-0.335]	0.838
Percentage change in ARV, %	38.5 [-19.1-129.9]	61.5 [-8.3-184.5]	0.072

ARV, average real variability. CV, coefficient of variation.

Supplementary Table 14.36 Comparison of changes in visit-to-visit HbA1c variability between types of androgen deprivation therapy. Medians and interquartile ranges are shown.

	Medical castration only (N=217)	Bilateral orchiectomy only (N=189)	Both medical castration and bilateral orchiectomy (N=88)	p value
Per-unit change in CV	0.023 [-0.009-0.068]	0.023 [-0.028-0.076]	0.020 [-0.011-0.069]	0.907
Percentage change in CV, %	48.0 [-12.4-139.5]	38.5 [-33.2-149.6]	28.9 [-17.4-154.3]	0.606
Per-unit change in ARV, %	0.175 [-0.060-0.493]	0.175 [-0.159-0.514]	0.119 [-0.140-0.500]	0.799
Percentage change in ARV, %	48.9 [-12.6-133.3]	25.7 [-25.0-136.7]	42.6 [-24.0-147.9]	0.346

ARV, average real variability. CV, coefficient of variation.

Supplementary Table 14.37 Cox regression results for changes in visit-to-visit HbA1c variability.

	Univariable hazard ratio [95% confidence interval]	Multivariable hazard ratio [95% confidence interval] [1]
Per-unit change in CV	5.85 [0.44, 78.62], p=0.182	6.29 [0.45, 87.20], p=0.170
Percentage change in CV (per 10%)	1.00 [0.99, 1.01], p=0.796	1.00 [0.99, 1.01], p=0.694
Per-unit change in ARV	1.26 [0.92, 1.71], p=0.146	1.23 [0.91, 1.67], p=0.181
Percentage change in ARV (per 10%)	1.00 [1.00, 1.01], p=0.635	1.00 [1.00, 1.01], p=0.513

ARV, average real variability. CV, coefficient of variation.

[1] Adjusted for age, medical castration, bilateral orchiectomy, ADT duration, hypertension, atrial fibrillation, and baseline HbA1c.

Supplementary Table 14.38 Results of subgroup analysis by prior diagnosis of diabetes mellitus. Hazard ratios and the corresponding 95% confidence intervals are shown, with adjustment for age, medical castration, bilateral orchiectomy, ADT duration, hypertension, atrial fibrillation, and baseline HbA1c.

	With diabetes mellitus (N=850)	Without diabetes mellitus (N=215)	$p_{interaction}$
CV of HbA1c (per SD)	1.25 [1.03, 1.52], p=0.024	1.25 [0.81, 1.94], p=0.318	0.396
ARV of HbA1c (per SD)	1.27 [1.06, 1.52], p=0.009	1.33 [0.73, 2.41], p=0.353	0.603

ARV, average real variability. CV, coefficient of variation.

Supplementary Table 14.39 Results of subgroup analysis by baseline use of antidiabetic medication(s). Hazard ratios and the corresponding 95% confidence intervals are shown, with adjustment for age, medical castration, bilateral orchiectomy, ADT duration, hypertension, atrial fibrillation, and baseline HbA1c.

	With use of antidiabetic medication(s) (N=788)	Without use of any antidiabetic medication(s) (N=277)	$p_{interaction}$
CV of HbA1c (per SD)	1.23 [1.01, 1.50], p=0.041	1.26 [0.88, 1.81], p=0.207	0.583
ARV of HbA1c (per SD)	1.24 [1.04, 1.49], p=0.020	1.45 [0.92, 2.29], p=0.113	0.972

ARV, average real variability. CV, coefficient of variation.

Supplementary Table 14.40 Results of subgroup analysis by the type of androgen deprivation therapy. Hazard ratios and the corresponding 95% confidence intervals are shown, with adjustment for age, bilateral orchiectomy (for patients who had both medical castration and bilateral orchiectomy), ADT duration, hypertension, atrial fibrillation, and baseline HbA1c.

	Medical castration only (N=635)	Bilateral orchiectomy only (N=303)	Both medical castration and bilateral orchiectomy (N=127)
CV of HbA1c (per SD)	1.32 [1.05, 1.67], p=0.017	1.09 [0.80, 1.49], p=0.585 [1]	1.23 [0.80, 1.89], p=0.338 [3]
ARV of HbA1c (per SD)	1.31 [1.04, 1.65], p=0.024	1.22 [0.93, 1.60], p=0.152 [2]	1.32 [0.73, 2.39], p=0.352 [4]

ARV, average real variability. CV, coefficient of variation.

[1] $p_{interaction}$=0.351 with medical castration subgroup as reference

[2] $p_{interaction}$=0.623 with medical castration subgroup as reference

[3] $p_{interaction}$=0.401 with medical castration subgroup as reference

[4] $p_{interaction}$=0.497 with medical castration subgroup as reference

Supplementary Table 14.41 Results of the post hoc sensitivity analysis using differences in restricted mean survival time to compare patients in each quartile of the coefficient of variation (CV) and average real variability (ARV) of HbA1c. Restricted mean survival time (in years) and the corresponding 95% confidence intervals are shown.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
CV of HbA1c	10.81 [9.94, 11.67] (reference)	11.03 [10.36, 11.70], p=0.690	10.23 [9.56, 10.91], p=0.307	9.39 [8.43, 10.35], p=0.031
ARV of HbA1c	10.00 [9.47, 10.52] (reference)	9.58 [9.06, 10.10], p=0.271	9.63 [9.14, 10.12], p=0.317	8.54 [7.90, 9.18], p=0.001

14.8. Appendices for Chapter 9

14.8.1. Supplementary tables for Chapter 9

Supplementary Table 14.42 International Classification of Diseases, Ninth Revision (ICD-9) codes used to identify outcomes and co-morbidities. All hereby listed codes include the corresponding sub-codes.

Prostate cancer	185								
Heart failure	428								
Myocardial infarction	410								
Diabetes mellitus	250								
Hypertension	401	402	403	404	405	437.2			
Atrial fibrillation	427.31								
Stroke	430	431	432	433	434	435			
Chronic obstructive pulmonary disease	490	491	492	496.0					
Ischaemic heart disease	410	411	412	413	414				
Chronic kidney disease	582	585	586						
Hyperlipidaemia	272.0	272.1	272.2	272.3	272.4				
Malignancy	140	141	142	143	144	145	146	147	148
		149	150	151	152	153	154	155	156
		157	158	159	160	161	162	163	164
		165	170	171	172	173	174	175	179
		179	180	181	182	183	184	185	186
		187	188	189	190	191	192	193	194
		195	196	197	198	199	200	201	202
		203	204	205	206	207	208	209.0	209.1
		209.2	209.3						

Supplementary Table 14.43 International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes used to identify the cause of death. All hereby listed codes include the corresponding sub-codes.

Type of mortality	ICD codes
Cardiovascular mortality	ICD-9: 390-438 ICD-10: I00-I79

14.9. Appendices for Chapter 10

14.9.1. Supplementary tables for Chapter 10

Supplementary Table 14.44 International Classification of Diseases, Ninth revision (ICD-9) diagnostic codes used for identifying diagnoses. All codes listed included the corresponding subcodes.

Condition	ICD-9 diagnostic codes
Lung cancer	162.3-162.9
Head and neck cancer	140-149.9
Nasopharyngeal cancer	147-147.9
Breast cancer	174-174.9
Colorectal cancer	153-154.1
Liver cancer	155.0, 155.2
Stomach cancer	151-151.9
Melanoma	172-172.9
Renal cell carcinoma	189
Esophageal cancer	150-150.9
Cervical cancer	180-180.9
Lymphoma	200-202.2, 202.7-202.8
Leukaemia	202.4, 204-208
Plasma cell dyscrasia	203-203.12
Myocardial infarction	410-411.0, 412
Heart failure	428, 402.01, 402.11, 402.91
Stroke	430, 431-432, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435
Hypertension	401-405, 437.2
Ischaemic heart disease	410-414
Atrial fibrillation	427.31
Diabetes mellitus	250
Dyslipidaemia	272.0-272.4
Chronic kidney disease	585
Peripheral vascular disease	440.2, 440.4

Supplementary Table 14.45 International Classification of Diseases, Ninth revision (ICD-9) and Tenth revision (ICD-10) codes used for identifying causes of death. All codes listed included the corresponding subcodes.

Cause of death	Codes
Cardiovascular	ICD-9: 390-438 ICD-10: I00-I79

Supplementary Table 14.46 International Classification of Diseases, Ninth revision (ICD-9) procedural codes used for identifying cardiovascular hospitalizations. All codes listed included the corresponding subcodes.

Type of procedures	ICD-9 procedural codes
Cardiovascular	17.5-17.56, 35-39.99, 88.4-88.45, 88.47-88.48, 88.5-88.59, 88.62-88.63, 88.72, 89.4-89.59, 89.62-89.64, 89.67-89.69, 99.6-99.69, 97.44

Supplementary Table 14.47 Baseline characteristics of patients included in the analysis of major adverse cardiovascular event (MACE).

	Patients with MACE	Patients without MACE
Number of patients, N	116	4055
Type of immune checkpoint inhibitor		
Anti-PD-1 user, N (%)	101 (87.1)	3293 (81.2)
Anti-PD-L1 user, N (%)	21 (18.1)	830 (20.5)
Anti-CTLA4 user, N (%)	10 (8.6)	304 (7.5)
Type of cancer		
Lung cancer, N (%)	50 (43.1)	1880 (46.4)
Head and neck cancer, N (%)	4 (3.5)	145 (3.6)
Nasopharyngeal cancer, N (%)	0 (0)	73 (1.8)
Breast cancer, N (%)	2 (1.7)	136 (3.4)
Colorectal cancer, N (%)	1 (0.9)	97 (2.4)
Liver cancer, N (%)	18 (15.5)	499 (12.3)
Stomach cancer, N (%)	0 (0)	95 (2.3)
Melanoma, N (%)	3 (2.6)	104 (2.6)
Renal cell carcinoma, N (%)	7 (6.0)	165 (4.1)
Esophageal cancer, N (%)	0 (0)	46 (1.1)
Cervical cancer, N (%)	1 (0.9)	25 (0.6)
Lymphoma, N (%)	8 (6.9)	167 (4.1)
Leukaemia, N (%)	1 (0.9)	39 (1.0)
Plasma cell dyscrasia, N (%)	0 (0)	8 (0.2)
Demographics		
Male, N (%)	85 (73.3)	2704 (66.7)
Age, years	63.2 [55.1-70.3]	67.5 [58.8-74.6]
Comorbid conditions		
Hypertension, N (%)	67 (57.8)	1819 (44.9)
Ischaemic heart disease, N (%)	8 (6.9)	129 (3.2)
Atrial fibrillation, N (%)	0 (0)	76 (1.9)
Diabetes mellitus, N (%)	26 (22.4)	708 (17.5)
Dyslipidaemia, N (%)	46 (39.7)	1066 (26.3)
Chronic kidney disease, N (%)	2 (1.7)	27 (0.7)
Peripheral arterial disease, N (%)	0 (0)	7 (0.2)
Use of other medications		
ACEI/ARB user, N (%)	34 (29.3)	843 (20.8)
Metformin user, N (%)	21 (18.1)	528 (13.0)
Sulfonylurea user, N (%)	15 (12.9)	336 (8.3)
Insulin user, N (%)	12 (10.3)	318 (7.8)
DPP4 inhibitor user, N (%)	6 (5.2)	157 (3.9)
Beta-blocker user, N (%)	34 (29.3)	835 (20.6)

Statin user, N (%)	46 (39.7)	985 (24.3)
Dihydropyridine CCB user, N (%)	50 (43.1)	1436 (35.4)
Chemotherapy user, N (%)	62 (53.5)	2434 (60.0)

ACEI, angiotensin-converting enzyme inhibitor. ARB, angiotensin receptor blocker. CCB, calcium channel blocker. CTLA4, cytotoxic T-lymphocyte associated protein 4. DPP4, dipeptidyl peptidase 4. PD-1, programmed cell death protein 1. PD-L1, programmed cell death ligand 1.

Supplementary Table 14.48 Results of sensitivity analysis which included only patients with at least one year of follow-up (N=2116).

	Proportion of patients with event (N, %)	Incidence rate [95% CI], episodes per 100 person-years	Annualized LOS [95% CI], days per 100 person-years
All admissions	2048 (96.8)	794.3 [761.0, 829.1]	1554.2 [1486.3, 1625.2]
All overnight admissions [1]	1375 (65.0)	91.0 [85.4, 96.9]	1112.1 [1025.6, 1205.9]
Cardiovascular admissions [1]	110 (5.2)	3.2 [2.5, 4.0]	23.1 [16.1, 33.2]
Overnight cardiovascular admissions [1]	79 (3.7)	2.7 [0.0, 196747.1]	414.2 [266.4, 644.1]

[1] Estimates calculated for patients with event using zero-inflated negative binomial regression

CI, confidence interval. LOS, length of stay.

14.10. Appendices for Chapter 12

14.10.1. Supplementary tables for Chapter 12

Supplementary Table 14.49 International Classification of Diseases, Ninth revision (ICD-9) diagnostic codes used for identifying diagnoses. All codes listed included the corresponding subcodes.

Condition	ICD-9 diagnostic codes
Lung cancer	162.3-162.9
Head and neck cancer	140-149.9
Nasopharyngeal cancer	147-147.9
Breast cancer	174-174.9
Colorectal cancer	153-154.1
Liver cancer	155.0, 155.2
Stomach cancer	151-151.9
Melanoma	172-172.9
Renal cell carcinoma	189
Esophageal cancer	150-150.9
Cervical cancer	180-180.9
Lymphoma	200-202.2, 202.7-202.8
Leukaemia	202.4, 204-208
Plasma cell dyscrasia	203-203.12
Myocardial infarction	410-411.0, 412
Heart failure	428, 402.01, 402.11, 402.91
Stroke	430, 431-432, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435
Hypertension	401-405, 437.2
Ischaemic heart disease	410-414
Atrial fibrillation	427.31
Ventricular arrhythmia or cardiac arrest	427.1, 427.4, 427.5
Valvular heart disease	394-397, 424
Diabetes mellitus	250
Dyslipidaemia	272.0-272.4
Chronic obstructive pulmonary disease	491-492, 496

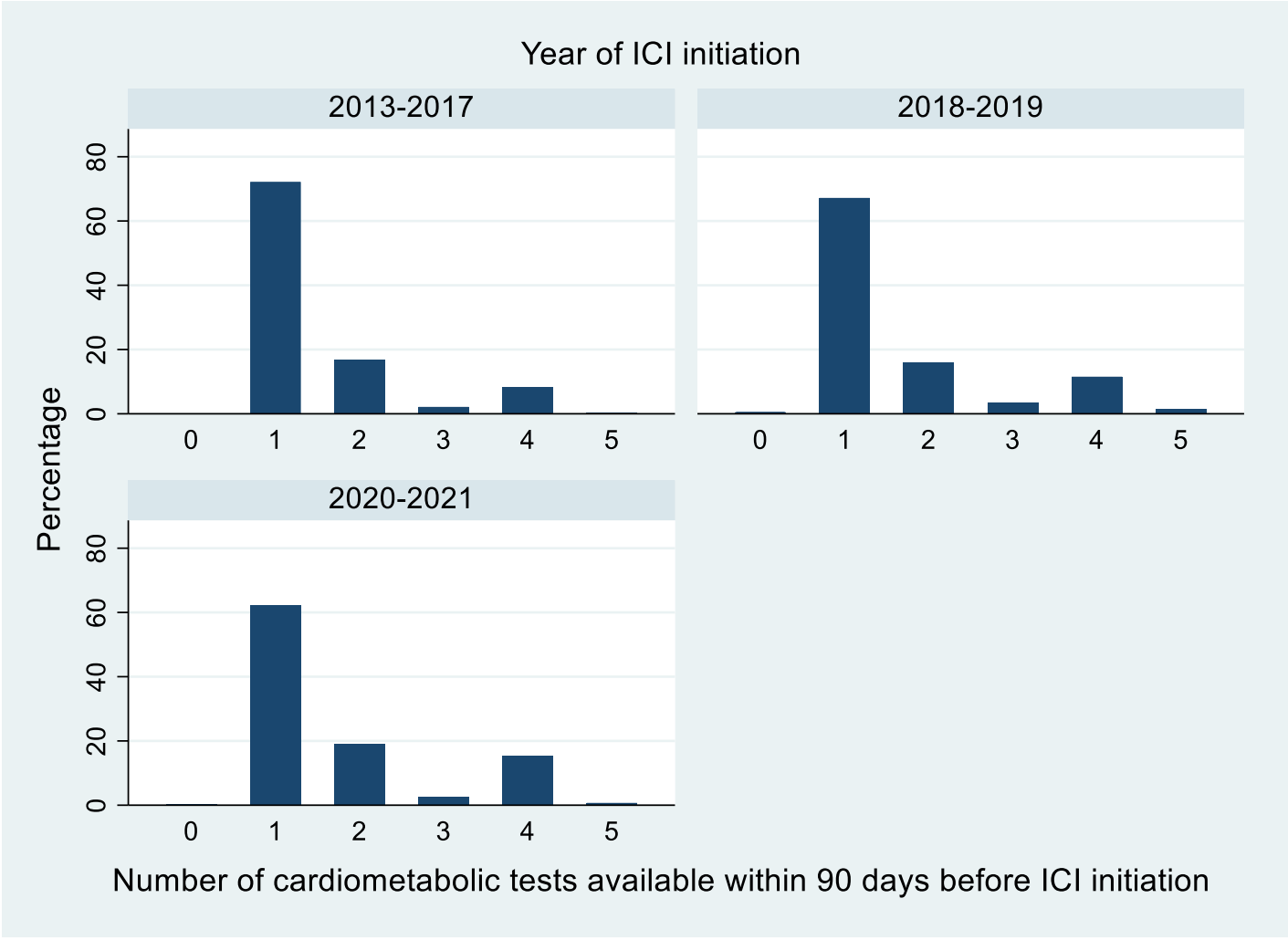
Chronic kidney disease	585
Peripheral arterial disease	440.2, 440.4

Supplementary Table 14.50 International Classification of Diseases, Ninth revision (ICD-9) and Tenth revision (ICD-10) codes used for identifying causes of death. All codes listed included the corresponding subcodes.

