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A comprehensive Swedish register study on disease burden, mortality, and socioeconomic factors in 65 173 patients with child, adolescent, and young adult cancer (CAYA) compared to 312 935 matched controls over six decades, the Rebuc Study.

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Abstract:	Background. Despite significant progress in managing cancer in children, adolescents, and young adults (CAYAs), persistent complications impact their quality of life. This study, from 1958 to 2021, comprehensively covers the morbidity, mortality, demographic and socioeconomic factors among CAYAs. The hypothesis was that morbidity and mortality are greater among CAYAs compared to matched controls. The aim of this study was to investigate the impact of patient-specific variables, demographics, and socioeconomic factors on outcomes. Methods. This retrospective matched cohort study included the entire Swedish population of individuals under 25 with cancer. The study population was identified from the Cancer Register, and controls were paired 1:5 based on age, sex, and residence. Multiple registers provided data on morbidity, mortality, and demographics.

	Findings. This survey covering 63 years, identified 65 173 CAYAs (1·24 million patient-years) and matched with 312 935 controls (7·45 million person-years), a total of 378 108 individuals (74% females). CAYAs exhibited a 3·0-times higher risk for subsequent cancer (95%CI 2·88-3·13,p<0·0001), a 1·21-times higher risk for cardiovascular disease (95%CI 1·20-1·26,p<0·0001), and a 1·38-times higher risk for injury, poisoning, suicide, or other external affliction (95%CI 1·31-1·45,p<0·0001). CAYAs had a higher mortality rate, and 5-years survivors lived a mean of 26·9 years shorter than controls. Males had a higher mortality risk than females. After adjusting for socioeconomic factors, individuals born outside Europe and those with greater sick-leave had a higher mortality risk, while education and marriage showed a beneficial association with mortality. (p<0·0001). Interpretation. The Rebuc study, covering six decades, showed a significantly increased risk for serious complications among young cancer patients in Sweden. Patient-specific variables, demographics, and socioeconomic factors affect morbidity and mortality risk. These results underscore the impact of cancer on the health and lifespan of young individuals and the necessity for further research to address socioeconomic disparities in cancer care.

A comprehensive Swedish register study on disease burden, mortality, and socioeconomic factors in 65 173 patients with child, adolescent, and young adult cancer (CAYA) compared to 312 935 matched controls over six decades, the Rebuc Study.

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Summary

Background. Despite significant progress in managing cancer in children, adolescents, and young adults (CAYAs), persistent complications impact their quality of life. This study, from 1958 to 2021, comprehensively covers the morbidity, mortality, demographic and socioeconomic factors among CAYAs. The hypothesis was that morbidity and mortality are greater among CAYAs compared to matched controls. The aim of this study was to investigate the impact of patient-specific variables, demographics, and socioeconomic factors on outcomes.

Methods: This retrospective matched cohort study included the entire Swedish population of individuals under 25 with cancer. The study population was identified from the Cancer Register, and controls were paired 1:5 based on age, sex, and residence. Multiple registers provided data on morbidity, mortality, and demographics.

Findings. This survey covering 63 years, identified 65 173 CAYAs (1·24 million patient-years) and matched with 312 935 controls (7·45 million person-years), a total of 378 108 individuals (74% females).

CAYAs exhibited a 3·0-times higher risk for subsequent cancer (95%CI 2·88-3·13,p<0·0001), a 1·21-times higher risk for cardiovascular disease (95%CI 1·20-1·26,p<0·0001), and a 1·38-times higher risk for injury, poisoning, suicide, or other external affliction (95%CI 1·31-1·45,p<0·0001). CAYAs had a higher mortality rate, and five-years survivors lived a mean of 26·9 years shorter than controls. Males had a higher mortality risk than females. After adjusting for socioeconomic factors, individuals born outside Europe and those with greater sick-leave had a higher mortality risk, while education and marriage showed a beneficial association with mortality. (p<0·0001).

Interpretation. The Rebuc study, covering six decades, showed a significantly increased risk for serious complications among young cancer patients in Sweden. Patient-specific variables, demographics, and socioeconomic factors affect morbidity and mortality risk. These results underscore the impact of cancer on the health and lifespan of young individuals and the necessity for further research to address socioeconomic disparities in cancer care.

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Keywords. Childhood cancer, CAYA, socio-economic, demographics, survival, treatment side effects.

Introduction.

Due to progress in research and medical interventions, cancer management in children, adolescents, and young adults (referred to as CAYAs) has achieved notable success. In Sweden, the five-year survival rate for children and adolescents with cancer is approximately 85%, with survival increasing to about 90% for young adults up to 25 years of age.[1]

Cancer survivors may face various long-term complications later in life, which may have a significant negative impact on their quality of life (QoL), and some of these can be severe or life-threatening. The primary nature of these conditions includes subsequent malignancy, cardiovascular disease (CVD), central nervous system (CNS) disease, endocrine disease, infertility, and others.[2] A Scandinavian study found a 10% overall mortality rate among young cancer survivors.[3] and similar mortality rates have been reported in large European and American studies.[4-6] It is well-known that treatment itself can cause late morbidity among young people with cancer. Radiotherapy (RT) increases the risk for secondary malignancy while cytostatics such as anthracyclines are associated with an increased risk for myelodysplastic disease and leukaemia and are associated with cardiovascular toxicity.[2,7-9] The long-term QoL and cancer outcomes depend on several common risk factors for malignancy and CVD that overlap. Smoking, age, sex, heredity, hypertension, and alcohol overconsumption are known risk factors for both cancer and CVD.[10] Children who survive cancer have an increased risk for developing metabolic syndrome with insulin resistance, glucose intolerance, type-2 diabetes, obesity, hypertension, dyslipidaemia, and infertility later in life. Poor dental health has an impact on general health, where dental infection, increases the risk for diabetes, hypertension, adverse pregnancy outcomes, and CVD.[11,12] Furthermore, physiologic weakness (frailty) and premature aging have been reported.[13,14]

In general, more boys develop childhood cancer than girls.[1] Females are at higher risk for CVD, and this is related to treatment, age at treatment, and the presence of certain risk factors such as obesity, diabetes, and high blood pressure. However, male survivors show CVD earlier than female survivors, possibly because they are more likely to have hyperlipidaemia and hypertension, and smoke more.[15] The risk for long-term sick-leave later in life is higher among female survivors.[16]

Healthcare inequality due to socioeconomic status is omnipresent and may have a significant impact on the outcome of cancer. Cancer survivors may suffer consequences due to an adverse financial situations and burdens to which the patients and their families are subjected. Financial embarrassment may have direct emotional, psychological, practical consequences as well as indirect consequences such as interruption of studies, reduced employability, and reduced lifetime income.[17-21] The socioeconomic status of the child's environment also plays

a role i.e., feeling of security, healthy living conditions, opportunity to exercise, and access to healthy foods important for physiologic reserve and avoidance of frailty after childhood cancer.[22]

Due to variations in general healthcare and demographics between countries, it is imperative to consider local conditions when formulating risk prevention strategies. Sweden benefits from a relatively small population, and easy access to healthcare and socioeconomic data over time allows comprehensive follow-up of the CAYA population over many years, encompassing aspects such as survival, health, education, and socioeconomic factors.