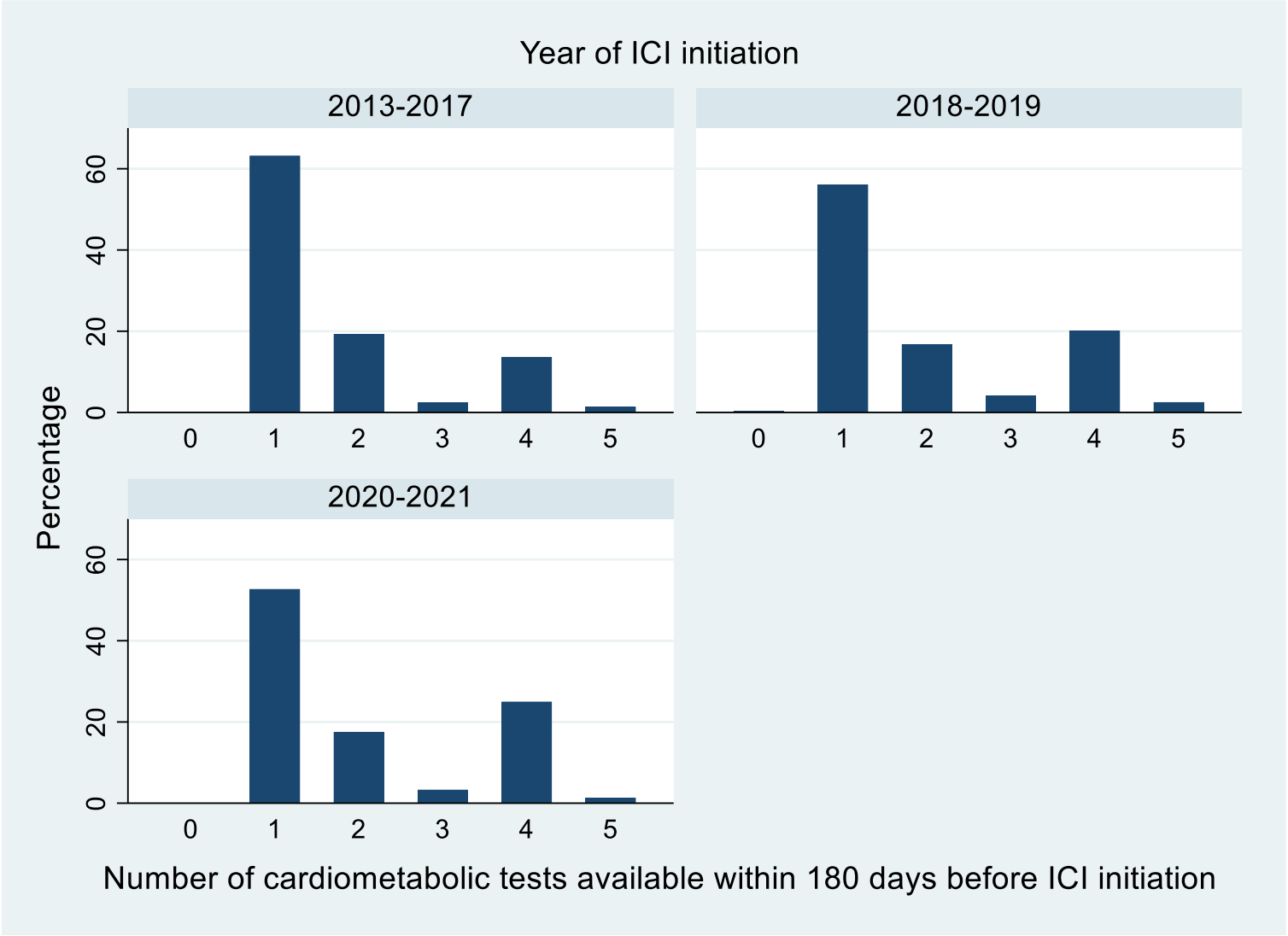
Cause of death	Codes
Cardiovascular	ICD-9: 390-438
	ICD-10: I00-I79

14.10.2. Supplementary figures for Chapter 12

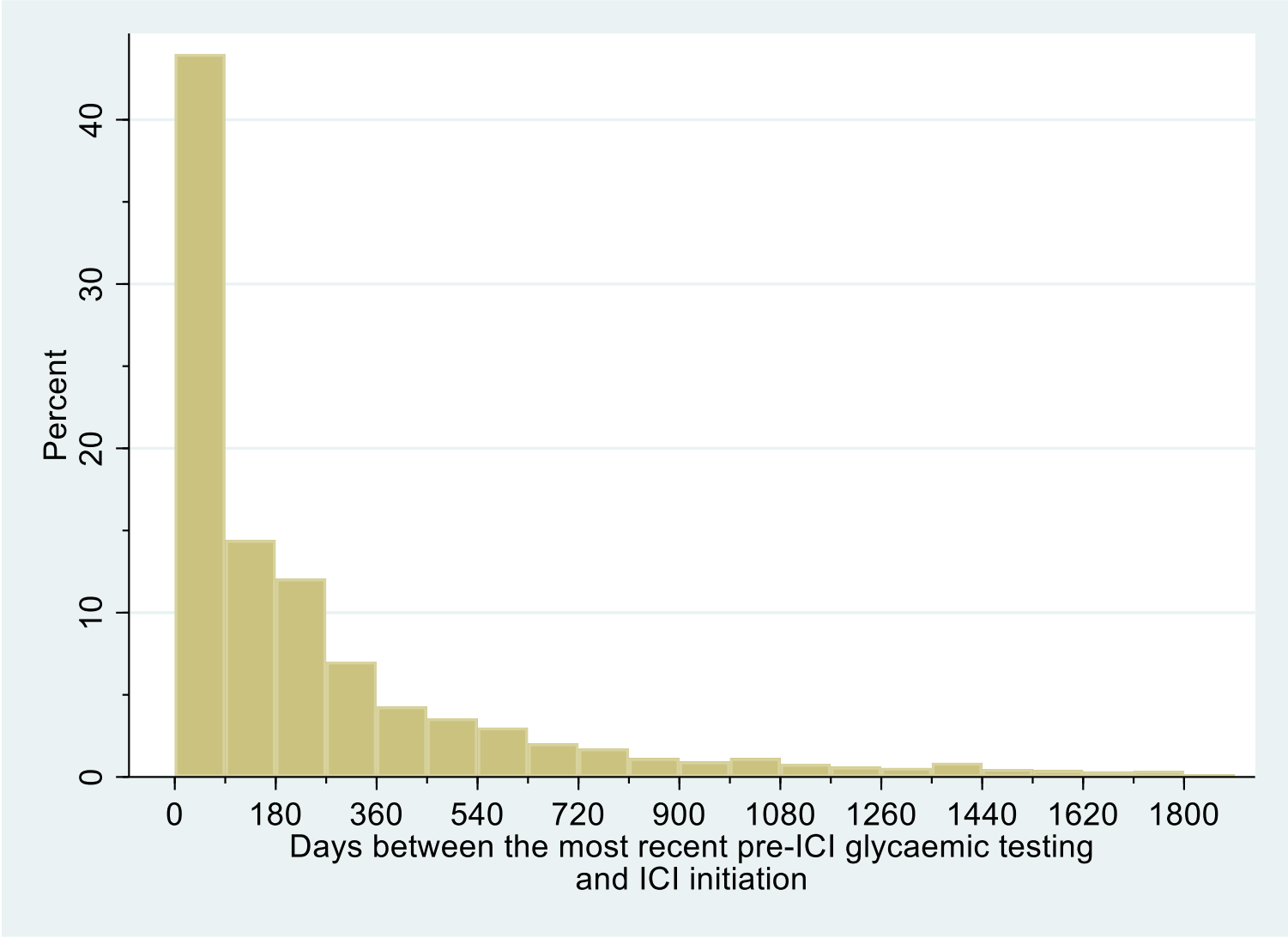
Supplementary Figure 14.17 Histogram showing the number of components of the cardiometabolic workups of interest performed for the analyzed patients within 90 days before immune checkpoint inhibitor (ICI) initiation, stratified by the year of ICI initiation.



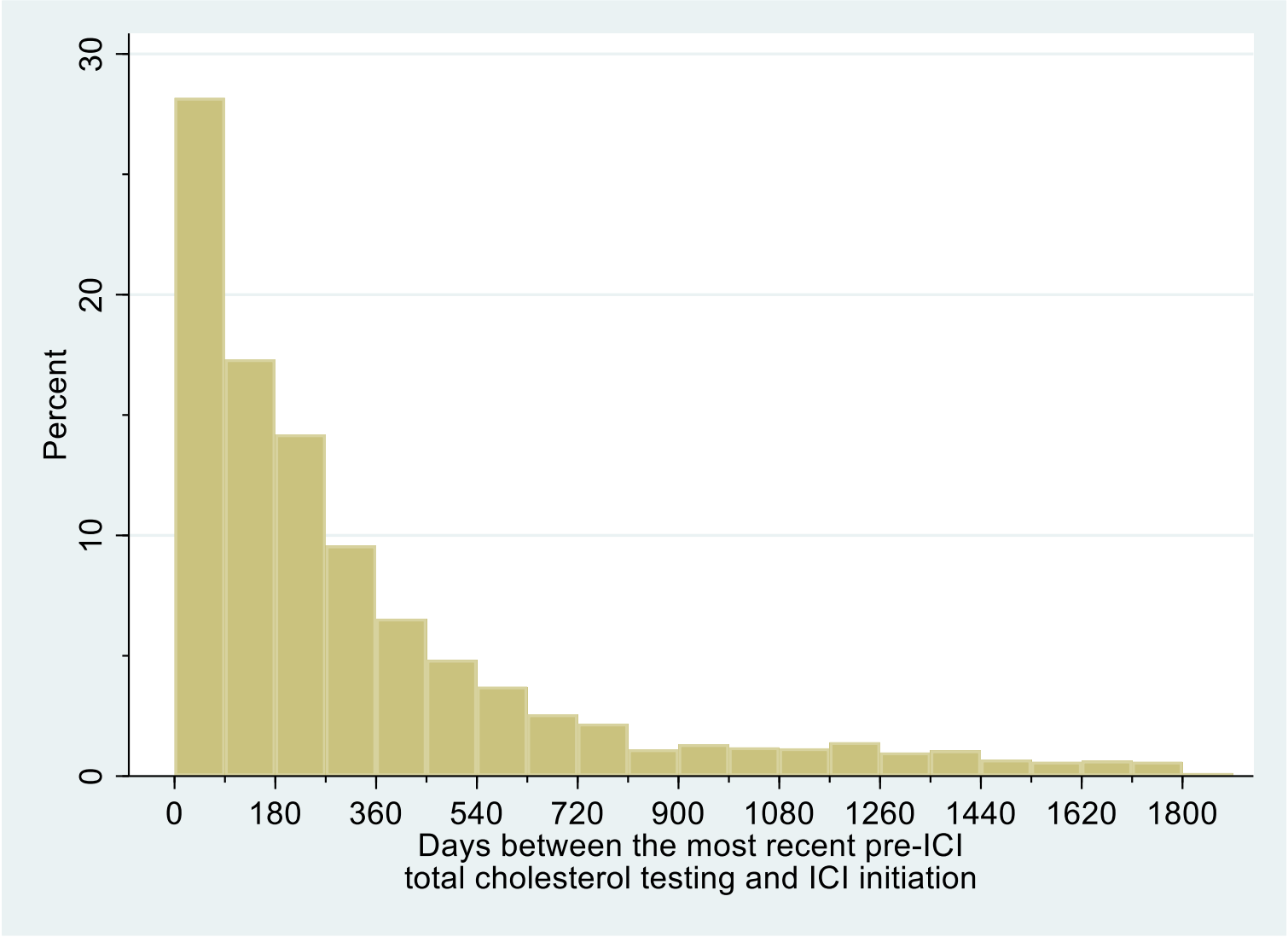
Supplementary Figure 14.18 Histogram showing the number of components of the cardiometabolic workups of interest performed for the analyzed patients within 180 days before immune checkpoint inhibitor (ICI) initiation, stratified by the year of ICI initiation.



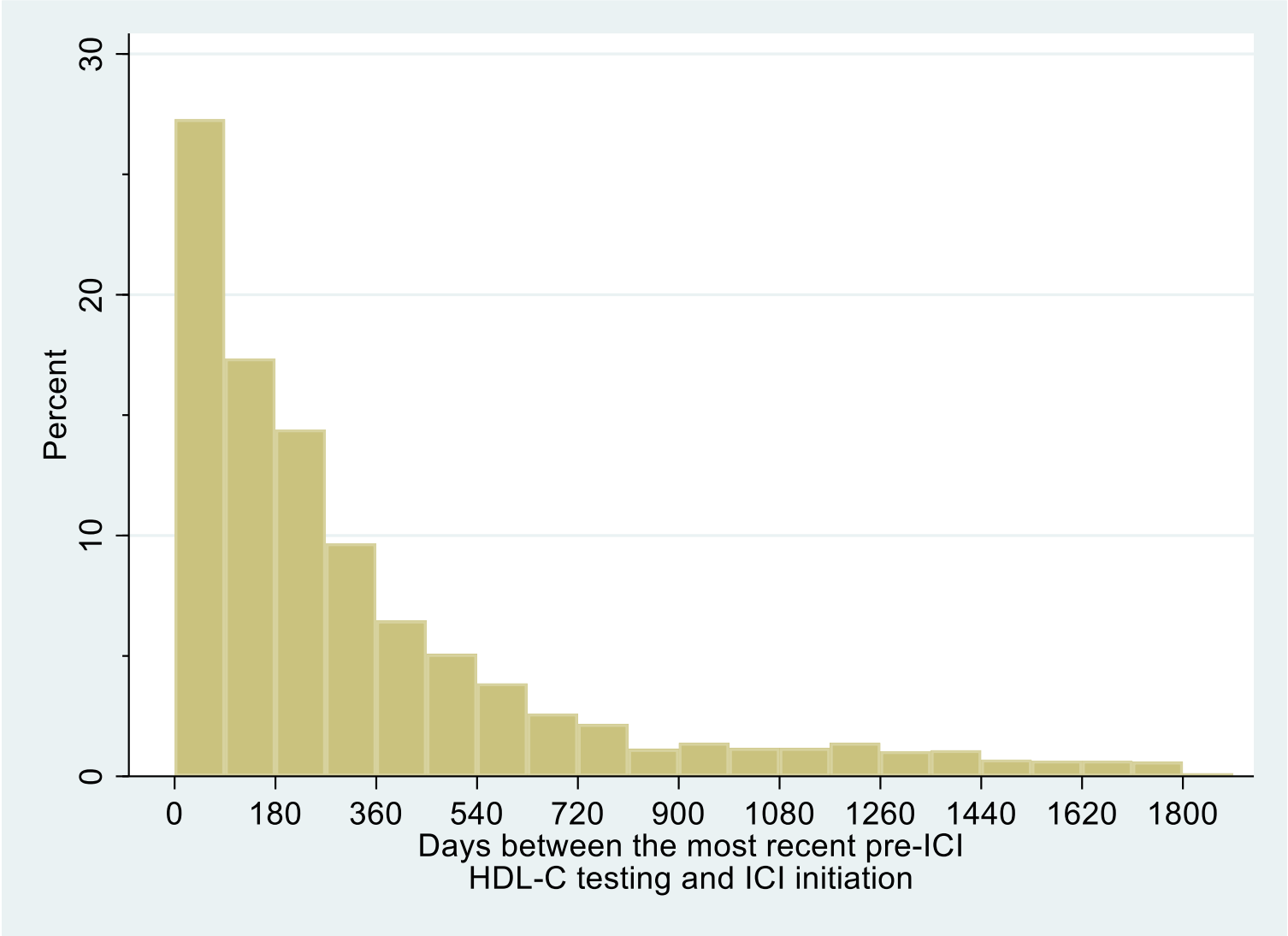
Supplementary Figure 14.19 Histogram showing the time between the most recent pre-immune checkpoint inhibitor (ICI) glycaemic testing and ICI initiation amongst those who ever had such testing within five years before ICI initiation (N=2891).



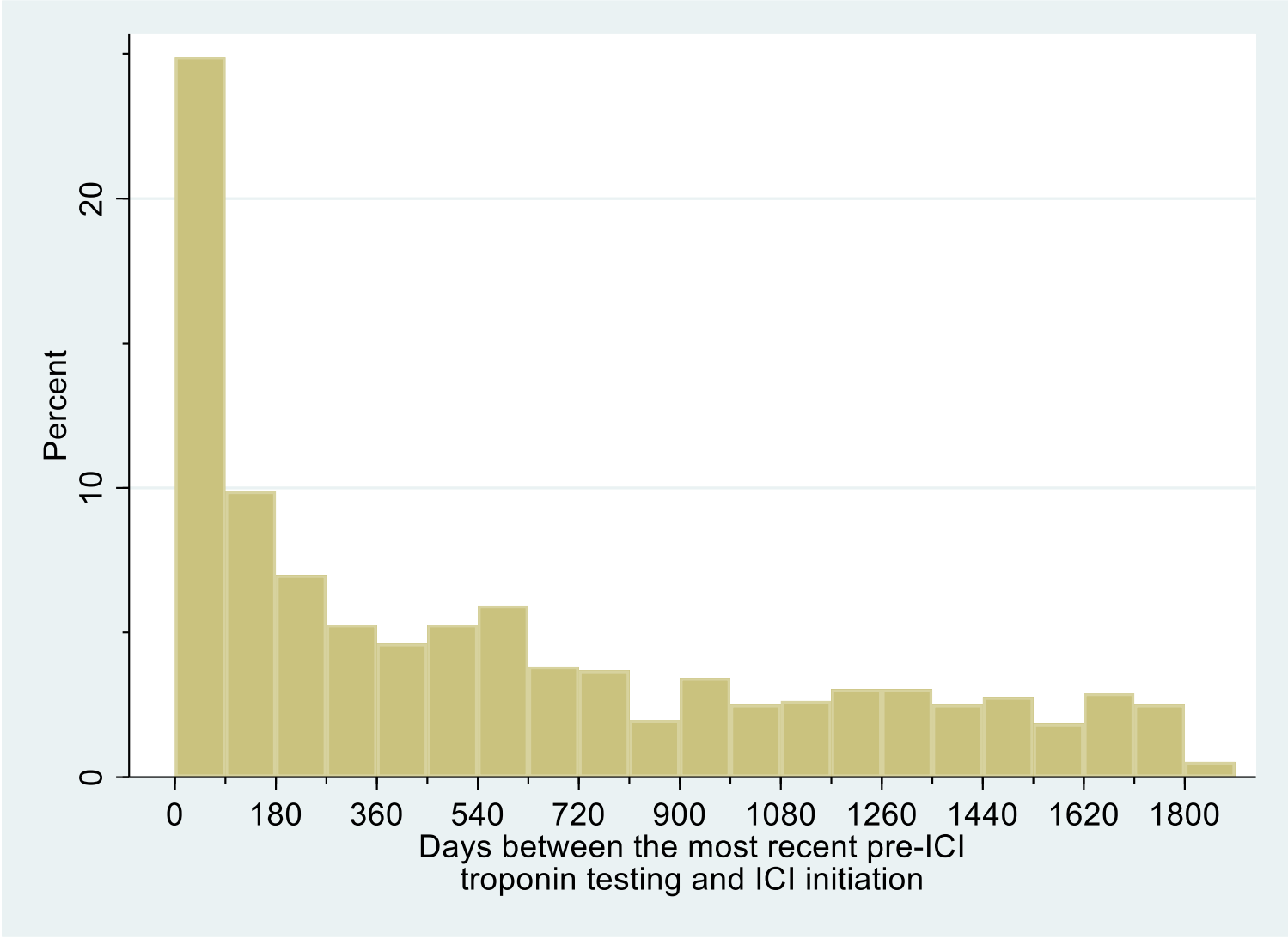
Supplementary Figure 14.20 Histogram showing the time between the most recent pre-immune checkpoint inhibitor (ICI) total cholesterol testing and ICI initiation amongst those who ever had such testing within five years before ICI initiation (N=2339).



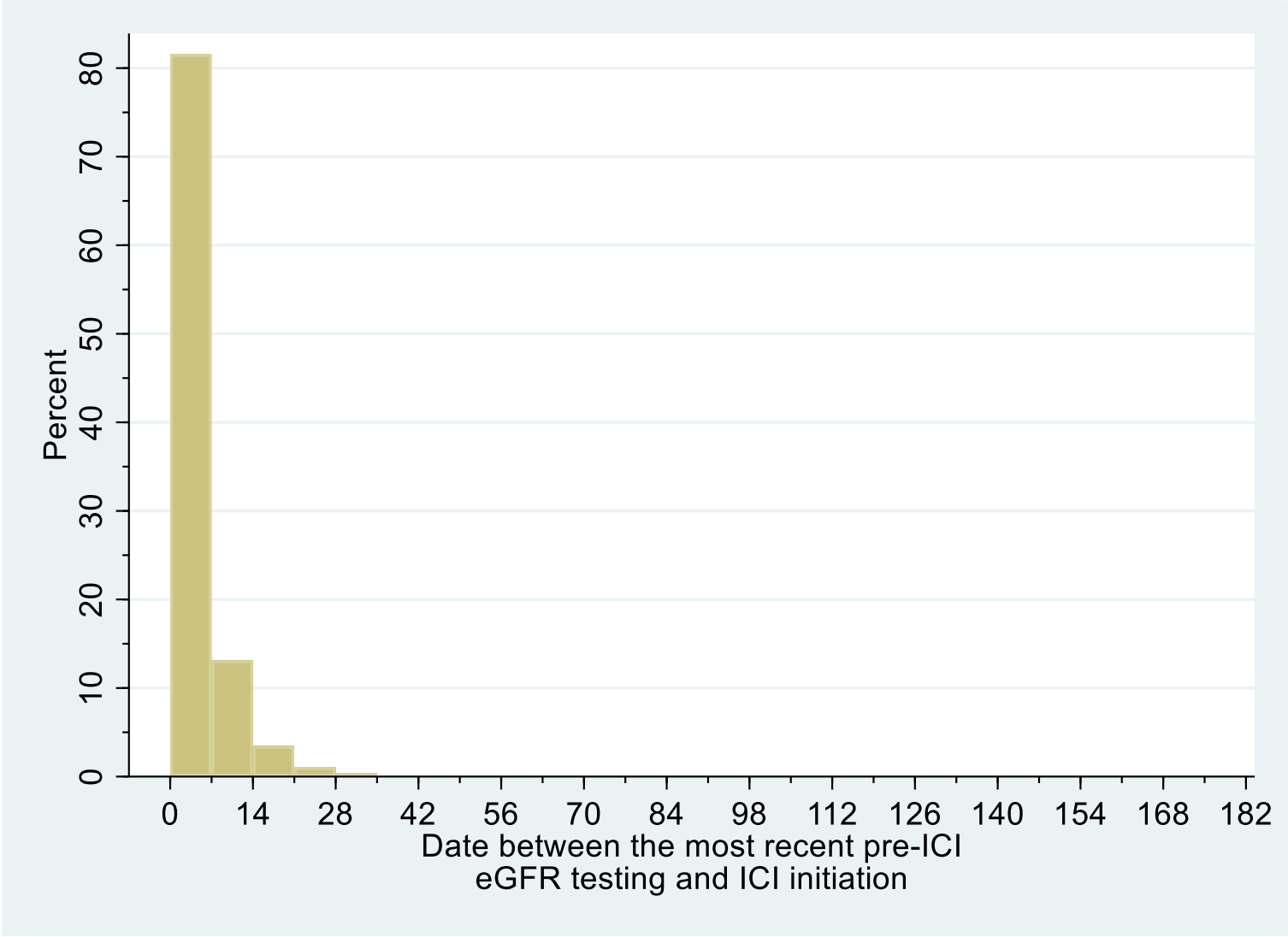
Supplementary Figure 14.21 Histogram showing the time between the most recent pre-immune checkpoint inhibitor (ICI) high density lipoprotein cholesterol (HDL-C) testing and ICI initiation amongst those who ever had such testing within five years before ICI initiation (N=2305).



Supplementary Figure 14.22 Histogram showing the time between the most recent pre-immune checkpoint inhibitor (ICI) troponin testing and ICI initiation amongst those who ever had such testing within five years before ICI initiation (N=759).



Supplementary Figure 14.23 Histogram showing the time between the most recent pre-immune checkpoint inhibitor (ICI) testing for estimated glomerular filtration rate and ICI initiation amongst those who ever had such testing within five years before ICI initiation (N=4318).



Glossary

ACEI, angiotensin-converting enzyme inhibitors.
ADT, androgen deprivation therapy.
aHR, adjusted hazard ratio.
aRR, adjusted risk ratio.
ANOVA, analysis of variance.
ARB, angiotensin receptor blockers.
ARSI, androgen receptor signalling inhibitors.
ARV, average real variability.
BO, bilateral orchidectomy.
CABG, coronary artery bypass graft.
CCB, calcium channel blocker.
CDARS, Clinical Data Analysis and Reporting System.
CI, confidence interval.
CMS, Centers for Medicare and Medicaid Services.
COPD, chronic obstructive pulmonary disease.
CTLA4, cytotoxic T-lymphocyte associated protein 4.
CV, coefficient of variation.
CVD, cardiovascular disease.
CVH, Cardiovascular health.
CVM, cardiovascular mortality.
DM, diabetes mellitus.
DPP4, dipeptidyl peptidase-4.
eGFR, estimated glomerular filtration rate.
ESC, European Society of Cardiology.
GLP1, glucagon-like peptide-1.
GnRH, gonadotropin-releasing hormone.
HbA1c, haemoglobin A1c.
HDL-C, high-density lipoprotein cholesterol.
HF, heart failure.
HFA-ICOS, Heart Failure Association – International Cardio-Oncology Society.
HR, hazard ratio.
ICD-9, International Classification of Diseases, Ninth Revision.
ICD-10, International Classification of Diseases, Tenth Revision.
ICI, immune checkpoint inhibitor.
IPTW, inverse probability of treatment weighting.
IPUMS, Integrated Public Use Microdata Series.
IQR, interquartile range.
IR, incidence rate.
IRR, incidence rate ratio.
LOS, length of stay.
LVEF, left ventricular ejection fraction.
MACE, major adverse cardiovascular events.
MI, myocardial infarction.
NA, not applicable / available.
NDI, National Death Index.

NHIS, National Health Interview Survey.
NPESC, neighbourhood, physical environment, and social cohesion.
OR, odds ratio.
PCa, prostate cancer.
PD-1, programmed cell death protein 1.
PD-L1, programmed cell death ligand 1.
PSA, prostate-specific antigen.
RCT, randomized controlled trial.
RMST, restricted mean survival time.
RP, radical prostatectomy.
SCCS, self-controlled case series.
SD, standard deviation.
SDOH, social determinants of health.
SGLT2i, sodium glucose cotransporter 2 inhibitor.
SHR, sub-hazard ratio.
SMD, standardized mean difference.
RR, risk ratio.
SPD, severe psychological distress.
STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.
US, United States.
VEGF, vascular endothelial growth factor.
VVHV, visit-to-visit HbA1c variability.
VVLV, visit-to-visit lipid variability.

References

1. Chan JSK, Chan RNC, Lee YHA, Satti DI, Dee EC, Ng K, et al. Cardiovascular health of patients with cancer: challenges abound. Trends Cardiovasc Med. 2024;
2. Global Burden of Disease 2019 Cancer Risk Factors Collaborators. Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019. JAMA Oncol. 2022 Mar 1;8(3):420–44.
3. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023 Jan 1;73(1):17–48.
4. Ian Paterson D, Natasha W, Cheung WY, Mackey JR, Edith P, Anthony R, et al. Incident Cardiovascular Disease Among Adults With Cancer. JACC CardioOncology. 2022 Mar 1;4(1):85–94.
5. Roberta F, Daya NR, Ndumele CE, Silvia K, Russell SD, Anna P, et al. Cardiovascular Disease Risk Among Cancer Survivors. J Am Coll Cardiol. 2022 Jul 5;80(1):22–32.
6. Yeh T-L, Hsu M-S, Hsu H-Y, Tsai M-C, Jhuang J-R, Chiang C-J, et al. Risk of cardiovascular diseases in cancer patients: A nationwide representative cohort study in Taiwan. BMC Cancer. 2022;22(1):1198.
7. Stoltzfus KC, Zhang Y, Sturgeon K, Sinoway LI, Trifiletti DM, Chinchilli VM, et al. Fatal heart disease among cancer patients. Nat Commun. 2020;11(1):2011.
8. Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J. 2019 Dec;40(48):3889–97.
9. Rohrmann S, Witassek F, Erne P, Rickli H, Radovanovic D. Treatment of patients with myocardial infarction depends on history of cancer. Eur Hear Journal Acute Cardiovasc Care. 2018 Oct;7(7):639–45.
10. Untaru R, Chen D, Kelly C, May A, Collins NJ, Leitch J, et al. Suboptimal Use of Cardioprotective Medications in Patients With a History of Cancer. JACC CardioOncology. 2020 Jun;2(2):312–5.
11. Agarwal MA, Aggarwal A, Rastogi S, Ventura HO, Lavie CJ. Cardiovascular disease burden in cancer patients from 2003 to 2014. Eur Hear J - Qual Care Clin Outcomes. 2018 Jan 1;4(1):69–70.
12. Shi S, Lv J, Chai R, Xue W, Xu X, Zhang B, et al. Opportunities and Challenges in Cardio-Oncology: A Bibliometric Analysis From 2010 to 2022. Curr Probl Cardiol. 2023;48(8):101227.
13. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022 Aug 26;
14. Razieh C, Zaccardi F, Miksza J, Davies MJ, Hansell AL, Khunti K, et al. Differences in the risk of cardiovascular disease across ethnic groups: UK Biobank observational study. Nutr Metab Cardiovasc Dis. 2022;32(11):2594–602.

15. Post WS, Watson KE, Hansen S, Folsom AR, Szklo M, Shea S, et al. Racial and Ethnic Differences in All-Cause and Cardiovascular Disease Mortality: The MESA Study. Circulation. 2022 Jul 19;146(3):229–39.

16. Chaturvedi N. Ethnic differences in cardiovascular disease. Heart. 2003 Jun;89(6):681–6.

17. Florido R, Daya NR, Ndumele CE, Koton S, Russell SD, Prizment A, et al. Cardiovascular Disease Risk Among Cancer Survivors: The Atherosclerosis Risk In Communities (ARIC) Study. J Am Coll Cardiol. 2022 Jul;80(1):22–32.

18. Strongman H, Gadd S, Matthews A, Mansfield KE, Stanway S, Lyon AR, et al. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using multiple linked UK electronic health records databases. Lancet. 2019 Sep 21;394(10203):1041–54.

19. Weberpals J, Jansen L, Müller OJ, Brenner H. Long-term heart-specific mortality among 347 476 breast cancer patients treated with radiotherapy or chemotherapy: a registry-based cohort study. Eur Heart J. 2018 Nov 14;39(43):3896–903.

20. de Vries S, Schaapveld M, van Nimwegen FA, Jóźwiak K, Lugtenburg PJ, Daniëls LA, et al. High burden of subsequent malignant neoplasms and cardiovascular disease in long-term Hodgkin lymphoma survivors. Br J Cancer. 2018;118(6):887–95.

21. Chen D-Y, Liu J-R, Tseng C-N, Hsieh M-J, Chuang C-K, Pang S-T, et al. Major Adverse Cardiovascular Events in Patients With Renal Cell Carcinoma Treated With Targeted Therapies. JACC CardioOncology. 2022 Jun;4(2):223–34.

22. Luo Z, Chi K, Zhao H, Liu L, Yang W, Luo Z, et al. Cardiovascular mortality by cancer risk stratification in patients with localized prostate cancer: a SEER-based study. Front Cardiovasc Med. 2023;10:1130691.

23. Feliciano EJG, Ho FD V, Yee K, Paguio JA, Eala MAB, Robredo JPG, et al. Cancer disparities in Southeast Asia: intersectionality and a call to action. Lancet Reg Heal – West Pacific. 2023 Dec 1;41.

24. Bloom MW, Hamo CE, Cardinale D, Ky B, Nohria A, Baer L, et al. Cancer Therapy–Related Cardiac Dysfunction and Heart Failure. Circ Hear Fail. 2016 Jan 1;9(1):e002661.

25. Hahn VS, Lenihan DJ, Ky B. Cancer Therapy–Induced Cardiotoxicity: Basic Mechanisms and Potential Cardioprotective Therapies. J Am Heart Assoc. 2014 Dec 7;3(2):e000665.

26. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared Risk Factors in Cardiovascular Disease and Cancer. Circulation. 2016 Mar 15;133(11):1104–14.

27. Dobbins M, Decorby K, Choi BCK. The Association between Obesity and Cancer Risk: A Meta-Analysis of Observational Studies from 1985 to 2011. ISRN Prev Med. 2013;2013:680536.

28. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med. 2010 Dec;363(23):2211–9.

29. Li T, Wei S, Shi Y, Pang S, Qin Q, Yin J, et al. The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. Br J Sports

Med. 2016 Mar;50(6):339–45.

30. Ling S, Brown K, Miksza JK, Howells L, Morrison A, Issa E, et al. Association of Type 2 Diabetes With Cancer: A Meta-analysis With Bias Analysis for Unmeasured Confounding in 151 Cohorts Comprising 32 Million People. Diabetes Care. 2020 Sep;43(9):2313–22.

31. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. Tobacco smoking and cancer: a meta-analysis. Int J cancer. 2008 Jan;122(1):155–64.

32. Tran KB, Lang JJ, Compton K, Xu R, Acheson AR, Henrikson HJ, et al. The global burden of cancer attributable to risk factors, 2010-19: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2022 Aug 20;400(10352):563–91.

33. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. Br J Cancer. 2015;112(3):580–93.

34. Zhang FF, Cudhea F, Shan Z, Michaud DS, Imamura F, Eom H, et al. Preventable Cancer Burden Associated With Poor Diet in the United States. JNCI cancer Spectr. 2019 Jun;3(2):pkz034.

35. Zhao Y, Jia H, Hua X, An T, Song J. Cardio-oncology: Shared Genetic, Metabolic, and Pharmacologic Mechanism. Curr Cardiol Rep. 2023;25(8):863–78.

36. Brancaccio M, Pirozzi F, Hirsch E, Ghigo A. Mechanisms underlying the cross-talk between heart and cancer. J Physiol. 2020 Jul 1;598(14):3015–27.

37. Herrmann J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. Nat Rev Cardiol. 2020;17(8):474–502.

38. Groarke JD, Nohria A. Anthracycline Cardiotoxicity. Circulation. 2015 Jun 2;131(22):1946–9.

39. Pondé NF, Lambertini M, de Azambuja E. Twenty years of anti-HER2 therapy-associated cardiotoxicity. ESMO Open. 2016;1(4):e000073.

40. Hu JR, Duncan MS, Morgans AK, Brown JD, Meijers WC, Freiberg MS, et al. Cardiovascular Effects of Androgen Deprivation Therapy in Prostate Cancer. Arterioscler Thromb Vasc Biol. 2020;40(3):e55.