By integrating register data on healthcare and socioeconomic factors with geographical information, valuable insights into the effects and complications of cancer and its treatment can be obtained. This approach sheds light on the impact of healthcare structure, education, socioeconomic status, and geographic factors on the lives of young cancer survivors. Such knowledge is crucial for shaping the future landscape of cancer treatment and care.

Objectives

The main objectives of the REBUC study were to describe the morbidity and mortality of all young Swedish cancer patients over the last six decades and compare them with matched controls to study the effect of patient-specific variables, demographic, and socioeconomic impact at cancer at a young age.

Methods

Study design and participants.

This was a register-based, matched cohort study on the total Swedish population of cancer patients below 25 years of age, from January 1958 to the time of mortality or end of study in December 2021.

The National Board of Health and Welfare's Cancer Register was used to identify the study population by retrieving data on cancer diagnoses and their corresponding dates (referred as index). All 65 173 cases in the index group were paired 1:5, by the Statistics Authority, Statistics Sweden (SCB), with controls based on year of birth, sex, and the same municipality of residence, and freedom from cancer at the time of index. This matching process resulted in 312 935 controls. (appendix p 2)

The Swedish Ethics Review Authority approved this study, and the work complied with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the Declaration of Helsinki. According to Swedish legislation, patients registered in a national healthcare quality register need not provide written informed consent for their data to be included in healthcare research or published. Data were extracted via the National Board of Health and Welfare's pseudonymised.

Procedures

Data on all 378 108 individuals were matched between several population and healthcare registers, using the personal identity number assigned to all Swedish residents. The personal identification numbers assigned at birth indicate the assigned sex by the penultimate. A new personal identification number provided during a gender change, is not automatically linked to the previous number.

Diagnosis information was collected using the WHO International Classification of Diseases ICD codes 7-10. (appendix p 4) The National Patient Register was used to obtain in-hospital care diagnoses, and others were collected from the outpatient section of the same register. Intensive care data were extracted from the Swedish Intensive Care Register, (SIR), and data on intact teeth remaining from the National Dental Health Register. The Swedish Cause of Death register was used for time and cause of death.

Residence at time of index cancer, 2021 years median income including income inequality (Gini-coefficient) at place of residence, latest registered civil status (unmarried, married), sex (at index), highest education level, (elementary school, upper secondary school, university, and postgraduate education), numbers of days sick-leave and disability pension were identified in the longitudinal integrated database for health insurance and labour market studies, (LISA) extracted from SCB and the National Insurance Agency. (appendix p 3)

The median income of the local municipality (2021) was used as a surrogate for income as well as the socioeconomic development of the place of residence over time. Previous municipality identification numbers were converted into numbers as of 2021 and used when calculating the driving distance to the nearest hospital using Google Maps API (Mountain View, CA, USA). Standard protocols for treatment since 1958 were used as surrogates for treatment with RT, anthracyclines, and other drugs (others) for leukaemia, CNS malignancies, Hodgkin's lymphoma, non-Hodgkins's lymphoma, and testis cancer.

Statistical analysis

The primary outcome measures were morbidity and mortality between index diagnosis date and the end of follow-up. The secondary outcome was the impact of socioeconomic status on mortality.

CAYAs and controls were grouped into <1-14, 15-18 and 19–24 years. CAYAs still alive five years after index were referred to as survivors. CAYAs and controls characteristics and baseline data are summarised with descriptive statistics for the entire cohort and for the different age groups. Handling of missing data is described in appendix p 3. Due to changes in cancer therapy and medical healthcare in general over the six decades of this

study, observations were also grouped into periods 1958–1970, 1971–1980, 1981–1990, 1991–2000, 2001–2010, and 2011–2021. Categorical variables were reported as counts and percentages and continuous variables with mean and standard deviation (SD) or median and interquartile ranges (IQR). CAYAs were compared with matched controls regarding baseline characteristics and all the measures described above. Between-group differences were tested for statistical significance using the $\chi 2$ test for categorical variables.

The incidence of morbidity and mortality was reported as mean (SD) with 95% confidence interval (CI) while cumulative mortality was illustrated with Kaplan-Meier curves. The risk of having a subsequent or new primary malignancy as well as other diseases was analysed and odds ratio (with a 95% CI) between CAYAs and controls was examined and presented on a forest plot. Using Cox regression models, the Hazard Ratio (HR) with a 95% CI was reported for CAYAs and Controls for various factors and covariates. Univariable Cox regression analysis was performed to examine the effects of each socioeconomic factor on all-cause mortality. Predictors are listed in appendix p 6. Additionally, multivariable Cox regression models was used to adjust for the impact of various socioeconomic factors on all-cause mortality. A p-value < 0·05 indicated statistical significance. The analysis was performed and validated independently by two researchers and presented as descriptive and comparative statistics using R 4·3·2, R Foundation (Vienna, Austria).

Role of the funding source

The funders of the study played no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The study spanned a 63-year observation period, involving a total of 378 108 individuals, (74% females). Among the participants, 65 173 were CAYAs aged between <1 and 24 years, who experienced an index cancer (1·24 million patient-years). A control group of 312 935 matched individuals was created, (7·45 million person-years). Baseline demographic, index cancers, clinical, and socioeconomic characteristics are presented in table 1.

Index cancer rate was consistent across the decades, apart from 1958-1970 (9·9%) and 2011-2021 (30·5%). (figure 1) Most CAYAs (66·3%) were in the 19-24 age group, followed by the <1-14 age group (23·5%). (figure 2) Differences in sex distribution between the three age groups were highly significant (p<0·0001).

The mean follow-up was 19·5 (SD16·9) years for CAYAs, and 23·8 (16·8) for controls, (p<0·001). At the end of the study, the median age of CAYAs was 33·4 (IQR 27·9) years and controls 39·2 (28·3) (p<0·0001), with an age span of <1-88 years in both groups. (table 2)

The highest subsequent cancer risk compared to controls was observed for bone, connective tissue, and soft tissue cancers, with a 36·2-times increased risk, followed by leukaemia and CNS cancers with 35·8 and 30·1-times higher risk, respectively. Among survivors, 5·6% experienced a subsequent malignancy, and 11·9% had a relapse of their index cancer. Among controls with primary cancer (2·0%), the predominant type was skin cancer at 1·5%, followed by leukaemia at 0·1%, showing significantly lower rates than in survivors (p<0·0001). (table 2 and figure 3)

CVD was detected in 16·9 % of the CAYAs, representing a 1·21-time elevated risk (95% CI 1·18-1·23, p<0·0001) compared to controls. The most common CVDs were arrhythmia and hypertension, both with similar risks as controls, but many CVDs had a significantly higher risk in CAYAs. Rate and risk for all other disease groups are listed in table 2 and figure 3.