41. Iacovelli R, Ciccarese C, Bria E, Romano M, Fantinel E, Bimbatti D, et al. The Cardiovascular Toxicity of Abiraterone and Enzalutamide in Prostate Cancer. Clin Genitourin Cancer. 2018 Jun 1;16(3):e645–53.

42. Drobni ZD, Alvi RM, Taron J, Zafar A, Murphy SP, Rambarat PK, et al. Association Between Immune Checkpoint Inhibitors With Cardiovascular Events and Atherosclerotic Plaque. Circulation. 2020 Dec 15;142(24):2299–311.

43. Ball S, Ghosh RK, Wongsaengsak S, Bandyopadhyay D, Ghosh GC, Aronow WS, et al. Cardiovascular Toxicities of Immune Checkpoint Inhibitors: JACC Review Topic of the Week. J Am Coll Cardiol. 2019;74(13):1714–27.

44. Chitturi KR, Burns EA, Muhsen IN, Anand K, Trachtenberg BH. Cardiovascular Risks with Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors and Monoclonal Antibody Therapy. Curr Oncol Rep. 2022 Apr;24(4):475–91.

45. Touyz RM, Herrmann J. Cardiotoxicity with vascular endothelial growth factor inhibitor therapy. NPJ Precis Oncol. 2018;2:13.

46. Belzile-Dugas E, Eisenberg MJ. Radiation-Induced Cardiovascular Disease: Review of an Underrecognized Pathology. J Am Heart Assoc. 2021 Sep 21;10(18):e021686.

47. Buza V, Rajagopalan B, Curtis AB. Cancer Treatment–Induced Arrhythmias. Circ Arrhythmia Electrophysiol. 2017 Aug 1;10(8):e005443.

48. Agarwal MA, Sridharan A, Pimentel RC, Markowitz SM, Rosenfeld LE, Fradley MG, et al. Ventricular Arrhythmia in Cancer Patients: Mechanisms, Treatment Strategies and Future Avenues. Arrhythmia Electrophysiol Rev. 2023;12:e16.

49. Leiva O, Beaty W, Soo S, Agarwal MA, Yang EH. Cancer Therapy-Associated Pulmonary Hypertension and Right Ventricular Dysfunction: Etiologies and Prognostic Implications. RCM. 2024;25(3):87-null.

50. Gürdoğan M, Demir M, Yalta K, Gülertop Y. Cancer Therapy-Related Pulmonary Hypertension: A Review of Mechanisms and Implications for Clinical Practice. Anatol J Cardiol. 2023 Jun;27(6):299–307.

51. Chan JSK, Tang P, Lee TTL, Chou OHI, Lee YHA, Li G, et al. Association between immune checkpoint inhibitors and myocardial infarction in Asians: A population-based self-controlled case series. Cancer Med. 2023 Feb 21;

52. Varricchi G, Galdiero MR, Marone G, Criscuolo G, Triassi M, Bonaduce D, et al. Cardiotoxicity of immune checkpoint inhibitors. ESMO Open. 2017;2(4):e000247.

53. Zhang M, Yang H, Xu C, Jin F, Zheng A. Risk Factors for Anthracycline-Induced Cardiotoxicity in Breast Cancer Treatment: A Meta-Analysis . Vol. 12, Frontiers in Oncology . 2022.

54. Hamnvik O-PR, Choueiri TK, Turchin A, McKay RR, Goyal L, Davis M, et al. Clinical risk factors for the development of hypertension in patients treated with inhibitors of the VEGF signaling pathway. Cancer. 2015 Jan 15;121(2):311–9.

55. Ezaz G, Long JB, Gross CP, Chen J. Risk Prediction Model for Heart Failure and Cardiomyopathy After Adjuvant Trastuzumab Therapy for Breast Cancer. J Am Heart Assoc. 2024 Jan 5;3(1):e000472.

56. Lee YHA, Hui JMH, Leung CH, Tsang CTW, Hui K, Tang P, et al. Major adverse cardiovascular events of enzalutamide versus abiraterone in prostate cancer: a retrospective cohort study. Prostate Cancer Prostatic Dis. 2023;

57. Palaskas N, Lopez-Mattei J, Durand JB, Iliescu C, Deswal A. Immune Checkpoint Inhibitor Myocarditis: Pathophysiological Characteristics, Diagnosis, and Treatment. J Am Heart Assoc. 2020 Jan 21;9(2).

58. Ho C-C, Wu S-L, Tsai H-Y, Hu Y-W, Chang Y-L. A retrospective cohort study on the cardiotoxicity incidence rates of immune checkpoint inhibitors for oncology patients. J Chinese Med Assoc. 2023;86(5).

59. Okura Y, Takayama T, Ozaki K, Tanaka H, Seki H, Takenouchi T, et al. Burden of cardiovascular disease in Japanese cancer patients and survivors: a single cancer-center study in Niigata City. Int J Clin Oncol. 2019;24(2):196–210.

60. Chan JSK, Tang P, Hui JMH, Lee YHA, Dee EC, Ng K, et al. Association between duration of gonadotrophin-releasing hormone agonist use and cardiovascular risks: A population-based competing-risk analysis. Prostate. 2022 Aug;

61. Chan JSK, Tang P, Ng K, Dee EC, Lee TTL, Chou OHI, et al. Cardiovascular risks of chemo-immunotherapy for lung cancer: A population-based cohort study. Lung Cancer. 2022 Dec 1;174:67–70.

62. Omland T, Heck SL, Gulati G. The Role of Cardioprotection in Cancer Therapy Cardiotoxicity: JACC: CardioOncology State-of-the-Art Review. JACC CardioOncology. 2022 Mar;4(1):19–37.

63. Qiu S, Zhou T, Qiu B, Zhang Y, Zhou Y, Yu H, et al. Risk Factors for Anthracycline-Induced Cardiotoxicity. Vol. 8, Frontiers in cardiovascular medicine. Switzerland; 2021. p. 736854.

64. Koulaouzidis G, Yung AE, Yung DE, Skonieczna-Żydecka K, Marlicz W, Koulaouzidis A, et al. Conventional cardiac risk factors associated with trastuzumab-induced cardiotoxicity in breast cancer: Systematic review and meta-analysis. Curr Probl Cancer. 2021 Oct;45(5):100723.

65. Naito T, Minegishi Y, Shiraishi H, Hoshino T, Maeda J, Yokota T, et al. Influence of background cardiovascular risk factors on VEGF inhibitor-related adverse vascular events in patients with non-small cell lung cancer: a retrospective study. J Cancer Res Clin Oncol. 2023 Oct;149(13):12435–42.

66. Kobat H, Elkonaissi I, Foreman E, Davidson M, Idaikkadar P, O'Brien M, et al. Smoking, Diabetes Mellitus, and Previous Cardiovascular Disease as Predictors of Anticancer Treatment-Induced Cardiotoxicity in Non-Small-Cell Lung Cancer: A Real-World Study. Clin Lung Cancer. 2024 Jan 1;25(1):e35–42.

67. Chen X, Jiang A, Zhang R, Fu X, Liu N, Shi C, et al. Immune Checkpoint Inhibitor-Associated Cardiotoxicity in Solid Tumors: Real-World Incidence, Risk Factors, and Prognostic Analysis. Front Cardiovasc Med. 2022;9.

68. Goldberg JF, Hyun G, Ness KK, Dixon SB, Towbin JA, Rhea IB, et al. Dyslipidemia and cardiovascular disease among childhood cancer survivors: a St. Jude Lifetime Cohort report. JNCI J Natl Cancer Inst. 2024 Mar 1;116(3):408–20.

69. Sun L, Brody R, Candelieri D, Lynch JA, Cohen RB, Li Y, et al. Risk of Cardiovascular Events Among Patients With Head and Neck Cancer. JAMA Otolaryngol Neck Surg. 2023 Aug 1;149(8):717–25.

70. Mitchell JD, Laurie M, Xia Q, Dreyfus B, Jain N, Jain A, et al. Risk profiles and incidence of cardiovascular events across different cancer types. ESMO Open. 2023 Dec 1;8(6).

71. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society. Eur J Heart Fail. 2020 Nov;22(11):1945–60.

72. Kim DY, Park M, Youn J, Lee S, Choi JH, Jung M, et al. Development and Validation of a Risk Score Model for Predicting the Cardiovascular Outcomes After Breast Cancer

Therapy: The CHEMO-RADIAT Score. J Am Heart Assoc. 2021 Aug 17;10(16):e021931.

73. Ma L, Wang Q, Li X, Shang Y, Zhang N, Wu J, et al. Development of a risk assessment model for cardiac injury in patients newly diagnosed with acute myeloid leukemia based on a multicenter, real-world analysis in China. BMC Cancer. 2024;24(1):132.

74. Stabellini N, Tan MC, Cullen J, Weintraub NL, Shanahan J, Agarwal N, et al. A novel cardiovascular disease risk score for prediction of atherosclerotic disease events in men with prostate cancer. J Clin Oncol. 2024 Jan 29;42(4_suppl):314.

75. Diamond A, Ayyappan S, Cao S, Tashtish N, Boughan KM, Cooper BW, et al. Development of a Risk Score for Cardiovascular Events in Anthracycline Treated DLBCL Patients. Blood. 2021;138:2536.

76. Felicetti F, D'Ascenzo F, Moretti C, Corrias A, Omedè P, Marra WG, et al. Prevalence of cardiovascular risk factors in long-term survivors of childhood cancer: 16 years follow up from a prospective registry. Eur J Prev Cardiol. 2015 Jun 1;22(6):762–70.

77. Lee H-H, Lee H, Bhatt DL, Lee G Bin, Han J, Shin DW, et al. Smoking habit change after cancer diagnosis: effect on cardiovascular risk. Eur Heart J. 2024 Jan 7;45(2):132–5.

78. Lee G, Jeong S, Choi S, Kim KH, Chang J, Kim SR, et al. Associations between alcohol consumption and cardiovascular disease among long-term survivors of colorectal cancer: a population-based, retrospective cohort study. BMC Cancer. 2021;21(1):710.

79. Ergas IJ, Cheng RK, Roh JM, Kushi LH, Kresovich JK, Iribarren C, et al. Diet quality and cardiovascular disease risk among breast cancer survivors in the Pathways Study. JNCI Cancer Spectr. 2024 Apr 1;8(2):pkae013.

80. de Baat EC, Mulder RL, Armenian S, Feijen EAM, Grotenhuis H, Hudson MM, et al. Dexrazoxane for preventing or reducing cardiotoxicity in adults and children with cancer receiving anthracyclines. Cochrane Database Syst Rev. 2022;(9).

81. van Dalen EC, Michiels EMC, Caron HN, Kremer LCM. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. Cochrane Database Syst Rev. 2010;(5).

82. Gregory HW, Ralph D, Teresa C, Karen C, Helen HM, H. JJ, et al. Statins and Left Ventricular Ejection Fraction Following Doxorubicin Treatment. NEJM Evid. 2022 Aug 23;1(9):EVIDoa2200097.

83. Neilan TG, Quinaglia T, Onoue T, Mahmood SS, Drobni ZD, Gilman HK, et al. Atorvastatin for Anthracycline-Associated Cardiac Dysfunction: The STOP-CA Randomized Clinical Trial. JAMA. 2023 Aug 8;330(6):528–36.

84. D'Amario D, Laborante R, Bianchini E, Galli M, Ciliberti G, Mennuni M, et al. Statins as preventive therapy for anthracycline cardiotoxicity: a meta-analysis of randomized controlled trials. Int J Cardiol. 2023 Nov;391:131219.

85. Titus A, Cheema HA, Shafiee A, Seighali N, Shahid A, Bhanushali KB, et al. Statins for Attenuating Cardiotoxicity in Patients Receiving Anthracyclines: A Systematic Review and Meta-Analysis. Curr Probl Cardiol. 2023;48(10):101885.

86. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al.

Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation. 2006 Dec;114(23):2474–81.

87. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J. 2016 Jun;37(21):1671–80.

88. Guglin M, Krischer J, Tamura R, Fink A, Bello-Matricaria L, McCaskill-Stevens W, et al. Randomized Trial of Lisinopril Versus Carvedilol to Prevent Trastuzumab Cardiotoxicity in Patients With Breast Cancer. J Am Coll Cardiol. 2019 Jun;73(22):2859–68.

89. Gao Y, Wang R, Jiang J, Hu Y, Li H, Wang Y. ACEI/ARB and beta-blocker therapies for preventing cardiotoxicity of antineoplastic agents in breast cancer: a systematic review and meta-analysis. Heart Fail Rev. 2023 Nov;28(6):1405–15.

90. Abdel-Qadir H, Carrasco R, Austin PC, Chen Y, Zhou L, Fang J, et al. The Association of Sodium-Glucose Cotransporter 2 Inhibitors With Cardiovascular Outcomes in Anthracycline-Treated Patients With Cancer. JACC CardioOncology. 2023 Jun;5(3):318–28.

91. Onoue T, Kang Y, Lefebvre B, Smith AM, Denduluri S, Carver J, et al. The Association of Metformin With Heart Failure in Patients With Diabetes Mellitus Receiving Anthracycline Chemotherapy. JACC CardioOncology. 2023 Oct;5(5):674–82.

92. Li X, Wu Z, Du X, Wu Y, Xie X, Shi L. Interventions for Preventing Cardiotoxicity in Breast Cancer Patients Receiving Trastuzumab: A Systemic Review and Bayesian Network Meta-Analysis. Front Pharmacol. 2021;12:718086.

93. Brown LJ, Meredith T, Yu J, Patel A, Neal B, Arnott C, et al. Heart Failure Therapies for the Prevention of HER2-Monoclonal Antibody-Mediated Cardiotoxicity: A Systematic Review and Meta-Analysis of Randomized Trials. Cancers (Basel). 2021 Nov;13(21).

94. Porter C, Azam TU, Mohananey D, Kumar R, Chu J, Lenihan D, et al. Permissive Cardiotoxicity: The Clinical Crucible of Cardio-Oncology. JACC CardioOncology. 2022 Sep 1;4(3):302–12.

95. Lopes RD, Higano CS, Slovin SF, Nelson AJ, Bigelow R, Sørensen PS, et al. Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Prostate Cancer: The Primary Results of the PRONOUNCE Randomized Trial. Circulation. 2021 Oct 19;144(16):1295–307.

96. Sciarra A, Busetto GM, Salciccia S, Del Giudice F, Maggi M, Crocetto F, et al. Does Exist a Differential Impact of Degarelix Versus LHRH Agonists on Cardiovascular Safety? Evidences From Randomized and Real-World Studies . Vol. 12, Frontiers in Endocrinology . 2021.

97. George G, Garmo H, Scailteux LM, Balusson F, De Coster G, De Schutter H, et al. Risk of cardiovascular disease following gonadotropin-releasing hormone agonists vs antagonists in prostate cancer: Real-world evidence from five databases. Int J Cancer. 2021 May 1;148(9):2203–11.

98. Duraes AR, de Souza Lima Bitar Y, Neto MG, Mesquita ET, Chan JS, Tse G, et al.

Effectiveness of sacubitril-valsartan in patients with cancer therapy-related cardiac dysfunction: a systematic review of clinical and preclinical studies. Minerva Med. 2022 Jun 1;113(3):551–7.

99. Mecinaj A, Gulati G, Heck SL, Holte E, Fagerland MW, Larsen AI, et al. Rationale and design of the PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy (PRADA II) trial: a randomized, placebo-controlled, multicenter trial. Cardio-oncology (London, England). 2021 Sep;7(1):33.

100. Cheung Y, Li VW, So EK, Cheng FW, Yau JP, Chiu S, et al. Remote Ischemic Conditioning in Pediatric Cancer Patients Receiving Anthracycline Chemotherapy: A Sham-Controlled Single-Blind Randomized Trial. JACC CardioOncology. 2023;5(3):332–42.

101. Mallouppas M, Chung R, Ghosh AK, Macklin A, Yellon DM, Walker JM. Anthracyclines and Biomarkers of Myocardial Injury: The Effect of Remote Ischemic Conditioning. JACC CardioOncology. 2023;5(3):343–55.

102. U.S. Department of Health and Human Services. Social Determinants of Health, Healthy People 2030 [Internet]. Available from: https://odphp.health.gov/healthypeople/priority-areas/social-determinants-health

103. Osei Baah F, Sharda S, Davidow K, Jackson S, Kernizan D, Jacobs JA, et al. Social Determinants of Health in Cardio-Oncology: Multi-Level Strategies to Overcome Disparities in Care: JACC: CardioOncology State-of-the-Art Review. JACC CardioOncology. 2024 Jun;6(3):331–46.

104. Rosengren A, Smyth A, Rangarajan S, Ramasundarahettige C, Bangdiwala SI, AlHabib KF, et al. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study. Lancet Glob Heal. 2019 Jun;7(6):e748–60.

105. Woodward M, Peters SAE, Batty GD, Ueshima H, Woo J, Giles GG, et al. Socioeconomic status in relation to cardiovascular disease and cause-specific mortality: a comparison of Asian and Australasian populations in a pooled analysis. BMJ Open. 2015 Mar;5(3):e006408.

106. Kucharska-Newton AM, Harald K, Rosamond WD, Rose KM, Rea TD, Salomaa V. Socioeconomic indicators and the risk of acute coronary heart disease events: comparison of population-based data from the United States and Finland. Ann Epidemiol. 2011 Aug;21(8):572–9.

107. Mosquera PA, San Sebastian M, Waenerlund A-K, Ivarsson A, Weinehall L, Gustafsson PE. Income-related inequalities in cardiovascular disease from mid-life to old age in a Northern Swedish cohort: A decomposition analysis. Soc Sci Med. 2016 Jan;149:135–44.

108. Batra A, Kong S, Cheung WY. Associations of Socioeconomic Status and Rurality With New-Onset Cardiovascular Disease in Cancer Survivors: A Population-Based Analysis. JCO Oncol Pract. 2021 Aug;17(8):e1189–201.

109. Appiah D, Farias RM, Olokede OA, Nwabuo CC, Bhende KM, Ebong IA, et al. The influence of individual and neighborhood-level characteristics on rural-urban disparities in cardiovascular disease mortality among U.S. women diagnosed with breast and gynecologic cancers. Gynecol Oncol. 2021 May;161(2):483–90.

110. Berkman AM, Andersen CR, Roth ME, Gilchrist SC. Cardiovascular disease in adolescent and young adult cancer survivors: Impact of sociodemographic and modifiable risk factors. Cancer. 2023 Feb;129(3):450–60.

111. Nasir K, Javed Z, Al-Kindi S. Embracing the Power of the Polysocial Risk Score: The Path to Health Equity∗. JACC CardioOncology. 2023;

112. Zhu W, Al-Kindi SG, Rajagopalan S, Rao X. Air Pollution in Cardio-Oncology and Unraveling the Environmental Nexus: JACC: CardioOncology State-of-the-Art Review. JACC CardioOncology. 2024 Jun;6(3):347–62.

113. Raisi-Estabragh Z, Kobo O, Freeman P, Petersen SE, Kolman L, Miller RJH, et al. Temporal trends in disease-specific causes of cardiovascular mortality amongst patients with cancer in the USA between 1999 and 2019. Eur Hear J - Qual Care Clin Outcomes. 2023 Jan 1;9(1):54–63.

114. Tan MC, Yeo YH, Ibrahim R, Tan MX, Lee JZ, Deshmukh AJ, et al. Trends and Disparities in Cardiovascular Death in Non-Hodgkin Lymphoma. Am J Cardiol. 2024;210:276–8.

115. Hahn RT, Wan EY, Leon MB. Inter-Ethnic Differences in Cardiovascular Disease: Impact on Therapies and Outcomes. JACC Asia. 2021 Jun;1(1):117–20.

116. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019 Sep;69(5):363–85.

117. Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, et al. Cancer treatment and survivorship statistics, 2022. CA Cancer J Clin. 2022 Sep;72(5):409–36.

118. Lenihan DJ, Cardinale DM. Late cardiac effects of cancer treatment. J Clin Oncol Off J Am Soc Clin Oncol. 2012 Oct;30(30):3657–64.

119. Jain V, Rifai M Al, Brinzevich D, Taj M, Saleh M, Krittanawong C, et al. Association of premature atherosclerotic cardiovascular disease with higher risk of cancer: a behavioral risk factor surveillance system study. Eur J Prev Cardiol. 2022 Mar;29(3):493–501.

120. Chan JSK, Lee YHA, Liu K, Hui JMH, Dee EC, Ng K, et al. Long-term cardiovascular burden in prostate cancer patients receiving androgen deprivation therapy. Eur J Clin Invest. 2022 Dec 5;53(4):e13932.

121. Chan JSK, Lakhani I, Lee TTL, Chou OHI, Lee YHA, Cheung YM, et al. Cardiovascular outcomes and hospitalizations in Asian patients receiving immune checkpoint inhibitors: a population-based study. Curr Probl Cardiol. 2022 Aug 27;101380.

122. Chan JSK, Satti DI, Lee YHA, Hui JMH, Dee EC, Ng K, et al. Temporal trends in cardiovascular burden among patients with prostate cancer receiving androgen deprivation therapy: a population-based cohort study. Br J Cancer. 2023;128(12):2253–60.

123. Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, et al. Socioeconomic Status and Cardiovascular Outcomes: Challenges and Interventions. Circulation. 2018 May;137(20):2166–78.

124. Powell-Wiley TM, Baumer Y, Baah FO, Baez AS, Farmer N, Mahlobo CT, et al. Social

Determinants of Cardiovascular Disease. Circ Res. 2022 Mar;130(5):782–99.

125. Witte J, Mehlis K, Surmann B, Lingnau R, Damm O, Greiner W, et al. Methods for measuring financial toxicity after cancer diagnosis and treatment: a systematic review and its implications. Ann Oncol Off J Eur Soc Med Oncol. 2019 Jul;30(7):1061–70.

126. Ian Paterson D, Wiebe N, Cheung WY, Mackey JR, Pituskin E, Reiman A, et al. Incident Cardiovascular Disease Among Adults With Cancer: A Population-Based Cohort Study. JACC CardioOncology. 2022 Mar;4(1):85–94.

127. Centers for Disease Control and Prevention. National health interview survey: methods. [Internet]. Available from: https://www.cdc.gov/nchs/nhis/about/nhis-methods.html

128. IPUMS. IPUMS Health Surveys: Sample Person Weight [Internet]. Available from: https://nhis.ipums.org/nhis/userNotes_weights.shtml

129. IPUMS Health Surveys: National Health Interview Survey. [Internet]. Available from: https://nhis.ipums.org/nhis/

130. Sanford NN, Lam MB, Butler SS, Ahn C, Beg MS, Aizer AA, et al. Self-reported Reasons and Patterns of Noninsurance Among Cancer Survivors Before and After Implementation of the Affordable Care Act, 2000-2017. JAMA Oncol. 2019 Oct;5(10):e191973.

131. Nipp RD, Shui AM, Perez GK, Kirchhoff AC, Peppercorn JM, Moy B, et al. Patterns in Health Care Access and Affordability Among Cancer Survivors During Implementation of the Affordable Care Act. JAMA Oncol. 2018 Jun;4(6):791–7.

132. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, et al. Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. Circulation. 2022 Aug 2;146(5):e18–43.

133. Sharma G, Grandhi GR, Acquah I, Mszar R, Mahajan S, Khan SU, et al. Social Determinants of Suboptimal Cardiovascular Health Among Pregnant Women in the United States. J Am Heart Assoc. 2022 Jan;11(2):e022837.

134. Artiga S, Hinton E. Beyond health care: the role of social determinants in promoting health and health equity. Kaiser Fam Found. 2018;10.

135. Khan SU, Acquah I, Javed Z, Valero-Elizondo J, Yahya T, Blankstein R, et al. Social Determinants of Health Among Non-Elderly Adults With Stroke in the United States. Mayo Clin Proc. 2022 Feb;97(2):238–49.

136. Harrell FE. With Applications to Linear Models, Logistic Regression, and Survival Analysis. In: Regression Modeling Strategies. New York: Springer; 2001.

137. National Institute of Health. Drinking Levels Defined [Internet]. Available from: https://www.niaaa.nih.gov/health-professionals-communities/core-resource-on-alcohol/basics-defining-how-much-alcohol-too-much

138. Javed Z, Valero-Elizondo J, Dudum R, Khan SU, Dubey P, Hyder AA, et al. Development and validation of a polysocial risk score for atherosclerotic cardiovascular disease. Am J Prev Cardiol. 2021 Dec;8:100251.

139. Al Rifai M, Jia X, Pickett J, Hussain A, Navaneethan SD, Birtcher KK, et al. Social

Determinants of Health and Comorbidities Among Individuals with Atherosclerotic Cardiovascular Disease: The Behavioral Risk Factor Surveillance System Survey. Popul Health Manag. 2022 Feb;25(1):39–45.

140. Makhlouf MHE, Motairek I, Chen Z, Nasir K, Deo S V, Rajagopalan S, et al. Neighborhood Walkability and Cardiovascular Risk in the United States. Curr Probl Cardiol. 2023 Mar;48(3):101533.

141. Saiz AMJ, Aul AM, Malecki KM, Bersch AJ, Bergmans RS, LeCaire TJ, et al. Food insecurity and cardiovascular health: Findings from a statewide population health survey in Wisconsin. Prev Med (Baltim). 2016 Dec;93:1–6.

142. Sims M, Kershaw KN, Breathett K, Jackson EA, Lewis LM, Mujahid MS, et al. Importance of Housing and Cardiovascular Health and Well-Being: A Scientific Statement From the American Heart Association. Circ Cardiovasc Qual Outcomes. 2020 Aug;13(8):e000089.

143. Figueroa JF, Frakt AB, Jha AK. Addressing Social Determinants of Health: Time for a Polysocial Risk Score. JAMA. 2020 Apr;323(16):1553–4.

144. Ganatra S, Dani SS, Kumar A, Khan SU, Wadhera R, Neilan TG, et al. Impact of Social Vulnerability on Comorbid Cancer and Cardiovascular Disease Mortality in the United States. JACC CardioOncology. 2022 Sep;4(3):326–37.

145. Lemstra M, Neudorf C, D'Arcy C, Kunst A, Warren LM, Bennett NR. A systematic review of depressed mood and anxiety by SES in youth aged 10-15 years. Can J Public Health. 2008;99(2):125–9.

146. Hudson DL, Puterman E, Bibbins-Domingo K, Matthews KA, Adler NE. Race, life course socioeconomic position, racial discrimination, depressive symptoms and self-rated health. Soc Sci Med. 2013 Nov;97:7–14.

147. Chan JSK, Satti DI, Dee EC, Sharma G, Virani SS, Liu T, et al. Association between psychological distress and cardiovascular health amongst cancer survivors in the United States: findings from nationally representative data. Eur J Prev Cardiol. 2023 Nov 1;30(16):e74–7.

148. Bassett E, Moore S. Social capital and depressive symptoms: the association of psychosocial and network dimensions of social capital with depressive symptoms in Montreal, Canada. Soc Sci Med. 2013 Jun;86:96–102.

149. Araya R, Dunstan F, Playle R, Thomas H, Palmer S, Lewis G. Perceptions of social capital and the built environment and mental health. Soc Sci Med. 2006 Jun;62(12):3072–83.

150. Fortmann AL, Gallo LC, Philis-Tsimikas A. Glycemic control among Latinos with type 2 diabetes: the role of social-environmental support resources. Heal Psychol Off J Div Heal Psychol Am Psychol Assoc. 2011 May;30(3):251–8.

151. O'Neal CW, Wickrama KAS, Ralston PA, Ilich JZ, Harris CM, Coccia C, et al. Examining change in social support and fruit and vegetable consumption in African American adults. J Nutr Health Aging. 2014 Jan;18(1):10–4.

152. Guite HF, Clark C, Ackrill G. The impact of the physical and urban environment on mental well-being. Public Health. 2006 Dec;120(12):1117–26.

153. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. J Psychosom Res. 2002 Oct;53(4):897–902.

154. Centers for Medicare & Medicaid Services Office of Minority Health. CMS Framework for Health Equity 2022-2032. 2023.

155. Safford MM, Reshetnyak E, Sterling MR, Richman JS, Muntner PM, Durant RW, et al. Number of Social Determinants of Health and Fatal and Nonfatal Incident Coronary Heart Disease in the REGARDS Study. Circulation. 2021 Jan;143(3):244–53.

156. Hoffman KE, McCarthy EP, Recklitis CJ, Ng AK. Psychological Distress in Long-term Survivors of Adult-Onset Cancer: Results From a National Survey. Arch Intern Med. 2009 Jul 27;169(14):1274–81.

157. Pimple P, Lima BB, Hammadah M, Wilmot K, Ramadan R, Levantsevych O, et al. Psychological Distress and Subsequent Cardiovascular Events in Individuals With Coronary Artery Disease. J Am Heart Assoc. 2019 May 7;8(9):e011866.

158. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022 Jan 1;72(1):7–33.

159. Blewett LA, Rivera Drew JA, King ML, Williams KCW, Del Ponte N, Convey P. IPUMS Health Surveys: National Health Interview Survey, Version 7.2. Minneapolis, MN: IPMUS; 2022.

160. Dee EC, Nipp RD, Muralidhar V, Yu Z, Butler SS, Mahal BA, et al. Financial worry and psychological distress among cancer survivors in the United States, 2013-2018. Support Care Cancer. 2021 Sep;29(9):5523–35.

161. Kessler RC, Barker PR, Colpe LJ, Epstein JF, Gfroerer JC, Hiripi E, et al. Screening for serious mental illness in the general population. Arch Gen Psychiatry. 2003 Feb;60(2):184–9.

162. Martin EA, Tan S-L, MacBride LR, Lavi S, Lerman LO, Lerman A. Sex differences in vascular and endothelial responses to acute mental stress. Clin Auton Res. 2008;18(6):339–45.

163. Ferrari AJ, Santomauro DF, Aali A, Abate YH, Abbafati C, Abbastabar H, et al. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systema. Lancet. 2024 May 18;403(10440):2133–61.

164. Mensah GA, Fuster V, Murray CJL, Roth GA, Mensah GA, Abate YH, et al. Global Burden of Cardiovascular Diseases and Risks, 1990-2022. J Am Coll Cardiol. 2023;82(25):2350–473.

165. Brandt EJ, Tobb K, Cambron JC, Ferdinand K, Douglass P, Nguyen PK, et al. Assessing and Addressing Social Determinants of Cardiovascular Health: JACC State-of-the-Art Review. J Am Coll Cardiol. 2023;81(14):1368–85.

166. Satti DI, Chan JSK, Dee EC, Lee YHA, Wai AKC, Dani SS, et al. Associations Between Social Determinants of Health and Cardiovascular Health of US Adult Cancer Survivors. JACC CardioOncology. 2024 Apr 28;0(0).

167. Pinheiro LC, Reshetnyak E, Akinyemiju T, Phillips E, Safford MM. Social determinants of health and cancer mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort study. Cancer. 2022 Jan;128(1):122–30.

168. Javed Z, Valero-Elizondo J, Cainzos-Achirica M, Sharma G, Mossialos E, Parekh T, et al. Race, Social Determinants of Health, and Risk of All-Cause and Cardiovascular Mortality in the United States. J racial Ethn Heal disparities. 2024 Apr;11(2):853–64.

169. Maqsood MH, Nguyen R, Chang R, Kundi H, Hagan K, Butt S, et al. Unfavorable social determinants of health and mortality risk by cardiovascular disease status: Findings from a National Study of United States Adults. Am Heart J. 2024;267:95–100.

170. Teshale AB, Htun HL, Owen A, Gasevic D, Phyo AZZ, Fancourt D, et al. The Role of Social Determinants of Health in Cardiovascular Diseases: An Umbrella Review. J Am Heart Assoc. 2023 Jul 4;12(13):e029765.

171. Jackson CA, Sudlow CLM, Mishra GD. Psychological Distress and Risk of Myocardial Infarction and Stroke in the 45 and Up Study. Circ Cardiovasc Qual Outcomes. 2018 Sep 1;11(9):e004500.

172. Welsh J, Banks E, Joshy G, Butterworth P, Strazdins L, Korda RJ. Does psychological distress directly increase risk of incident cardiovascular disease? Evidence from a prospective cohort study using a longer-term measure of distress. BMJ Open. 2021 Feb;11(2):e039628.

173. Garcia M, Moazzami K, Almuwaqqat Z, Young A, Okoh A, Shah AJ, et al. Psychological Distress and the Risk of Adverse Cardiovascular Outcomes in Patients With Coronary Heart Disease. JACC Adv. 2024;3(2):100794.

174. von Känel R, Hari R, Schmid J-P, Saner H, Begré S. Distress related to myocardial infarction and cardiovascular outcome: a retrospective observational study. BMC Psychiatry. 2011;11(1):98.

175. Sher L. Type D personality: the heart, stress, and cortisol. QJM An Int J Med. 2005 May 1;98(5):323–9.

176. Osborne MT, Shin LM, Mehta NN, Pitman RK, Fayad ZA, Tawakol A. Disentangling the Links Between Psychosocial Stress and Cardiovascular Disease. Circ Cardiovasc Imaging. 2020 Aug 1;13(8):e010931.

177. El Baou C, Desai R, Cooper C, Marchant NL, Pilling S, Richards M, et al. Psychological therapies for depression and cardiovascular risk: evidence from national healthcare records in England. Eur Heart J. 2023 May 7;44(18):1650–62.

178. Carmin CN, Ownby RL, Fontanella C, Steelesmith D, Binkley PF. Impact of Mental Health Treatment on Outcomes in Patients With Heart Failure and Ischemic Heart Disease. J Am Heart Assoc. 2024 Apr 2;13(7):e031117.

179. Hamer M, Chida Y, Molloy GJ. Psychological distress and cancer mortality. J Psychosom Res. 2009;66(3):255–8.

180. Roche KN, Cooper D, Armstrong TS, King AL. The link between psychological distress and survival in solid tumor patients: A systematic review. Cancer Med. 2023 Feb;12(3):3343–64.

181. Zeng Y, Hu C-H, Li Y-Z, Zhou J-S, Wang S-X, Liu M-D, et al. Association between

pretreatment emotional distress and immune checkpoint inhibitor response in non-small-cell lung cancer. Nat Med. 2024;

182. Berchuck JE, Meyer CS, Zhang N, Berchuck CM, Trivedi NN, Cohen B, et al. Association of Mental Health Treatment With Outcomes for US Veterans Diagnosed With Non-Small Cell Lung Cancer. JAMA Oncol. 2020 Jul;6(7):1055–62.

183. Ramsey SD, Bansal A, Fedorenko CR, Blough DK, Overstreet KA, Shankaran V, et al. Financial Insolvency as a Risk Factor for Early Mortality Among Patients With Cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2016 Mar;34(9):980–6.

184. Inoue S, Yorifuji T, Takao S, Doi H, Kawachi I. Social cohesion and mortality: a survival analysis of older adults in Japan. Am J Public Health. 2013 Dec;103(12):e60-6.

185. Arsanjani R, Khera N. Financial Toxicity in Cancer and Cardiovascular Disease: A Threat to Access and Quality of Care. Vol. 3, JACC. CardioOncology. United States; 2021. p. 247–9.

186. Marôco JL, Manafi MM, Hayman LL. Race and Ethnicity Disparities in Cardiovascular and Cancer Mortality: the Role of Socioeconomic Status—a Systematic Review and Meta-analysis. J Racial Ethn Heal Disparities. 2023;

187. Zhang C, Yang Z, Du R, Feng Y, Zhang X, Zhang J. Cardio-Oncologic Knowledge of Nurses in the Oncology Service: A Multi-Center Survey in China. J Multidiscip Healthc. 2023;16:4027–38.