Throughout the study period, CAYAs spent more days in the hospital (46·5 vs 18·0) and hours in the intensive care unit, (ICU) (6·6 vs 1·9) (p<0·0001) compared to controls, and the difference remained among survivors.

CAYAs had a significantly higher all-cause mortality; 17·9% compared to 2·6% in controls (p <0·0001). The highest rate was observed in children 36·2% and decreasing with age groups.

The mean time to death was 8·0 (SD14·0) years after index diagnosis, ranging from 3·6 (8·1) in children to 7·0 (13·1) years in young adults. (table 2 and appendix p 8) The mean age at death for CAYAs was 21.5 years (SD 18.3), children being the youngest at 9.7 years (SD 9.7) and increasing to 35.69 years (SD 17.8) among young adults. Controls outlived CAYAs an average of 30·6 years. Among the survivors, the mean age at all-cause mortality was 25·3 (17·7) years, dying 26·9 years before the controls (p<0·0001).

Male CAYAs had a 2·2-times higher risk for all-cause mortality compared to females (95%CI 1·94-2·60) compared to 1·3 times increased risk among controls (95%CI 1·14-1·39). (table 2, figure 4)

CAYAs had a higher cancer mortality (9·8% compared to 0·1% in controls) of their index or subsequent cancer at a mean age of 15·8 (SD10·8) years, 2·8 (6·2) years after index. Survivors died of cancer at the age of 30 (15·4) years and lived a mean of 34·6 years shorter than their controls (p<0·0001).

CV mortality was also increased in CAYAs, (1·9% compared to 0·7% in controls) but at a higher age than in all-cause or cancer specific mortality, although at a mean of 22·8 years younger than their controls. The survivors were older at CV mortality and lived in mean 6·5 years shorter (p<0·0001) than controls. (table 2, figure 5)
Regarding other deaths, 0·8% of CAYAs died due to injury, poisoning, suicide, or other external causes which was higher than in controls (p<0·0001) with CAYAs dying a mean of 1·5 years earlier (p=0·0225).
All mortality causes are listed in table 2 and figure 5 and mortality rates for the 12 most common index diagnoses, age groups, and sex over the 6 decades are shown in appendix p 7-8.
The mortality risk for CAYAs, compared to controls, is illustrated in figure 6, taking into consideration age, groups, demographic factors, and other socioeconomic factors. Most CAYAs and controls were born in Sweden (92·8% and 88·5%). After adjusting for demographic and socioeconomic factors those CAYAs born outside Sweden had a 1·5-times (95% CI 1·10-2·11,p=0,0119) increased mortality risk and those born outside Europe a 2·3-times (95%CI 1·56-3·48,p<0,0001) increased risk. Most lived in the southern and middle parts of Sweden and only 12·3% in the north. None of municipality median income, residence in north or south, living in an urban or a rural area or close to a hospital had an impact on mortality. (appendix p 5-6)
Among CAYAs, 15·5% had no more than primary school education, while 33·1% reached university and postgraduate levels, showing significant differences between CAYAs and controls (p<0·0001). (table 2) Of those who survived to the age of 30 years or more, 22% reached university level compared to 28% among the controls. Higher level of education had a beneficial influence on mortality for both CAYAs and controls. (p<0·0001)
In the CAYA group, 59·8% had not married, while 23·5% were married or had a registered partner. A significantly higher marriage rate was seen in the control group (p<0·0001). In those that survived to an age of 30 years or more, 15·6% of the CAYAs were married compared to 20·6% controls. Being married was associated with a 53% lower mortality risk for CAYAs, and 56% for controls (p<0·0001).
Disability pension was not associated with mortality, whereas having >180 days sick-leave was associated with increased mortality risk in CAYAs with 3·3-times and in controls 2·3-times (p<0·0001). The number of intact teeth remaining was the same in both groups, with a higher number associated with increased mortality risk after adjusting for other socioeconomic factors. (appendix p 5-6)

Discussion

In this comprehensive survey over the entire population of cancer patients diagnosed under the age of 25 in Sweden, our hypothesis that young cancer patients have increased morbidity and mortality risks across all forms

of diseases was supported. The study further revealed that socioeconomic factors are associated with an increased risk for mortality in CAYAs compared to matched controls.

The distribution of index malignancies was comparable to other international register studies,[2,4] apart from the large number of young adults with cervical cancer, including high-grade squamous intraepithelial lesions, which has not been included in comprehensive reports from similar populations before. Human papillomavirus (HPV) infection is associated with cervical cancers, and it is known that survivors of cancer have a higher risk of HPV-associated cancers and CVD.[23]

Of the CAYAs that suffered from subsequent cancer, the children were at greatest risk. In a cancer population under 21 years of age, Sue *et al.*[2] reported a 19·7% morbidity rate in children under 15 years compared to 13·6% in adolescents and young adults. Unfortunately, there are no reports on similar populations to enable comparisons with our results, so to what extent cervical cancer affects future health in this large population remains to be seen.

The proportion of CVD in the CAYAs was age-dependent and similar to that reported by Sue *et al.*[2]

The risk for other diseases was significantly higher in the CAYAs who showed much higher rates of pulmonary, endocrine, and neurological diseases, than reported by Sue *et al*. Notably, they reported diseases of greater severity, which makes comparisons difficult since we included all diagnoses regardless of severity.

Cancer accounted for 54·7% of the total mortality. Fidler-Benaoudia *et al*.[6] compared survivors between United States (US) and British childhood cancer survivor studies (CCSS and BCCSS) and found cancer mortalities of 57% and 75%, respectively. That study also showed that there were substantial differences in risk for late all-cause mortality between the countries and suggested that US survivors may have received more intensive treatment and more late effects. While interpreting these and our results, it is essential to consider that variations in other healthcare factors may contribute to mortality differences between countries and continents, as they could highly impact the outcomes observed.

In a study by L. Wang *et al,*[24] a 1·4-times greater CV mortality risk was observed among survivors aged 15-39 in the US compared to the general population which is consistent with the present study comparing young adults with matched controls. In the present study, morbidity, and mortality risk from external causes was higher for CAYAs. This was also reported from the CCSS, and the same applied to the BCCSS cohort, though not to the same degree.[2,7]

In Sweden, the proportion of children with a foreign background and a low-income standard is 23% compared to 4% for their Swedish counterparts. Having a background from outside Sweden for CAYAs, and outside Europe

for controls had a negative association with mortality (no information on ethnicity). The most prosperous municipalities in Sweden i.e., those with good access to education, healthcare, and transportation, are found in the southern and middle parts. Other studies have revealed that a distance greater than 80 km to the nearest hospital may delay cancer diagnosis,[25] increases mortality from leukaemia,[26] and increase all-cause mortality rate.[27,28] In current study neither greater distance to nearest hospital nor lower population density affected mortality for CAYAs, however this has yet to be analysed in different subgroups of index cancer such as leukaemia. Healthcare and socioeconomic factors strongly influence the challenges regarding education and careers of cancer survivors. Previous studies have shown that cancer survivors often have their education and career plans disrupted, resulting in fewer receiving a college and university education.[29] In current study, we observed that even though CAYAs passed primary school, subsequent education, even at higher ages, seemed to be hampered compared to controls, and that completing a university education was associated with significantly lower mortality. Civil status may be used as a surrogate for how well adapted the person became in adulthood. Living together in a joint household is as common as being married in Sweden, but this status is not registered so half of all households in Sweden are officially single. In this study, CAYAs did not marry as much as their controls. They also had a valid difference in education and civil status when they were older than 30, and these factors were linked to mortality.

Caries and number of teeth remaining is individual depending on age, nutrition, genetics, access to dental care, smoking and tobacco use, comorbidities, financial resources, education, and single living. The number of teeth needed for oral function is related to age, with a minimum of 24 teeth required under the age of 50.[30] Both groups had the same number of teeth remaining, probably due to free dental care, but a high number of teeth was associated with higher mortality, an apparent contradiction that needs to be analysed more thoroughly.

This study has strong internal validity because of the use of data from national high-quality patient registers with low dropout rates. However, register studies always have selection, confounding, measurement, and reporting biases. The assessment of changes in the management of cancer in CAYAs over time in this comprehensive study may be considered somewhat broad to drawing any definitive conclusions. However, it serves as a foundational framework, and construction of a large database, for initiating more in-depth studies to gain a deeper understanding of the subject and to draw conclusions of, and on a deeper level.

Increased morbidity and higher risk for other disease over time in the CAYA group probably reduces quality of life, but the significance of this has yet to be shown. The long-term consequences and cost-effectiveness of modern forms of cancer management also need investigating.

Conclusion

This study shows that young cancer patient survivors not only face a significantly higher risk for developing a new malignancy but also suffer increased cardiovascular and other morbidities. The higher mortality risk before middle age underscores the severity of the health challenges they face. Furthermore, these young individuals are more prone to socioeconomic factors that may adversely affect their survival.

Contributors

All authors contributed to the study's conception and design. The entire team collaborated on translating ICD codes and all other data collection was performed by LH, MSt, JA, BE and LE. RK data managed and established the database. MSi, LH and PM did the statistical analyses. The first drafts of the manuscript were written by LH, PM and EH and all authors commented on subsequent versions of the manuscript. All authors have read and approved the final manuscript.

Declarations of interest

LH reports unrelated modest consultation fees from Astellas, Bayer, and Orion Pharma. EH is Co-Founder and board member of MedTech-company TrueDose AB, producing at-home blood sampling kits. EH has received speaker's and consultancy fees from Bristol-Myers Squibb, Pfizer, and Amgen. KRW reports unrelated speaker's and consultancy fees from Roche, Pfizer, Organon, Ibsa, Merck and Ferring pharmaceuticals and unrelated grants from Novo Nordisk and Ferring. LE is a board member of the Swedish Intensive Care Register. JA has received lecture fees from Boehringer Ingelheim, Astra Zeneca, MSD, Bayer and Novartis (modest) and advisory board reimbursement from Astra Zeneca and Bayer (modest). He is chair of the board of SWEDEHEART ACS register and the SWEDEHEART Register Research Council and member of the SWEDEHEART steering committee. JM is unpaid member of the board of the Swedish Multiple Sclerosis Society. ME reports unrelated consultation fees from Bayer, Thea Pharma and Novartis. All remaining authors declare that they have no conflict of interest.

Data sharing

The datasets generated and analysed in this study are not available to the public due to Swedish laws and regulations. However, they can be made accessible with the support of investigators and upon reasonable request, in accordance with Swedish healthcare secrecy legislation.

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References

1. National Board of Health and Welfare. Statistics and Data. 2023. https://www.socialstyrelsen.se/en/statistics-and-data/.
2. Suh E, Stratton KL, Leisenring WM, et al. Late mortality and chronic health conditions in long-term survivors of early-adolescent and young adult cancers: a retrospective cohort analysis from the Childhood Cancer Survivor Study. Lancet Oncol 2020; **21**(3): 421-35.
3. de Fine Licht S, Rugbjerg K, Gudmundsdottir T, et al. Long-term inpatient disease burden in the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study: A cohort study of 21,297 childhood cancer survivors. PLoS Med 2017; **14**(5): e1002296.
4. Grabow D, Kaiser M, Hjorth L, et al. The PanCareSurFup cohort of 83,333 five-year survivors of childhood cancer: a cohort from 12 European countries. Eur J Epidemiol 2018; **33**(3): 335-49.
5. Dixon SB, Liu Q, Chow EJ, et al. Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. Lancet 2023; **401**(10386): 1447-57.
6. Fidler-Benaoudia MM, Oeffinger KC, Yasui Y, et al. A Comparison of Late Mortality Among Survivors of Childhood Cancer in the United States and United Kingdom. J Natl Cancer Inst 2021; **113**(5): 562-71.
7. Fidler MM, Reulen RC, Henson K, et al. Population-Based Long-Term Cardiac-Specific Mortality Among 34 489 Five-Year Survivors of Childhood Cancer in Great Britain. Circulation 2017; **135**(10): 951-63.
8. Feijen EAM, van Dalen EC, van der Pal HJH, et al. Increased risk of cardiac ischaemia in a pan-European cohort of 36 205 childhood cancer survivors: a PanCareSurFup study. Heart 2021; **107**(1): 33-40.
9. Lyon AR, Lopez-Fernandez T, Couch LS, 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; **43**(41): 4229-361.
10. Meijers WC, de Boer RA. Common risk factors for heart failure and cancer. Cardiovasc Res 2019; **115**(5): 844-53.
11. Niazi SA, Bakhsh A. Association between Endodontic Infection, Its Treatment and Systemic Health: A Narrative Review. Medicina (Kaunas) 2022; **58**(7).
12. Herrera D, Sanz M, Shapira L, et al. Association between periodontal diseases and cardiovascular diseases, diabetes and respiratory diseases: Consensus report of the Joint Workshop by the European Federation of Periodontology (EFP) and the European arm of the World Organization of Family Doctors (WONCA Europe). J Clin Periodontol 2023; **50**(6): 819-41.
13. Ness KK, Howell CR, Bjornard KL. Frailty and quality of life in adult survivors of childhood cancer. Expert Rev Qual Life Cancer Care 2017; **2**(2): 79-85.
14. Delaney A, Howell CR, Krull KR, et al. Progression of Frailty in Survivors of Childhood Cancer: A St. Jude Lifetime Cohort Report. J Natl Cancer Inst 2021; **113**(10): 1415-21.
15. Lipshultz SE, Franco VI, Miller TL, Colan SD, Sallan SE. Cardiovascular disease in adult survivors of childhood cancer. Annu Rev Med 2015; **66**: 161-76.