188. Chan JSK, Chou OHI, Lee TTL, Lee YHA, Chan RNC, Dee EC, et al. Temporal trends in guideline-recommended cardiometabolic testing completeness before initiating immune checkpoint inhibitors: A cohort study. Journal of internal medicine. England; 2023.

189. Salazar E, Ren C, Rostron BL, Solomon G. Modeling mortality risk effects of cigarettes and smokeless tobacco: results from the National Health Interview Survey Linked Mortality File Data. BMC Public Health. 2021;21(1):1773.

190. Mirel LB, El Bural Félix S, Zhang C, Golden C, Cox CS. Comparative Analysis of the National Health Interview Survey Public-use and Restricted-use Linked Mortality Files. Natl Health Stat Report. 2020 Jun;(143):1–32.

191. Wang Y, Nie J, Ferrari G, Rey-Lopez JP, Rezende LFM. Association of Physical Activity Intensity With Mortality: A National Cohort Study of 403 681 US Adults. JAMA Intern Med. 2021 Feb 1;181(2):203–11.

192. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May 1;71(3):209–49.

193. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico A V., Davis BJ, Dorff T, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(5):479–505.

194. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2021 Feb 1;79(2):243–62.

195. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006 Sep 20;24(27):4448–56.

196. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020 Dec 22;76(25):2982–3021.

197. Culp MBB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. Eur Urol. 2020 Jan 1;77(1):38–52.

198. Guo Y, Dong X, Mao S, Yang F, Wang R, Ma W, et al. Causes of Death after Prostate Cancer Diagnosis: A Population-Based Study. Oxid Med Cell Longev. 2022;2022.

199. Kong X, Yang Y, Gao J, Guan J, Liu Y, Wang R, et al. Overview of the health care system in Hong Kong and its referential significance to mainland China. J Chinese Med Assoc. 2015 Oct 1;78(10):569–73.

200. Chan JSK, Zhou J, Lee S, Li A, Tan M, Leung KSK, et al. Fragmented QRS Is Independently Predictive of Long-Term Adverse Clinical Outcomes in Asian Patients Hospitalized for Heart Failure: A Retrospective Cohort Study. Front Cardiovasc Med. 2021 Nov 11;0:1634.

201. Lee YHA, Zhou J, Hui JMH, Liu X, Lee TTL, Hui K, et al. Risk of New-Onset Prostate Cancer for Metformin Versus Sulfonylurea Use in Type 2 Diabetes Mellitus: A Propensity Score-Matched Study. J Natl Compr Canc Netw. 2022 Jun 1;20(6):674–82.

202. Zhou J, Li H, Chang C, Wu WKK, Wang X, Liu T, et al. The association between blood pressure variability and hip or vertebral fracture risk: A population-based study. Bone. 2021 Sep 1;150.

203. Wai AKC, Wong CKH, Wong JYH, Xiong X, Chu OCK, Wong MS, et al. Changes in Emergency Department Visits, Diagnostic Groups, and 28-Day Mortality Associated With the COVID-19 Pandemic: A Territory-Wide, Retrospective, Cohort Study. Ann Emerg Med. 2022 Feb;79(2):148–57.

204. Wong JYH, Luk LYF, Yip TF, Lee TTL, Wai AKC, Ho JWK. Incidence of Emergency Department Visits for Sexual Abuse Among Youth in Hong Kong Before and During the COVID-19 Pandemic. JAMA Netw open. 2022 Oct;5(10):e2236278.

205. Cuzick J. A Wilcoxon-type test for trend. Stat Med. 1985;4(1):87–90.

206. Wilk M, Waśko-Grabowska A, Szmit S. Cardiovascular Complications of Prostate Cancer Treatment. Front Pharmacol. 2020 Dec 22;11.

207. Di Lorenzo G, Autorino R. Androgen Receptor Signaling Inhibitors in Nonmetastatic Castration-resistant Prostate Cancer and Risk of Cardiovascular Toxicity: All That Glitters Isn't Gold. Eur Urol. 2020 Nov 1;78(5):647–9.

208. Schubbe ME, Gellhaus PT, Tobert CM, Mott SL, Garje R, Erickson BA. Knowledge and Attitudes Regarding Surgical Castration in Men Receiving Androgen Deprivation Therapy for Metastatic Prostate Cancer and Their Relationship to Health-Related Quality of Life. Urology. 2021 Sep 1;155:179–85.

209. Anderson PT, Rowe NE. Current attitudes of Canadian urologists towards surgical castration in the treatment of prostate cancer. Can Urol Assoc J. 2021;15(5):E281.

210. Schaeffer E, Srinivas S, Antonarakis ES, Armstrong AJ, Bekelman JE, Cheng H, et al. NCCN Guidelines Insights: Prostate Cancer, Version 1.2021. J Natl Compr Canc Netw. 2021 Feb 2;19(2):134–43.

211. Rot I, Wassersug RJ, Walker LM. What do urologists think patients need to know when starting on androgen deprivation therapy? The perspective from Canada versus countries with lower gross domestic product. Transl Androl Urol. 2016 Apr 1;5(2):235–47.

212. Agrawal V, Ma X, Hu JC, Barbieri CE, Nagar H. Trends in Androgen Deprivation Use in Men With Intermediate-Risk Prostate Cancer Who Underwent Radiation Therapy. Adv Radiat Oncol. 2022 Jul 1;7(4):100904.

213. Leong DP, Fradet V, Shayegan B, Duceppe E, Siemens R, Niazi T, et al. Cardiovascular Risk in Men with Prostate Cancer: Insights from the RADICAL PC Study. J Urol. 2020 Jun 1;203(6):1109–16.

214. Davis MK, Rajala JL, Tyldesley S, Pickles T, Virani SA. The Prevalence of Cardiac Risk Factors in Men with Localized Prostate Cancer Undergoing Androgen Deprivation Therapy in British Columbia, Canada. J Oncol. 2015;2015:820403.

215. Sun L, Parikh RB, Hubbard RA, Cashy J, Takvorian SU, Vaughn DJ, et al. Assessment and Management of Cardiovascular Risk Factors Among US Veterans With Prostate Cancer. JAMA Netw Open. 2021 Feb 1;4(2):e210070–e210070.

216. Wilding S, Downing A, Selby P, Cross W, Wright P, Watson EK, et al. Decision regret in men living with and beyond nonmetastatic prostate cancer in the United Kingdom: A population-based patient-reported outcome study. Psychooncology. 2020 May 1;29(5):886–93.

217. Montazeri K, Unitt C, Foody JM, Harris JR, Partridge AH, Moslehi J. ABCDE steps to prevent heart disease in breast cancer survivors. Circulation. 2014;130(18):e157–9.

218. Bhatia N, Santos M, Jones LW, Beckman JA, Penson DF, Morgans AK, et al. Cardiovascular Effects of Androgen Deprivation Therapy for the Treatment of Prostate Cancer: ABCDE Steps to reduce Cardiovascular Disease in Patients with Prostate Cancer. Circulation. 2016 Feb 2;133(5):537.

219. Trapani D, Zagami P, Nicolò E, Pravettoni G, Curigliano G. Management of Cardiac Toxicity Induced by Chemotherapy. J Clin Med 2020, Vol 9, Page 2885. 2020 Sep 7;9(9):2885.

220. Alexandre J, Cautela J, Ederhy S, Damaj GL, Salem JE, Barlesi F, et al. Cardiovascular toxicity related to cancer treatment: A pragmatic approach to the american and european cardio-oncology guidelines. J Am Heart Assoc. 2020 Sep 15;9(18):18403.

221. Okwuosa TM, Morgans A, Rhee JW, Reding KW, Maliski S, Plana JC, et al. Impact of Hormonal Therapies for Treatment of Hormone-Dependent Cancers (Breast and Prostate) on the Cardiovascular System: Effects and Modifications: A Scientific Statement From the American Heart Association. Circ Genomic Precis Med. 2021 Jun 1;14(3):E000082.

222. Clemens J, Gottlieb JD. Do Physicians' Financial Incentives Affect Medical Treatment and Patient Health? Am Econ Rev. 2014;104(4):1320–49.

223. Wendt C, Kohl J. Translating Monetary Inputs into Health Care Provision: A Comparative Analysis of the Impact of Different Modes of Public Policy. J Comp Policy

Anal Res Pract. 2010 Feb 1;12(1–2):11–31.

224. Wong HF, Yee CH, Teoh JYC, Chan SYS, Chiu PKF, Cheung HY, et al. Time trend and characteristics of prostate cancer diagnosed in Hong Kong (China) in the past two decades. Asian J Androl. 2019 Jan 1;21(1):104.

225. Wong AYS, Root A, Douglas IJ, Chui CSL, Chan EW, Ghebremichael-Weldeselassie Y, et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. BMJ. 2016 Jan 14;352.

226. Lau WCY, Chan EW, Cheung CL, Sing CW, Man KKC, Lip GYH, et al. Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients With Nonvalvular Atrial Fibrillation. JAMA. 2017 Mar 21;317(11):1151–8.

227. Klil-Drori AJ, Yin H, Tagalakis V, Aprikian A, Azoulay L. Androgen Deprivation Therapy for Prostate Cancer and the Risk of Venous Thromboembolism. Eur Urol. 2016 Jul 1;70(1):56–61.

228. Blas L, Onozawa M, Shiota M, Hinotsu S, Sakamoto S, Kitagawa Y, et al. Long-term outcomes of androgen deprivation therapy in prostate cancer among Japanese men over 80 years old. Cancer Sci. 2021 Aug 1;112(8):3074–82.

229. Elmehrath AO, Afifi AM, Al-Husseini MJ, Saad AM, Wilson N, Shohdy KS, et al. Causes of Death Among Patients With Metastatic Prostate Cancer in the US From 2000 to 2016. JAMA Netw Open. 2021 Aug 4;4(8).

230. Simera I, Moher D, Hoey J, Schulz KF, Altman DG. A catalogue of reporting guidelines for health research. Eur J Clin Invest. 2010 Jan;40(1):35–53.

231. Tse G, Zhou J, Lee S, Wong W, Li X, Liu T, et al. Relationship between angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and COVID-19 incidence or severe disease. J Hypertens. 2021 Aug 1;39(8):1717–24.

232. Tsoi MF, Chung MH, Cheung BMY, Lau CS, Cheung TT. Epidemiology of gout in Hong Kong: A population-based study from 2006 to 2016. Arthritis Res Ther. 2020 Sep 4;22(1):1–9.

233. Lee YHA, Hui JMH, Chan JSK, Liu K, Dee EC, Ng K, et al. Metformin use and mortality in Asian, diabetic patients with prostate cancer on androgen deprivation therapy: A population-based study. Prostate. 2022 Sep 30;

234. Department of Health of the Hong Kong Special Administrative Region. Health facts of Hong Kong (2021 edition). 2021.

235. Wai AKC, Wong CKH, Wong JYH, Xiong X, Chu OCK, Wong MS, et al. Changes in Emergency Department Visits, Diagnostic Groups, and 28-Day Mortality Associated With the COVID-19 Pandemic: A Territory-Wide, Retrospective, Cohort Study. Ann Emerg Med. 2022 Feb 1;79(2):148–57.

236. Chan EW, Lau WCY, Siu CW, Lip GYH, Leung WK, Anand S, et al. Effect of suboptimal anticoagulation treatment with antiplatelet therapy and warfarin on clinical outcomes in patients with nonvalvular atrial fibrillation: A population-wide cohort study. Hear Rhythm. 2016 Aug 1;13(8):1581–8.

237. Lau WCY, Chan EW, Cheung C-L, Sing CW, Man KKC, Lip GYH, et al. Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients

With Nonvalvular Atrial Fibrillation. JAMA. 2017 Mar 21;317(11):1151–8.

238. Choi AWM, Wong JYH, Kam CW, Lau CL, Wong JKS, Lo RTF. Injury Patterns and Help-seeking Behavior in Hong Kong Male Intimate Partner Violence Victims. J Emerg Med. 2015 Aug 1;49(2):217–26.

239. Nielsen RO, Bertelsen ML, Ramskov D, Møller M, Hulme A, Theisen D, et al. Time-to-event analysis for sports injury research part 2: time-varying outcomes. Br J Sports Med. 2019 Jan 1;53(1):70–8.

240. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II—2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. Eur Urol. 2021 Feb 1;79(2):263–82.

241. Boland J, Choi W, Lee M, Lin J. Cardiovascular Toxicity of Androgen Deprivation Therapy. Curr Cardiol Rep. 2021 Jul;23(8):109.

242. Moudgil R, Yeh ETH. Mechanisms of Cardiotoxicity of Cancer Chemotherapeutic Agents: Cardiomyopathy and Beyond. Can J Cardiol. 2016 Jul;32(7):863-870.e5.

243. SCORE2-OP working group and ESC Cardiovascular risk collaboration. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J. 2021 Jul 1;42(25):2455–67.

244. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021 Jul;42(25):2439–54.

245. Wang H, Sun X, Zhao L, Chen X, Zhao J. Androgen deprivation therapy is associated with diabetes: Evidence from meta-analysis. J Diabetes Investig. 2016 Jul 1;7(4):629.

246. Keating NL, Liu PH, O'Malley AJ, Freedland SJ, Smith MR. Androgen Deprivation Therapy and Diabetes Control among Diabetic Men with Prostate Cancer. Eur Urol. 2014 Apr;65(4):816.

247. Haidar A, Yassin A, Saad F, Shabsigh R. Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes. http://dx.doi.org/101080/13685530701653538. 2009;10(4):189–96.

248. Bradley MC, Zhou Y, Freedman AN, Yood MU, Quesenbery CP, Haque R, et al. Risk of diabetes complications among those with diabetes receiving androgen deprivation therapy for localized prostate cancer. Cancer Causes Control. 2018 Aug 1;29(8):785–91.

249. Skriver M V, Sandbaek A, Kristensen JK, Støvring H. Relationship of HbA1c variability, absolute changes in HbA1c, and all-cause mortality in type 2 diabetes: a Danish population-based prospective observational study. BMJ Open Diabetes Res Care. 2015 Jan 1;3(1):e000060.

250. Kim HU, Park SP, Kim YK. Long-term HbA1c variability and the development and progression of diabetic retinopathy in subjects with type 2 diabetes. Sci Reports 2021 111. 2021 Feb 26;11(1):1–10.

251. Yang CY, Su PF, Hung JY, Ou HT, Kuo S. Comparative predictive ability of visit-to-

visit HbA1c variability measures for microvascular disease risk in type 2 diabetes. Cardiovasc Diabetol. 2020 Jul 6;19(1):1–10.

252. Lee S, Zhou J, Wong WT, Liu T, Wu WKK, Wong ICK, et al. Glycemic and lipid variability for predicting complications and mortality in diabetes mellitus using machine learning. BMC Endocr Disord. 2021 Dec 1;21(1):1–15.

253. Lee S, Liu T, Zhou J, Zhang Q, Wong WT, Tse G. Predictions of diabetes complications and mortality using hba1c variability: a 10-year observational cohort study. Acta Diabetol. 2021 Feb 1;58(2):171–80.

254. Mulè G, Calcaterra I, Costanzo M, Morreale M, D'Ignoto F, Castiglia A, et al. Average real variability of 24-h systolic blood pressure is associated with microalbuminuria in patients with primary hypertension. J Hum Hypertens 2016 303. 2015 Jun 18;30(3):164–70.

255. Mena L, Pintos S, Queipo N V., Aizpúrua JA, Maestre G, Sulbarán T. A reliable index for the prognostic significance of blood pressure variability. J Hypertens. 2005;23(3):505–11.

256. Royston P, Parmar MKB. Restricted mean survival time: An alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Med Res Methodol. 2013 Dec 7;13(1):1–15.

257. Ghouse J, Skov MW, Kanters JK, Lind B, Isaksen JL, Blanche P, et al. Visit-to-Visit Variability of Hemoglobin A 1c in People Without Diabetes and Risk of Major Adverse Cardiovascular Events and All-Cause Mortality. Diabetes Care. 2019 Jan 1;42(1):134–41.

258. Bancks MP, Carson AP, Lewis CE, Gunderson EP, Reis JP, Schreiner PJ, et al. Fasting glucose variability in young adulthood and incident diabetes, cardiovascular disease and all-cause mortality. Diabetologia. 2019 Aug 1;62(8):1366–74.

259. Zhou JJ, Investigators for the V, Koska J, Investigators for the V, Bahn G, Investigators for the V, et al. Fasting Glucose Variation Predicts Microvascular Risk in ACCORD and VADT. J Clin Endocrinol Metab. 2021 Mar 25;106(4):e1150–62.

260. Akrivos J, Ravona-Springer R, Schmeidler J, Leroith D, Heymann A, Preiss R, et al. Glycemic control, inflammation, and cognitive function in older patients with type 2 diabetes. Int J Geriatr Psychiatry. 2015 Oct 1;30(10):1093–100.

261. Chang CM, Hsieh CJ, Huang JC, Huang IC. Acute and chronic fluctuations in blood glucose levels can increase oxidative stress in type 2 diabetes mellitus. Acta Diabetol. 2012 Dec;49 Suppl 1(1 SUPPL.).

262. Golia E, Limongelli G, Natale F, Fimiani F, Maddaloni V, Pariggiano I, et al. Inflammation and cardiovascular disease: From pathogenesis to therapeutic target. Curr Atheroscler Rep. 2014 Jul 19;16(9):1–7.

263. Greten FR, Grivennikov SI. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. Immunity. 2019 Jul 16;51(1):27–41.

264. Cirne F, Aghel N, Petropoulos J-A, Klotz L, Lenihan DJ, Saad F, et al. The cardiovascular effects of gonadotropin-releasing hormone antagonists in men with prostate cancer. Eur Hear J - Cardiovasc Pharmacother. 2021 Jan 20;8(3):253–62.

265. Abufaraj M, Iwata T, Kimura S, Haddad A, Al-Ani H, Abusubaih L, et al. Differential Impact of Gonadotropin-releasing Hormone Antagonist Versus Agonist on Clinical Safety and Oncologic Outcomes on Patients with Metastatic Prostate Cancer: A Meta-analysis of Randomized Controlled Trials. Eur Urol. 2021 Jan 1;79(1):44–53.

266. Klotz L, Miller K, Crawford ED, Shore N, Tombal B, Karup C, et al. Disease Control Outcomes from Analysis of Pooled Individual Patient Data from Five Comparative Randomised Clinical Trials of Degarelix Versus Luteinising Hormone-releasing Hormone Agonists. Eur Urol. 2014;66(6):1101–8.

267. Bernard B, Muralidhar V, Chen Y-H, Sridhar SS, Mitchell EP, Pettaway CA, et al. Impact of ethnicity on the outcome of men with metastatic, hormone-sensitive prostate cancer. Cancer. 2017 May;123(9):1536–44.

268. Hahn RT, Wan EY, Leon MB. Inter-Ethnic Differences in Cardiovascular Disease: Impact on Therapies and Outcomes. JACC Asia. 2021 Jun 1;1(1):117–20.

269. Dee EC, Paguio JA, Yao JS, Lim J, Lasco G. Asian minorities in Asian countries: intersecting disparities affecting minoritised groups. Lancet Oncol. 2021 Sep 1;22(9):e381.

270. Lee TTL, Hui JMH, Lee YHA, Satti DI, Shum YKL, Kiu PTH, et al. Sulfonylurea Is Associated With Higher Risks of Ventricular Arrhythmia or Sudden Cardiac Death Compared With Metformin: A Population-Based Cohort Study. J Am Heart Assoc. 2022 Sep 20;11(18):e026289.

271. Aalen OO, Johansen S. An Empirical Transition Matrix for Non-Homogeneous Markov Chains Based on Censored Observations. Scand J Stat. 1978;5(3):141–50.

272. Discacciati A, Oskarsson V, Orsini N. STPHCOXRCS: Stata module to check proportional-hazards assumption using restricted cubic splines. Statistical Software Components, Boston College Department of Economics; 2015.

273. Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol. 2014 Mar;65(3):565–73.

274. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry: diabetes mellitus -- evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. 2008.

275. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. 2012.

276. Shore ND, Saad F, Cookson MS, George DJ, Saltzstein DR, Tutrone R, et al. Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer. N Engl J Med. 2020 Jun 4;382(23):2187–96.

277. Race Relations Unit. The Demographics: Ethnic Groups [Internet]. Home Affairs Department, The Government of the Hong Kong Special Administrative Region; 2022 [cited 2023 Feb 15]. Available from: https://www.had.gov.hk/rru/english/info/demographics.htm

278. Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. Int Immunopharmacol. 2018 Sep 1;62:29–39.

279. Dong M, Yu T, Zhang Z, Zhang J, Wang R, Tse G, et al. ICIs-Related Cardiotoxicity in Different Types of Cancer. J Cardiovasc Dev Dis. 2022 Jun 28;9(7):203.

280. Zhou J, Chau YLA, Yoo JW, Lee S, Ng K, Dee EC, et al. Liver Immune-related Adverse Effects of Programmed Cell Death 1 (PD-1) and Programmed Cell Death Ligand 1 (PD-L1) Inhibitors: A Propensity Score Matched Study with Competing Risk Analyses. Clin Oncol (R Coll Radiol). 2022 Jul 1;34(7):e316–7.

281. Zhou J, Lee S, Lakhani I, Yang L, Liu T, Zhang Y, et al. Adverse Cardiovascular Complications following prescription of programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors: a propensity-score matched Cohort Study with competing risk analysis. Cardio-oncology (London, England). 2022 Dec 1;8(1).

282. Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. Lancet Oncol. 2018 Sep 1;19(9):e447–58.

283. Zhang N, Tse G, Liu T. Neutrophil-lymphocyte ratio in the immune checkpoint inhibitors-related atherosclerosis. Eur Heart J. 2021 Jun 7;42(22):2215.

284. Li L, Li G, Rao B, Dong AH, Liang W, Zhu JX, et al. Landscape of immune checkpoint inhibitor-related adverse events in Chinese population. Sci Rep. 2020 Dec 1;10(1).

285. Hospital Authority. Chapter 113. In: Hospital Authority Ordinance. 2020.

286. Rubio-Infante N, Ramírez-Flores YA, Castillo EC, Lozano O, García-Rivas G, Torre-Amione G. Cardiotoxicity associated with immune checkpoint inhibitor therapy: a meta-analysis. Eur J Heart Fail. 2021 Oct 1;23(10):1739–47.

287. Dolladille C, Akroun J, Morice PM, Dompmartin A, Ezine E, Sassier M, et al. Cardiovascular immunotoxicities associated with immune checkpoint inhibitors: a safety meta-analysis. Eur Heart J. 2021 Dec 21;42(48):4964–77.

288. Wang DY, Salem JE, Cohen J V., Chandra S, Menzer C, Ye F, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Oncol. 2018 Dec 1;4(12):1721–8.

289. Escudier M, Cautela J, Malissen N, Ancedy Y, Orabona M, Pinto J, et al. Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor-Related Cardiotoxicity. Circulation. 2017 Nov 1;136(21):2085–7.

290. Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. Lancet (London, England). 2018 Mar 10;391(10124):933.

291. Brumberger ZL, Branch ME, Klein MW, Seals A, Shapiro MD, Vasu S. Cardiotoxicity risk factors with immune checkpoint inhibitors. Cardio-Oncology. 2022 Dec 1;8(1):1–8.

292. Upadhrasta S, Elias H, Patel K, Zheng L. Managing cardiotoxicity associated with immune checkpoint inhibitors. Chronic Dis Transl Med. 2019 Mar;5(1):6.

293. Zhou YW, Zhu YJ, Wang MN, Xie Y, Chen CY, Zhang T, et al. Immune checkpoint inhibitor-associated cardiotoxicity: Current understanding on its mechanism, diagnosis and management. Front Pharmacol. 2019;10:1350.

294. Mahmood SS, Fradley MG, Cohen J V., Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol. 2018 Apr 24;71(16):1755–64.

295. Jain P, Gutierrez Bugarin J, Guha A, Jain C, Patil N, Shen T, et al. Cardiovascular adverse events are associated with usage of immune checkpoint inhibitors in real-world clinical data across the United States. ESMO Open. 2021 Oct 1;6(5).

296. Yuan M, Zang L, Xu A, Gong M, Liu Q, Huo B, et al. Dynamic Changes of Serum Heart Type-Fatty Acid Binding Protein in Cancer Patients Treated With Immune Checkpoint Inhibitors. Front Pharmacol. 2021 Oct 1;12.

297. Peravali M, Gomes-Lima C, Tefera E, Baker M, Sherchan M, Farid S, et al. Racial disparities in immune-related adverse events of immune checkpoint inhibitors and association with survival based on clinical and biochemical responses. World J Clin Oncol. 2021 Feb 2;12(2):103.

298. Resnick K, Zang P, Larsen T, Ye S, Choi A, Yu X, et al. Impact of ethnicity and immune-related adverse events (IRAE) on outcomes for non-small cell lung cancer (NSCLC) patients treated with immune checkpoint inhibitors. https://doi.org/101200/JCO20224016_suppl.e21115. 2022 Jun 2;40(16_suppl):e21115–e21115.

299. Song W, Zheng Y, Dong M, Zhong L, Bazoukis G, Perone F, et al. Electrocardiographic features of immune checkpoint inhibitor-associated myocarditis. Curr Probl Cardiol. 2022 Nov;101478.

300. Budoff MJ, Nasir K, Mao S, Tseng PH, Chau A, Liu ST, et al. Ethnic differences of the presence and severity of coronary atherosclerosis. Atherosclerosis. 2006 Aug;187(2):343–50.

301. Joseph KS, Mehrabadi A, Lisonkova S. Confounding by Indication and Related Concepts. Curr Epidemiol Reports. 2014;1(1):1–8.

302. Kerr S, Joy M, Torabi F, Bedston S, Akbari A, Agrawal U, et al. First dose ChAdOx1 and BNT162b2 COVID-19 vaccinations and cerebral venous sinus thrombosis: A pooled self-controlled case series study of 11.6 million individuals in England, Scotland, and Wales. PLoS Med. 2022 Feb;19(2):e1003927.

303. Ghisoni E, Wicky A, Bouchaab H, Imbimbo M, Delyon J, Gautron Moura B, et al. Late-onset and long-lasting immune-related adverse events from immune checkpoint-inhibitors: An overlooked aspect in immunotherapy. Eur J Cancer. 2021 May;149:153–64.

304. Hosseiny AD, Moloi S, Chandrasekhar J, Farshid A. Mortality pattern and cause of death in a long-term follow-up of patients with STEMI treated with primary PCI. Open Hear. 2016 Apr 1;3(1):e000405.

305. Poels K, van Leent MMT, Boutros C, Tissot H, Roy S, Meerwaldt AE, et al. Immune Checkpoint Inhibitor Therapy Aggravates T Cell-Driven Plaque Inflammation in Atherosclerosis. JACC CardioOncology. 2020 Nov;2(4):599–610.

306. Achim A, Liblik K, Gevaert S. Immune checkpoint inhibitors – the revolutionary cancer immunotherapy comes with a cardiotoxic price. Trends Cardiovasc Med. 2022;

307. Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-

term implications of toxicity. Nat Rev Clin Oncol. 2022 Apr;19(4):254–67.

308. Poels K, Neppelenbroek SIM, Kersten MJ, Antoni ML, Lutgens E, Seijkens TTP. Immune checkpoint inhibitor treatment and atherosclerotic cardiovascular disease: an emerging clinical problem. J Immunother Cancer. 2021 Jun 1;9(6):e002916.

309. Lee GA, Aktaa S, Baker E, Gale CP, Yaseen IF, Gulati G, et al. European Society of Cardiology quality indicators for the prevention and management of cancer therapy-related cardiovascular toxicity in cancer treatment. Eur Hear J - Qual Care Clin Outcomes. 2023 Jan 1;9(1):1–7.

310. Cheung N-T, Fung V, Wong WN, Tong A, Sek A, Greyling A, et al. Principles-based medical informatics for success--how Hong Kong built one of the world's largest integrated longitudinal electronic patient records. Stud Health Technol Inform. 2007;129(Pt 1):307–10.

311. Chan EW, Lau WCY, Leung WK, Mok MTC, He Y, Tong TSM, et al. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. Gastroenterology. 2015 Sep 1;149(3):586-595.e3.

312. Yang A, Shi M, Lau ESH, Wu H, Zhang X, Fan B, et al. Clinical outcomes following discontinuation of renin-angiotensin-system inhibitors in patients with type 2 diabetes and advanced chronic kidney disease: a prospective cohort study. eClinicalMedicine. 2023 Jan 1;55.

313. Wong MCS, Jiang JY, Tang J, Lam A, Fung H, Mercer SW. Health services research in the public healthcare system in Hong Kong: An analysis of over 1 million antihypertensive prescriptions between 2004–2007 as an example of the potential and pitfalls of using routinely collected electronic patient data. BMC Health Serv Res. 2008;8(1):138.

314. Centre for Health Protection of the Department of Health - The Hong Kong Special Administrative Region Government. Death Rates by Leading Causes of Death, 2001 - 2022 [Internet]. 2023. Available from: https://www.chp.gov.hk/en/statistics/data/10/27/117.html

315. American Diabetes Association Professional Practice Committee. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care. 2022 Jan 1;45(Supplement_1):S17–38.

316. Liu Y. A novel cardio-oncology service line model in optimizing care access, quality and equity for large, multi-hospital health systems. Cardio-Oncology. 2023;9(1):16.

317. Tse G, Shao Q, Liu J, Zhang Y. The Potential Impact of the 2022 ESC Cardio-Oncology Guidelines on Clinical Practice in China. Vol. 5, JACC. CardioOncology. United States; 2023. p. 153–5.

318. Satti DI, Chan JSK, Dee EC, Lee YHA, Wai AKC, Dani SS, et al. Associations Between Social Determinants of Health and Cardiovascular Health of US Adult Cancer Survivors. JACC CardioOncology. 2024 Feb 3;0(0).

319. Chan JSK, Satti DI, Ching YLA, Lee Q, Dee EC, Ng K, et al. Associations between social determinants of health and cardiovascular and cancer mortality in cancer survivors: a prospective cohort study. Eur J Prev Cardiol. 2024 Oct 30;zwae318.

320. Chebrolu S, Kazibwe R, Soliman EZ. Association Between Family Income, Subclinical

Myocardial Injury, and Cardiovascular Mortality in the General Population. Clin Cardiol. 2024 Oct;47(10):e70036.

321. Rebouillat P, Mattisson K, Gefenaite G, Nilsson P, Björk J. Outdoor living environment and cardiovascular disease risk: results from a Swedish cohort. Eur J Public Health. 2024 Nov 1;34(Supplement_3):ckae144.910.

322. Sun Y, Liu B, Rong S, Du Y, Xu G, Snetselaar LG, et al. Food Insecurity Is Associated With Cardiovascular and All-Cause Mortality Among Adults in the United States. J Am Heart Assoc. 2020 Oct;9(19):e014629.

323. Hayes RB, Lim C, Zhang Y, Cromar K, Shao Y, Reynolds HR, et al. PM2.5 air pollution and cause-specific cardiovascular disease mortality. Int J Epidemiol. 2020 Feb;49(1):25–35.

324. Coleman NC, Ezzati M, Marshall JD, Robinson AL, Burnett RT, Pope CA 3rd. Fine Particulate Matter Air Pollution and Mortality Risk Among US Cancer Patients and Survivors. JNCI cancer Spectr. 2021 Feb;5(1).

325. Lubas MM, Wang M, Jefferies JL, Ness KK, Ehrhardt MJ, Krull KR, et al. The Contribution of Stress and Distress to Cardiovascular Health in Adult Survivors of Childhood Cancer. Cancer Epidemiol biomarkers Prev a Publ Am Assoc Cancer Res cosponsored by Am Soc Prev Oncol. 2021 Feb;30(2):286–94.

326. Hong Y-R, Wang R, Case S, Jo A, Turner K, Ross KM. Association of food insecurity with overall and disease-specific mortality among cancer survivors in the US. Support care cancer Off J Multinatl Assoc Support Care Cancer. 2024 Apr;32(5):309.

327. Liu J, Yang L, Xiao L, Tao Z. Perceived Neighborhood Environment Impacts on Health Behavior, Multi-Dimensional Health, and Life Satisfaction. Front Public Heal. 2022;10.

328. Bou Khalil R. "Emotional Chemobrain": A new concept for chemotherapy adverse drug effect? Encephale. 2021 Dec;47(6):613–5.

329. Dahlgren G, Whitehead M. The Dahlgren-Whitehead model of health determinants: 30 years on and still chasing rainbows. Public Health. 2021;199:20–4.

330. Commision on Social Determinants of Health. Closing the gap in a generation: health equity through action on the social determinants of health - Final report of the commission on social determinants of health. Geneva; 2008.

331. Röbl M, de Souza M, Schiel R, Gellhaus I, Zwiauer K, Holl RW, et al. The key role of psychosocial risk on therapeutic outcome in obese children and adolescents. Results from a longitudinal multicenter study. Obes Facts. 2013;6(3):297–305.

332. He Y, Lakhani CM, Rasooly D, Manrai AK, Tzoulaki I, Patel CJ. Comparisons of Polyexposure, Polygenic, and Clinical Risk Scores in Risk Prediction of Type 2 Diabetes. Diabetes Care. 2021 Apr;44(4):935–43.

333. Li Y, Zeng Z, Zhuang Z, Zhao Y, Zhang L, Wang W, et al. Polysocial and Polygenic Risk Scores and All-Cause Dementia, Alzheimer's Disease, and Vascular Dementia. J Gerontol A Biol Sci Med Sci. 2024 Mar;79(3).

334. Javed Z, Valero-Elizondo J, Maqsood MH, Mahajan S, Taha MB, Patel K V, et al. Social determinants of health and obesity: Findings from a national study of US adults. Obesity. 2022 Feb 1;30(2):491–502.

335. Singh N, Jonas C, Pinheiro LC, Lau JD, Cui J, Long L, et al. Examining Healthy Lifestyles as a Mediator of the Association Between Socially Determined Vulnerabilities and Incident Heart Failure. Circ Cardiovasc Qual Outcomes. 2025 Jan 19;0(0):e011107.

336. Abdalla S. Global Determinants of Health Datasets -- Data for Global Health equity: Data Repository. [Internet]. 2023 [cited 2025 Jan 17]. Available from: DataForHealthEquity.org

337. Khorram AA, Pourasgharian R, Shams AS, Toufani S, Mostafaei M, Khademi R, et al. Androgen deprivation therapy use and the risk of heart failure in patients with prostate cancer: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2024;24(1):756.

338. Saylor PJ, Smith MR. Metabolic Complications of Androgen Deprivation Therapy for Prostate Cancer. J Urol. 2013;189(1, Supplement):S34–44.

339. Cheung AS, Hoermann R, Dupuis P, Joon DL, Zajac JD, Grossmann M. Relationships between insulin resistance and frailty with body composition and testosterone in men undergoing androgen deprivation therapy for prostate cancer. Eur J Endocrinol. 2016 Sep 1;175(3):229–37.

340. Li X, Chan JSK, Guan B, Peng S, Wu X, Lu X, et al. Triglyceride-glucose index and the risk of heart failure: Evidence from two large cohorts and a mendelian randomization analysis. Cardiovasc Diabetol 2022 211. 2022 Nov 3;21(1):1–12.

341. Khalaji A, Behnoush AH, Khanmohammadi S, Ghanbari Mardasi K, Sharifkashani S, Sahebkar A, et al. Triglyceride-glucose index and heart failure: a systematic review and meta-analysis. Cardiovasc Diabetol. 2023 Sep;22(1):244.