16. Baecklund F, Alexanderson KAE, Mittendorfer-Rutz E, Chen L. Sickness absence and disability pension trajectories in childhood cancer survivors and references- a Swedish prospective cohort study. PLoS One 2022; **17**(4): e0265827.
17. Hjelmstedt S, Lindahl Norberg A, Montgomery S, Hed Myrberg I, Hovén E. Sick leave among parents of children with cancer - a national cohort study. Acta Oncol 2017; **56**(5): 692-7.
18. Ritter J, Allen S, Cohen PD, et al. Financial hardship in families of children or adolescents with cancer: a systematic literature review. Lancet Oncol 2023; **24**(9): e364-e75.
19. Boman KK, Lindblad F, Hjern A. Long-term outcomes of childhood cancer survivors in Sweden: a population-based study of education, employment, and income. Cancer 2010; **116**(5): 1385-91.
20. Di Giuseppe G, Pagalan L, Jetha A, Pechlivanoglou P, Pole JD. Financial toxicity among adolescent and young adult cancer survivors: A systematic review of educational attainment, employment, and income. Crit Rev Oncol Hematol 2023; **183**: 103914.
21. Ruiz S, Hudson MM, Ehrhardt MJ, Maki J, Ackermann N, Waters EA. Childhood Cancer Survivors, Financial Toxicity, and the Need for Multilevel Interventions. Pediatrics 2023; **152**(1).
22. Schwartz LF, Dhaduk R, Howell CR, et al. The Association of Neighborhood Characteristics and Frailty in Childhood Cancer Survivors: A Report from the St. Jude Lifetime Cohort Study. Cancer Epidemiol Biomarkers Prev. 2023 Aug 1; **32**(8): 1021–1029.
23. Liang X, Chou OHI, Cheung BMY. The Effects of Human Papillomavirus Infection and Vaccination on Cardiovascular Diseases, NHANES 2003-2016. Am J Med 2023; **136**(3): 294-301.e2.
24. Wang L, Wang F, Chen L, Geng Y, Yu S, Chen Z. Long-term cardiovascular disease mortality among 160 834 5-year survivors of adolescent and young adult cancer: an American population-based cohort study. Eur Heart J 2021; **42**(1): 101-9.
25. Johnson KJ, Wang X, Barnes JM, Delavar A. Associations between geographic residence and US adolescent and young adult cancer stage and survival. Cancer 2021; **127**(19): 3640-50.
26. Rotz SJ, Wei W, Thomas SM, Hanna R. Distance to treatment center is associated with survival in children and young adults with acute lymphoblastic leukemia. Cancer 2020; **126**(24): 5319-27.
27. Nicholl J, West J, Goodacre S, Turner J. The relationship between distance to hospital and patient mortality in emergencies: an observational study. Emerg Med J 2007; **24**(9): 665-8.
28. Wei L, Lang CC, Sullivan FM, et al. Impact on mortality following first acute myocardial infarction of distance between home and hospital: cohort study. Heart 2008; **94**(9): 1141-6.
29. Devine KA, Christen S, Mulder RL, et al. Recommendations for the surveillance of education and employment outcomes in survivors of childhood, adolescent, and young adult cancer: A report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Cancer 2022; **128**(13): 2405-19.
30. Edman K, Öhrn K, Nordström B, Holmlund A. Prevalence of dental caries and influencing factors, time trends over a 30-year period in an adult population. Epidemiological studies between 1983 and 2013 in the county of Dalarna, Sweden. Acta Odontol Scand 2016; **74**(5): 385-92.

Figure 1.

Age groups (<1-14, 15-18, and 19-24) distribution across time for 65,173 young individuals <25 years of age in Sweden between 1958 and 2021. The left panel (a) displays females, and the right panel (b) shows males.

Figure 2.

Age distribution of all 65 173 young individuals <25 year of age with index cancer in Sweden between 1958 and 2021.

Figure 3.

Odds ratio (OR) plot (95% confidence interval (CI) and logarithmic scale) comparing the risk for subsequent (CAYAS) and new (controls) malignancy, cardiovascular, pulmonary, and other diseases between CAYAs and controls from 1958 to 2021. Abbreviations: CAYAs= children, adolescents, and young adults. IQR=interquartile range. SD=standard deviation. CNS= central nervous system.

Figure 4.

All-cause cumulative mortality of 65 173 females and male young individuals <25 year of age with index cancer (CAYAs) (a), and their 312 935 matched controls (b) between 1958 and 2021.

Figure 5.

All-cause (a), cancer specific (b), and cardiovascular (c) cumulative mortality of 65 173 young individuals <25 year of age, showing improvement in survival during the decades.

Figure 6.

Hazard ratio (HR) plot (95% confidence interval (CI) and logarithmic scale) comparing 65 173 CAYAs and 312 935 matched controls, assessing the risk for demographic and socioeconomic factors between the groups. Abbreviations: CAYAs= children, adolescents, and young adults. No= number. Gini= coefficient ranging from 0-1, indicates income inequality within each municipality, with a higher value signifying greater inequality calculated as high and low according to the 10th and 90th percentiles.

Research in context

Evidence before the study

Previous large cohort studies on young cancer survivors have extensively documented long-term morbidity and mortality across diverse age groups and populations. It is well-established that cancer treatment itself can lead to lifelong or life-threatening conditions in this population. Furthermore, differences across countries in living conditions, access to healthcare, and variations in healthcare systems may influence long-term outcomes. To identify relevant studies, we conducted a thorough search using terms such as cohort study, register study, childhood cancer, adolescence cancer, CAYA, AYA, long-term survivor, late mortality, late morbidity, cardiovascular toxicity, subsequent malignancy, secondary malignancy, socioeconomic disparity, and financial toxicity. A systematic search from 2000-2023 was performed in UniSearch, Linkoping University's library search tool, encompassing 154 licensed databases and a vast collection of printed and electronic material, including 747 434 papers/books, 454 007 e-books, and 21 180 e-journals. Furthermore, searches were conducted in PubMed and the Cochrane Library, and subsequent searches thereafter.

Added value of this study

This study significantly contributes to the existing literature in that it is the first comprehensive report that compares an entire population of young cancer patients in Sweden with matched controls. This approach adds a novel dimension to our understanding of what long-term outcomes and challenges young cancer survivors face. With a dataset of 378 108 individuals, including 65 173 child, adolescent, and young adults (CAYAs) matched with 312 935 controls over 63 years between 1958 and 2021, this retrospective register study fills a critical gap in our knowledge, laying the foundation for evidence-based healthcare policies.

Beyond quantification of risks, the study systematically investigates morbidity, mortality, and a spectrum of individual and demographic variables. This in-depth analysis sheds light on long-term socioeconomic disparities, enabling tailored interventions and support systems. Notably, this study breaks new ground by including all non-malignant diseases occurring after cancer diagnosis, a facet often omitted in previous cohort studies. This comprehensive approach enriches our understanding of the multifaceted health challenges facing CAYAs.

Furthermore, this study goes beyond childhood cancer by following patients up to 25 years of age. Inclusion of this previously underexplored age group enhances the generalisability of our findings, catering for the wide spectrum of young cancer survivors. Indeed, this groundbreaking expansion of analyses to include older

survivors led to the inclusion of cervical cancer, shedding light on a large group of young women with cancer whose long-term outcome has been poorly investigated.