342. Chan JSK, Lee YHA, Hui JMH, Liu K, Dee EC, Ng K, et al. Long-term prognostic impact of cardiovascular comorbidities in patients with prostate cancer receiving androgen deprivation therapy: A population-based competing risk analysis. Int J Cancer. 2023 Aug 15;153(4):756–64.

343. Khan SS, Coresh J, Pencina MJ, Ndumele CE, Rangaswami J, Chow SL, et al. Novel Prediction Equations for Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular-Kidney-Metabolic Health: A Scientific Statement From the American Heart Association. Circulation. 2023 Dec 12;148(24):1982–2004.

344. Fox KAA, Lucas JE, Pieper KS, Bassand J-P, Camm AJ, Fitzmaurice DA, et al. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. BMJ Open. 2017 Dec;7(12):e017157.

345. Nashef SAM, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. Eur J cardio-thoracic Surg Off J Eur Assoc Cardio-thoracic Surg. 2012 Apr;41(4):734–5.

346. Wang Y, Zeller M, Auffret V, Georgiopoulos G, Räber L, Roffi M, et al. Sex-specific prediction of cardiogenic shock after acute coronary syndromes: the SEX-SHOCK score. Eur Heart J. 2024 Nov 14;45(43):4564–78.

347. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM, Andresen D, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation

using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010 Feb 1;137(2):263–72.

348. Pisters R, Lane DA, Nieuwlaat R, De Vos CB, Crijns HJGM, Lip GYH, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010 Nov 1;138(5):1093–100.

349. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):762–74.

350. SCORE2 Asia-Pacific writing group, Hageman SHJ, Huang Z, Lee H, Kaptoge S, Dorresteijn JAN, et al. Risk prediction of cardiovascular disease in the Asia-Pacific region: the SCORE2 Asia-Pacific model. Eur Heart J. 2024 Sep 1;ehae609.

351. Zheng Y, Chen Z, Huang S, Zhang N, Wang Y, Hong S, et al. Machine Learning in Cardio-Oncology: New Insights from an Emerging Discipline. Rev Cardiovasc Med. 2023 Oct;24(10):296.

352. Chan JSK, Lee YHA, Liu K, Hui JMH, Dee EC, Ng K, et al. HbA1c Variability and Cardiovascular Events in Patients with Prostate Cancer Receiving Androgen Deprivation Therapy. Eur Urol Open Sci. 2023 Jan;47:3–11.

353. Ceriello A, Ofstad AP, Zwiener I, Kaspers S, George J, Nicolucci A. Empagliflozin reduced long-term HbA1c variability and cardiovascular death: insights from the EMPA-REG OUTCOME trial. Cardiovasc Diabetol. 2020 Oct;19(1):176.

354. Lee S, Jeevaratnam K, Liu T, Chang D, Chang C, Wong WT, et al. Risk stratification of cardiac arrhythmias and sudden cardiac death in type 2 diabetes mellitus patients receiving insulin therapy: A population-based cohort study. Clin Cardiol. 2021 Nov 1;44(11):1602–12.

355. Wang M-C, Li C-I, Liu C-S, Lin C-H, Yang S-Y, Li T-C, et al. Effect of blood lipid variability on mortality in patients with type 2 diabetes: a large single-center cohort study. Cardiovasc Diabetol. 2021 Dec 25;20(1):228.

356. Chan JSK, Satti DI, Lee YHA, Hui JMH, Lee TTL, Chou OHI, et al. High visit-to-visit cholesterol variability predicts heart failure and adverse cardiovascular events: a population-based cohort study. Eur J Prev Cardiol. 2022 Jun 3;

357. Bhalraam U, Veerni RB, Paddock S, Meng J, Piepoli M, López-Fernández T, et al. Impact of sodium-glucose cotransporter-2 inhibitors on heart failure outcomes in cancer patients and survivors: a systematic review and meta-analysis. Eur J Prev Cardiol. 2025 Mar;

358. Koutroumpakis E, Patel R, Khadke S, Bedrosian A, Kumar A, Kong Y, et al. Associations of SGLT2i with Cardiorenal Outcomes Among Diabetics with Prostate Cancer on Hormone Therapy. Cardiovasc drugs Ther. 2024 Nov;

359. Chan JSK, Lee YHA, Hui JMH, Liu K, Dee EC, Ng K, et al. Long-term Cardiovascular Risks of Gonadotropin-releasing Hormone Agonists and Antagonists: A Population-based Cohort Study. Clin Oncol. 2023 Jun;35(6):e376–83.

360. Tivesten Å, Pinthus JH, Clarke N, Duivenvoorden W, Nilsson J. Cardiovascular risk with androgen deprivation therapy for prostate cancer: Potential mechanisms. Urol Oncol Semin Orig Investig. 2015;33(11):464–75.

361. Knutsson A, Hsiung S, Celik S, Rattik S, Mattisson IY, Wigren M, et al. Treatment with a GnRH receptor agonist, but not the GnRH receptor antagonist degarelix, induces atherosclerotic plaque instability in ApoE−/− mice. Sci Rep. 2016;6(1):26220.

362. Patel S, Zhu K, Dave C V, Ghajar M, Zhang Y, Saraiya B, et al. Comparative Cardiovascular Safety of Gonadotropin-releasing Hormone Antagonists and Agonists Among Patients Diagnosed with Prostate Cancer: A Systematic Review and Meta-analysis of Real-world Evidence Studies. Eur Urol Oncol. 2024;

363. Nelson AJ, Lopes RD, Hong H, Hua K, Slovin S, Tan S, et al. Cardiovascular Effects of GnRH Antagonists Compared With Agonists in Prostate Cancer: A Systematic Review. JACC CardioOncology. 2023 Oct;5(5):613–24.

364. Ball S, Ghosh RK, Wongsaengsak S, Bandyopadhyay D, Ghosh GC, Aronow WS, et al. Cardiovascular Toxicities of Immune Checkpoint Inhibitors: JACC Review Topic of the Week. J Am Coll Cardiol. 2019 Oct 1;74(13):1714–27.

365. Tan S, Nelson AJ, Muthalaly RG, Ramkumar S, Hamilton J, Nerlekar N, et al. Cardiovascular risk in cancer patients treated with immune checkpoint inhibitors: challenges and future directions. Eur J Prev Cardiol. 2024 Jun 13;zwae204.

366. Vuong JT, Stein-Merlob AF, Nayeri A, Sallam T, Neilan TG, Yang EH. Immune Checkpoint Therapies and Atherosclerosis: Mechanisms and Clinical Implications: JACC State-of-the-Art Review. J Am Coll Cardiol. 2022 Feb;79(6):577–93.

367. Chan A, Torelli S, Cheng E, Batchelder R, Waliany S, Neal J, et al. Immunotherapy-Associated Atherosclerosis: A Comprehensive Review of Recent Findings and Implications for Future Research. Curr Treat Options Cardiovasc Med. 2023;25(12):715–35.

368. Mahmood SS, Fradley MG, Cohen J V, Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol. 2018 Apr;71(16):1755–64.

369. Newman JL, Stone JR. Immune checkpoint inhibition alters the inflammatory cell composition of human coronary artery atherosclerosis. Cardiovasc Pathol Off J Soc Cardiovasc Pathol. 2019;43:107148.

370. Oishi H, Morimoto R, Shimoyama Y, Kuroda K, Urata T, Kondo T, et al. Myocardial Vasculitis Associated With the Immune Checkpoint Inhibitor Pembrolizumab. JACC Case reports. 2020 Oct;2(12):1937–41.

371. Kumamoto T, Kawano H, Kurobe M, Akashi R, Yonekura T, Ikeda S, et al. Vasospastic Angina: An Immune-related Adverse Event. Intern Med. 2022 Jul;61(13):1983–6.

372. Nguyen C, Kaur R, Vaishnav M, Kurup R. Coronary Artery Vasospasm Presenting as Myocardial Infarction With Non-obstructive Coronary Arteries (MINOCA) in a Patient on Previous Immunotherapy for Melanoma. Hear Lung Circ. 2024;33:S299.

373. Wu D, Nam RHK, Leung KSK, Waraich H, Purnomo AF, Chou OHI, et al. Population-Based Clinical Studies Using Routinely Collected Data in Hong Kong, China: A Systematic Review of Trends and Established Local Practices. Cardiovasc Innov Appl. 2023;8(1).

374. Lee J, Tan S, Ramkumar S. Challenges in the implementation of cardio-oncology trials: lessons learnt from investigating statins in the prevention of anthracycline cardiotoxicity.

Cardio-Oncology. 2024;10(1):88.

375. Kim MK, Han K, Kim HS, Park YM, Kwon HS, Yoon KH, et al. Cholesterol variability and the risk of mortality, myocardial infarction, and stroke: a nationwide population-based study. Eur Heart J. 2017 Dec 21;38(48):3560–6.

376. Han BH, Han K, Yoon KH, Kim MK, Lee SH. Impact of mean and variability of high-density lipoprotein-cholesterol on the risk of myocardial infarction, stroke, and mortality in the general population. J Am Heart Assoc. 2020 Apr 9;9(7):15493.

377. Lee S, Zhou J, Wong WT, Liu T, Wu WKK, Wong ICK, et al. Glycemic and lipid variability for predicting complications and mortality in diabetes mellitus using machine learning. BMC Endocr Disord. 2021 May 4;21(1):94.

378. Zhao L, Zhao L, Xu T, Xu T, Li Y, Li Y, et al. Variability in blood lipids affects the neutrophil to lymphocyte ratio in patients undergoing elective percutaneous coronary intervention: a retrospective study. Lipids Health Dis. 2020 Jun 3;19(1).

379. Chan JSK, Satti DI, Lee YHA, Waleed K Bin, Tang P, Mahalwar G, et al. Association between visit-to-visit lipid variability and incident cancer: a population-based cohort study. Curr Probl Cardiol. 2022 Sep 24;101421.

380. Chan JSK, Satti DI, Chan RNC, Chevli P, Mehta A, Martin SS, et al. Visit-to-visit lipid variability, coronary artery calcification, inflammation, and mortality in the Multi-Ethnic Study of Atherosclerosis. Eur J Prev Cardiol. 2025 Feb 20;zwaf085.

381. Mauro MJ. Lifelong TKI therapy: how to manage cardiovascular and other risks. Hematology. 2021 Dec 10;2021(1):113–21.

382. Feijen EAM, Leisenring WM, Stratton KL, Ness KK, van der Pal HJH, van Dalen EC, et al. Derivation of Anthracycline and Anthraquinone Equivalence Ratios to Doxorubicin for Late-Onset Cardiotoxicity. JAMA Oncol. 2019 Jun 1;5(6):864–71.

383. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. Stat Methods Med Res. 2009 Feb;18(1):7–26.

384. Teske AJ, Moudgil R, López-Fernández T, Barac A, Brown SA, Deswal A, et al. Global Cardio Oncology Registry (G-COR): Registry Design, Primary Objectives, and Future Perspectives of a Multicenter Global Initiative. Circ Cardiovasc Qual Outcomes. 2023 Oct 1;16(10):e009905.

385. Tseng C, Wong WK. Analysis of a composite endpoint with longitudinal and time-to-event data. Stat Med. 2011 Apr;30(9):1018–27.

386. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2012 Jan;33(2):176–82.

387. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018 Sep;379(11):1007–16.

388. Gillmore JD, Judge DP, Cappelli F, Fontana M, Garcia-Pavia P, Gibbs S, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2024 Jan;390(2):132–42.

389. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022 Mar;28(3):568–74.

390. Sorajja P, Whisenant B, Hamid N, Naik H, Makkar R, Tadros P, et al. Transcatheter Repair for Patients with Tricuspid Regurgitation. N Engl J Med. 2023 May;388(20):1833–42.

391. Pocock SJ, Gregson J, Collier TJ, Ferreira JP, Stone GW. The win ratio in cardiology trials: lessons learnt, new developments, and wise future use. Eur Heart J. 2024 Nov 21;45(44):4684–99.

392. Wang B, Zhou D, Zhang J, Kim Y, Chen L-W, Dunnmon P, et al. Statistical power considerations in the use of win ratio in cardiovascular outcome trials. Contemp Clin Trials. 2023;124:107040.

393. Forsythe LP, Carman KL, Szydlowski V, Fayish L, Davidson L, Hickam DH, et al. Patient Engagement In Research: Early Findings From The Patient-Centered Outcomes Research Institute. Health Aff. 2019 Mar 1;38(3):359–67.

394. Addario B, Geissler J, Horn MK, Krebs LU, Maskens D, Oliver K, et al. Including the patient voice in the development and implementation of patient-reported outcomes in cancer clinical trials. Heal Expect an Int J public Particip Heal care Heal policy. 2020 Feb;23(1):41–51.

395. Domecq JP, Prutsky G, Elraiyah T, Wang Z, Nabhan M, Shippee N, et al. Patient engagement in research: a systematic review. BMC Health Serv Res. 2014;14(1):89.

396. Easley J, Wassersug R, Matthias S, Tompson M, Schneider ND, O'Brien MA, et al. Patient Engagement in Health Research: Perspectives from Patient Participants. Curr Oncol. 2023 Feb;30(3):2770–80.

397. Rao VU, Deswal A, Lenihan D, Dent S, Lopez-Fernandez T, Lyon AR, et al. Quality-of-Care Measures for Cardio-Oncology: An IC-OS and ACC Cardio-Oncology Leadership Council Perspective. JACC CardioOncology. 2025;

Bibliography related to this thesis

Chapter 1

Chan JSK, Chan RNC, Lee YHA, Satti DI, Dee EC, Ng K, Achim A, Ng CF, Liu T, Matthews GDK, Tse G, Vassiliou VS. Cardiovascular health of patients with cancer: challenges abound. *Trends Cardiovasc Med*. 2025; 35(1): 24-31. doi: 10.1016/j.tcm.2024.04.004

Chapter 2

Satti DI*, **Chan JSK***, Dee EC, Lee YHA, Wai AKC, Dani SS, Virani SS, Shapiro MD, Sharma G, Liu T, Tse G. Associations between social determinants of health and cardiovascular health of US adult cancer survivors. *JACC CardioOnc.* 2023; 6(3): 439-450. doi: 10.1016/j.jaccao.2023.07.010
* co-first authors

Chapter 3

Chan JSK, Satti DI, Dee EC, Sharma G, Virani SS, Liu T, Tse G. Association between psychological distress and cardiovascular health amongst cancer survivors in the United States: findings from nationally representative data. *Eur J Prev Cardiol.* 2023; 30(16): e74-e77. doi: 10.1093/eurjpc/zwad162

Chapter 4

Chan JSK, Satti DI, Ching YLA, Lee Q, Dee EC, Ng K, Chou OHI, Liu T, Tse G, Lai A. Associations between social determinants of health and cardiovascular and cancer mortality in cancer survivors: a prospective cohort study. *Eur J Prev Cardiol*. 2024. doi: 10.1093/eurjpc/zwae318 [Online ahead of print]

Chapter 5

Chan JSK, Satti DI, Lee YHA, Hui JMH, Dee EC, Ng K, Liu K, Tse G, Ng CF. Temporal trends in cardiovascular burden among patients with prostate cancer receiving androgen deprivation therapy: a population-based cohort study. *Br J Cancer.* 2023; 128: 2253-2260. doi: 10.1038/s41416-023-02271-5

Chapter 6

Chan JSK, Lee YHA, Liu K, Hui JMH, Dee EC, Ng K, Satti DI, Tang P, Tse G, Ng CF. Long-term cardiovascular burden in prostate cancer patients receiving androgen deprivation therapy. *Eur J Clin Invest*. 2023; 53(4): e13932. doi: 10.1111/eci.13932

Chapter 7

Chan JSK, Lee YHA, Hui JMH, Liu K, Dee EC, Ng K, Liu T, Tse G, Ng CF. Long-term prognostic impact of cardiovascular comorbidities in patients with prostate cancer receiving androgen deprivation therapy: a population-based competing risk analysis. *Int J Cancer.* 2023; 153(4): 756-764. doi: 10.1002/ijc.34557

Chapter 8

Chan JSK, Lee YHA, Liu K, Hui JMH, Dee EC, Ng K, Satti DI, Liu T, Tse G, Ng CF. HbA1c variability and cardiovascular events in patients with prostate cancer receiving androgen deprivation therapy. *Eur Urol Open Sci*. 2023; 47: 3-11. doi: 10.1016/j.euros.2022.11.002

Chapter 9

Chan JSK[*], Lee YHA[*], Hui JMH, Liu K, Dee EC, Ng K, Tang P, Tse G, Ng CF. Long-term cardiovascular risks of gonadotropin-releasing hormone agonists and antagonists: a population-based cohort study. *Clin Oncol.* 2023; 35(6): E376-E383. doi: 10.1016/j.clon.2023.03.014
* co-first authors

Chapter 10

Chan JSK, Lakhani I, Lee TTL, Chou OHI, Lee YHA, Cheung YM, Yeung HW, Tang P, Ng K, Dee EC, Liu T, Wong WT, Tse G, Leung FP. Cardiovascular outcomes and hospitalizations in Asian patients receiving immune checkpoint inhibitors: a population-based study. *Curr Probl Cardiol.* 2023; 48(1): 101380. doi: 10.1016/j.cpcardiol.2022.101380

Chapter 11

Chan JSK, Tang P, Lee TTL, Chou OHI, Lee YHA, Li G, Leung FP, Wong WT, Liu T, Tse G. Association between immune checkpoint inhibitors and myocardial infarction in Asians: a population-based self-controlled case series. *Cancer Med.* 2023; 12(8): 9541-9546. doi: 10.1002/cam4.5729

Chapter 12

Chan JSK, Chou OHI, Lee TTL, Lee YHA, Chan RNC, Dee EC, Ng K, Liu T, Tse G. Temporal trends in guideline-recommended cardiometabolic testing completeness before initiating immune checkpoint inhibitors: a cohort study. *J Intern Med.* 2024; 295(3): 375-378. doi: 10.1111/joim.13754