Implication of all the available evidence

The findings of this study, together with our existing knowledge, will have crucial implications for healthcare practice and policy regarding young patients with cancer. Based on the risks identified, healthcare practitioners will now be able to tailor interventions to the needs of their young cancer survivors. Subsequent long-term care of cancer survivors is imperative considering the substantial reduction in life expectancy for many, and policymakers must allocate resources to improve the situation of these individuals. Comprehensive cancer registers must include all malignancies over time, and the data thus gathered used to guide healthcare planning for equitable post cancer care, particularly for those with socioeconomic disparity.

Furthermore, this study stresses the need to address the underexplored aspects of care of young women survivors, and we urge policymakers to incorporate these insights into the healthcare of these women. Future research should focus on causal relationships, with emphasis on long-term survival experiences of young adults. Evaluating the effectiveness of interventions is key to guiding evidence-based practice, improving the outcomes of young cancer survivors. Together, such efforts will contribute to a more nuanced understanding of the challenges faced by this population, providing informed strategies for comprehensive care tailored to the individual patient.

Table

Table 1. Baseline demographic and clinical and socioeconomic characteristics of 65 173 patients with index malignancy and their 312 935 matched controls. All the cancer in Sweden between January 1958 to December 2021 in patients under the age of 25 years.

	CAYAs n=65 173				Controls n=312 935			
Age group at index cancer	**<1-14**	**15-18**	**19-24**	**Total**	**<1-14**	**15-18**	**19-24**	**Total**
n (%)	15 293(23·5)	6639 (10·2)	43241 (66·3)	65 173	69 189 (22·1)	31 071 (9·9)	21 2675(68·0)	31 2935
Age at diagnosis· years median (IQR)	5 (2-10)	17 (16-18)	23 (21-24)	21 (15-23)	5 (2-10)	17 (16-18)	23 (22-24)	22 (23-16)
Sex **n (%)**								
Female	6985 (45·7)	3751 (56·5)	36 937 (85,4)	47 673 (73·1)	31 630 (45·7)	17 901 (57·6)	183 113 (86·1)	232 644 (74·3)
Male	8308 (54·3)	2888 (43·5)	6304 (14·6)	17 500 (26·9)	37 559 (54·3)	13 170 (42·4)	29 562 (13·9)	80 291 (25·7)
Area of birth n (%)								
Sweden	14 616 (95·6)	6088 (91·7)	39 775 (92·0)	60 479 (92·8)	65 693 (94·9)	28 105 (90·5)	183 043 (86·1)	276 841 (88·5)
Europe	306 (2·0)	280 (4·2)	2134 (4·9)	2720 (4·2)	1465 (2·1)	1331 (4·3)	14737 (6·9)	17 533 (5·6)
Other[b]	371 (2·4)	271 (4·1)	1332 (3·1)	1974 (3·0)	2031 (2·9)	1635 (5·3)	14895 (7·0)	18 561 (5·9)
Decade at index diagnosis								
1958-1970	2436 (15·9)	928 (14·0)	3064 (7·1)	6428 (9·9)	5332 (7·7)	2641 (8·5)	121 56 (5·7)	20 129 (6·4)
1971-1980	2134 (14·0)	1105 (16·6)	6260 (14·5)	9499 (14·6)	10 504 (15·2)	5505 (17·7)	31 179 (14·7)	47 188 (15·1)
1981-1990	2223 (14·5)	1054 (15·9)	6634 (15·3)	9911 (15·2)	11 031 (15·9)	5250 (16·9)	33 109 (15·6)	49 390 (15·8)
1991-2000	2654 (17·4)	1048 (15·8)	5468 (12·6)	9170 (14·1)	13 233 (19·1)	5230 (16·8)	27 285 (12·8)	45 748 (14·6)
2001-2010	2630 (17·2)	1146 (17·3)	6482 (15·0)	10 258(15·7)	13 102 (18·9)	5705 (18·4)	32 341 (15·2)	51 148 (16·3)
2011-2021	3216 (21·0)	1358 (20·5)	15 333 (35·5)	19 907 (30·5)	15 987 (23·1)	6740 (21·7)	76 605 (36·0)	99 332 (31·7)
Living conditions at index n (%)								
Part of Sweden[c]								
North	1929 (12·6)	835 (12·6)	5226 (12·1)	7990 (12·3)	8708 (12·6)	3880 (12·5)	25 814 (12·1)	38 402 (12·3)
Middle	5378 (35·2)	2216 (33·4)	13 920 (32·2)	21 514 (33·0)	26 167 (37·8)	10 825 (34·8)	69 091 (32·5)	106 083 (33·9)
South	7418 (48·5)	3452 (52·0)	23 855 (55·2)	34 725 (53·3)	34 314 (49·6)	16 366 (52·7)	117 770 (55·4)	168 450 (53·8)
Na for (living area/condition)	568 (3·7)	136 (2·0)	240 (0·6)	944 (1·4)	··	··	··	··
Inhabitant/km^2 in municipal n (%)								
<16	1842 (12·0)	797 (12·0)	3940 (9·1)	6579 (10·1)	8342 (12·1)	3715 (12·0)	19 423 (9·1)	31 480 (10·1)
16 to 2241	11 132 (72·8)	4972 (74·9)	33 156 (76·7)	49 260 (75·6)	52 947 (76·5)	23 971 (77·1)	164 280 (77·2)	241 198 (77·1)
≥ 2241	1751 (11·4)	734 (11·1)	5905 (13·7)	8390 (12·9)	7900 (11·4)	3385 (10·9)	28 972 (13·6)	40 257 (12·9)
Median income[d] **in municipal (SEK) n (%)**								
>363.000	1284 (8·4)	497 (7·5)	2757 (6·4)	4538 (7·0)	6345 (9·2)	2455 (7·9)	13690 (6·4)	22 490 (7·2)
286.000 to 363.000	11 773 (77·0)	5272 (79·4)	36 305 (84·0)	53 350 (81·9)	55 102 (79·6)	25 156 (81·0)	179 540 (84·4)	259 798 (83·0)
<286.000	1668 (10·9)	734 (11·1)	3939 (9·1)	6341 (9·7)	7742 (11·2)	3460 (11·1)	19 445 (9·1)	30 647 (9·8)
Gini coefficient[e]								
> 0·42	1581 (10·3)	588 (8·9)	4646 (10·7)	6815 (10·5)	7250 (10·5)	2730 (8·8)	22 831 (10·7)	32 811 (10·5)
0·31 to 0·42	11 401 (74·6)	5144 (77·5)	34 571 (79·9)	51 116 (78·4)	54 106 (78·2)	24 726 (79·6)	171236 (80·5)	250 068 (79·9)
<0·31	1743 (11·4)	771 (11·6)	3784 (8·8)	6298 (9·7)	7833 (11·3)	3615 (11·6)	18 608 (8·7)	30 056 (9·6)
Proximity to hospital								
<30 km (19 miles)	11 511(75·3)	5056 (76·2)	35 684 (82·5)	52 251 (80·2)	54 240 (78·4)	24 246 (78·0)	176 538 (83·0)	255 024 (81·5)
30 to 100 km	30 66(20·0)	1380 (20·8)	7091 (16·4)	11 537 (17·7)	14 294 (20·7)	6530 (21·0)	35 048 (16·5)	55 872 (17·9)
>100 km (62 miles)	148 (1·0)	67 (1·0)	226 (0·5)	441 (0·7)	655 (0·9)	295 (0·9)	1089 (0·5)	2039 (0·7)

Index Cancer Diagnosis n (%)								
Leukaemia	4693 (30·7)	645 (9·7)	772 (1·8)	6110 (9·4)	··	··	··	··
Acute lymphoblastic leukaemia	3072 (20·1)	307 (4·6)	240 (0·6)	3619 (5·6)	··	··	··	··
Acute myeloid leukaemia	688 (4·5)	226 (3·4)	396 (0·9)	1310 (2·0)	··	··	··	··
Hodgkin lymphoma	405 (2·6)	567 (8·5)	1159 (2·7)	2131 (3·3)	··	··	··	··
Non-Hodgkin lymphoma	674 (4·4)	279 (4·2)	430 (1·0)	1383 (2·1)	··	··	··	··
CNS Tumours	3981 (26·0)	849 (12·8)	1371 (3·2)	6201 (9·5)	··	··	··	··
Soft tissue sarcoma	594 (3·9)	219 (3·3)	311 (0·7)	1124 (1·7)	··	··	··	··
Bone tumours	685 (4·5)	468 (7·0)	406 (0·9)	1559 (2·4)	··	··	··	··
Gastrointestinal	433 (2·8)	348 (5·2)	830 (1·9)	1611 (2·5)	··	··	··	··
Kidney and urorenal tract	919 (6·0)	59 (0·9)	176 (0·4)	1154 (1·8)	··	··	··	··
Male reproductive organs	179 (1·2)	303 (4·6)	1689 (3·9)	2171 (3·3)	··	··	··	··
Prostate	1 (0·01)	4 (0·1)	6 (0·01)	11 (0·02)	··	··	··	··
Testis	162 (1·1)	286 (4·3)	1582 (3·7)	2030 (3·1)	··	··	··	··
Female reproduction organ	193 (1·3)	1491 (22·5)	31 728 (73·4)	33 412 (51·3)	··	··	··	··
Cervix	8 (0·1)	940[f] (14·2)	29 573[f](68·4)	30 521 (46·8)	··	··	··	··
Breast	6 (0·04)	17 (0·3)	172 (0·4)	195 (0·3)	··	··	··	··
Eye	431 (2·8)	17 (0·3)	32 (0·1)	480 (0·7)	··	··	··	··
Thyroid and other endocrine glands	677 (4·4)	614 (9·2)	1482 (3·4)	2773 (4·3)	··	··	··	··
Skin	192 (1·3)	443 (6·7)	1946 (4·5)	2581 (4·0)	··	··	··	··
Other malignancies	1206 (7·9)	290 (4·4)	635 (1·5)	2131 (3·3)	··	··	··	··
Cancer treatment (%) (n=15 949)[g]								
Radiotherapy	5199 (59·9)	1363 (58·0)	2796 (56·8)	9358 (58·7)	··	··	··	··
Anthracycline	4227 (48·7)	1084 (46·1)	1693 (34·4)	7004(43·9)	··	··	··	··
Other drugs	7580 (87·3)	1956 (83·2)	4010 (81·5)	13 546 (84·9)	··	··	··	··

Patients included were between <1 years and 24 years at the time of the index cancer diagnosis and their 1:5 matched controls regarding age· sex and place of residence.
Abbreviations: CAYAs children, adolescents, and young adults IQR=interquartile range. SD=standard deviation. CNS= central nervous system. ··=not applicable. n=numbers.
[a] = assigned at birth
[b] Other= North America 0·1%, Soth America 0·4%, Africa 1·0 %, Asia 3·7%, Russia 0·02%, Oceanian 0·03% and unknown 0·03%
[c] North (Norrland) 11·4%· Middle (Svealand) 40·8% and South (Gotaland) 47·8% of Sweden's population.
[d] Median income high and low according to 10th and 90th percentiles.
[e] Gini coefficient ranges from 0-1, indicates income inequality within each municipality, with a higher value signifying greater unevenness. calculated high and low according to 10th and 90th percentiles.
[f] Including cervical intraepithelial neoplasia (CIN) and high-grade squamous intraepithelial lesion (HSIL)
[g] Treatment for leukaemia, CNS malignancies, Hodgkin's lymphoma, non-Hodgkins's lymphoma, and testis cancer according to standard protocols (0-14 years: n=8678, 15-18: n=2351, 19-24: n=4920).

Table

Table 2. Outcome of morbidities. mortality and socioeconomic factors of 65173 in child, adolescent, and young adult patients with cancer and their 312935 matched controls. All the cancer patients in Sweden under the age of 25 years between January 1958 to December 2021.

	CAYAs n=65 173				Controls n=312 935				
Age group at index cancer	**<1-14**	**15-18**	**19-24**	**Total**	**<1-14**	**15-18**	**19-24**	**Total**	p-value
n (%)	15 293 (23·5)	6639 (10·2)	43 241 (66·3)	65 173	69 189 (22·1)	31 071 (9·9)	212 675 (68·0)	312 935	
Age at index date (IQR)	5 (2-10)	17 (16-18)	23 (21-24)	21 (15-23)	5 (2-10)	17 (16-18)	23 (22-24)	22 (23-16)	<0·0001
Follow up years									
Years of follow up mean (SD)	15·8 (16·2)	20·5 (17·6)	20·7 (16·8)	19·5 (16·9)	26·0 (16·3)	27·1 (16·5)	22·6 (16·9)	23·8 (16·8)	<0·0001
Age at study end years n (%)									
0-5	2284 (14·9)	··	··	2284 (3·5)	1971 (2·8)	··	··	1971 (0·6)	<0·0001
6-10	2268 (14·8)	··	··	2268 (3·5)	4408 (6·4)	··	··	4408 (1·4)	<0·0001
11-20	3958 (25·9)	1583 (23·8)	225 (0·5)	5766 (8·8)	13 398 (19·4)	2103 (6·8)	256 (0·1)	15 757 (5·0)	<0·0001
21-30	2373 (15·5)	1425 (21·5)	13199 (30·5)	16 997 (26·1)	13 536 (19·6)	6369 (20·5)	54 938 (25·8)	74 843 (23·9)	<0·0001
31-40	1887 (12·3)	931 (14·0)	9052 (20·9)	11 870 (18·2)	12 742 (18·4)	5265 (16·9)	45 500 (21·4)	63 507 (20·3)	<0·0001
41-50	1330 (8·7)	916 (13·8)	5482 (12·7)	7728 (11·9)	10 816 (15·6)	5494 (17·7)	28 354 (13·3)	44 664 (14·3)	<0·0001
51-60	759 (5·0)	808 (12·2)	6173 (14·3)	7740 (11·9)	8792 (12·7)	5255 (16·9)	32 564 (15·3)	46 611 (14·9)	<0·0001
61-70	349 (2·3)	710 (10·7)	5897 (13·6)	6956 (10·7)	3031 (4·4)	4945 (15·9)	32 119 (15·1)	40 095 (12·8)	<0·0001
≥71	85 (0·6)	265 (4·0)	3213 (7·4)	3563 (5·5)	495 (0·7)	1640 (5·3)	18 944 (8·9)	21 079 (6·7)	<0·0001
Median age (IQR)	16·7 (24·3)	32·9 (30·8)	38·7 (29·0)	33·4 (27·9)	30·8 (27·4)	43·5 (28·9)	42·0 (29·6)	39·2 (28·3)	<0·0001
Highest level of Education n (%)									
Elementary school 9 years	2389 (15·6)	1760 (26·5)	5974 (13·8)	10 123 (15·5)	8340 (12·1)	4265 (13·7)	20037 (9·4)	32 642 (10·4)	<0·0001
Upper secondary school	3224 (21·1)	2474 (37·3)	19 315 (44·7)	25 013 (38·4)	24 119 (34·9)	13 922 (44·8)	88 581 (41·7)	126 622 (40·5)	<0·0001
University	2719 (17·8)	1810 (27·3)	16 734 (38·7)	21 263 (32·6)	21 099 (30·5)	11 945 (38·4)	96 373 (45·3)	129 417 (41·4)	<0·0001
Postgraduate education	41 (0·3)	39 (0·6)	232 (0·5)	312 (0·5)	432 (0·6)	247 (0·8)	1590 (0·7)	2269 (0·7)	<0·0001
na	6920 (45·2)	556 (8·4)	986 (2·3)	8462 (13·0)	15199 (22·0)	692 (2·2)	6094 (2·9)	21 985 (7·0)	<0·0001
Civil status[a] n (%)									
Unmarried	12 583 (82·3)	4202 (63·3)	22 210 (51·4)	38 995 (59·8)	48 827 (70·6)	16 341 (52·6)	101 211 (47·6)	166 379 (53·2)	<0·0001
Married or registered partner	1550 (10·1)	1430 (21·5)	12 315 (28·5)	15 295 (23·5)	14 641 (21·2)	9667 (31·1)	72 303 (34·0)	96 611 (30·9)	<0·0001
Subsequent malignancy[b] n (%)									
All malignancy	1573 (10·3)	482 (7·3)	1618 (3·7)	3673 (5·6)	574 (0·8)	623 (2·0)	4913 (2·3)	6110 (2·0)	<0·0001
Lip oral cavity pharynx	40 (0·3)	25 (0·4)	53 (0·1)	118 (0·2)	13 (0·0)	20 (0·1)	130 (0·1)	163 (0·1)	<0·0001
Oesophagus stomach small intestine	21 (0·1)	6 (0·1)	16 (0·0)	43 (0·1)	4 (0·0)	6 (0·0)	30 (0·0)	40 (0·0)	<0·0001
Colon	13 (0·1)	4 (0·1)	23 (0·1)	40 (0·1)	4 (0·0)	5 (0·0)	69 (0·0)	78 (0·0)	<0·0001
Liver gallbladder	7 (0·0)	2 (0·0)	24 (0·1)	33 (0·1)	6 (0·0)	8 (0·0)	46 (0·0)	60 (0·0)	<0·0001
Pancreas	3 (0·0)	4 (0·1)	21 (0·0)	28 (0·0)	10 (0·0)	7 (0·0)	61 (0·0)	78 (0·0)	0·0176
Other gastrointestinal	12 (0·1)	1 (0·0)	8 (0·0)	21 (0·0)	1 (0·0)	0 (0·0)	3 (0·0)	4 (0·0)	··
Mouth airways lungs	34 (0·2)	16 (0·2)	52 (0·1)	102 (0·2)	11 (0·0)	9 (0·0)	98 (0·0)	118 (0·0)	<0·0001
Bone connective soft tissue	91 (0·6)	21 (0·3)	31 (0·1)	143 (0·2)	3 (0·0)	2 (0·0)	14 (0·0)	19 (0·0)	<0·0001
Skin cancers	219 (1·4)	142 (2·1)	790 (1·8)	1151 (1·8)	439 (0·6)	499 (1·6)	3841 (1·8)	4779 (1·5)	<0·0001
Breast	9 (0·1)	6 (0·1)	35 (0·1)	50 (0·1)	13 (0·0)	11 (0·0)	131 (0·1)	155 (0·0)	0·0088

Female reproductive	18 (0·1)	11 (0·2)	53 (0·1)	82 (0·1)	10 (0·0)	9 (0·0)	111 (0·1)	130 (0·0)	<0·0001
Cervix	1 (0·0)	2 (0·0)	5 (0·0)	8 (0·0)	0 (0·0)	1 (0·0)	14 (0·0)	15 (0·0)	··
Prostate	10 (0·1)	1 (0·0)	8 (0·0)	19 (0·0)	6 (0·0)	10 (0·0)	21 (0·0)	37 (0·0)	0·0017
Testis	9 (0·1)	5 (0·1)	9 (0·0)	23 (0·0)	3 (0·0)	2 (0·0)	1 (0·0)	6 (0·0)	··
Other genitourinary	26 (0·2)	6 (0·1)	16 (0·0)	48 (0·1)	13 (0·0)	7 (0·0)	73 (0·0)	93 (0·0)	<0·0001
Kidney and bladder	289 (1·9)	49 (0·7)	73 (0·2)	411 (0·6)	9 (0·0)	7 (0·0)	50 (0·0)	66 (0·0)	<0·0001
CNS	79 (0·5)	16 (0·2)	20 (0·0)	115 (0·2)	5 (0·0)	4 (0·0)	30 (0·0)	39 (0·0)	<0·0001
Thyroid, and other endocrine glands	194 (1·3)	75 (1·1)	117 (0·3)	386 (0·6)	8 (0·0)	6 (0·0)	67 (0·0)	81 (0·0)	<0·0001
Lymphoma	270 (1·8)	34 (0·5)	59 (0·1)	363 (0·6)	4 (0·0)	3 (0·0)	42 (0·0)	49 (0·0)	<0·0001
Leukaemia	106 (0·7)	42 (0·6)	95 (0·2)	243 (0·4)	21 (0·0)	10 (0·0)	194 (0·1)	225 (0·1)	<0·0001
Benign meningioma	266 (1·7)	46 (0·7)	106 (0·2)	418 (0·6)	17 (0·0)	14 (0·0)	119 (0·1)	150 (0·0)	<0·0001
All other specified neoplasms	1573 (10·3)	482 (7·3)	1618 (3·7)	3673 (5·6)	574 (0·8)	623 (2·0)	4913 (2·3)	6110 (2·0)	<0·0001
Relapse of index cancer n (%)									
> 5 years	4141 (27·1)	1117 (16·8)	2502 (5·8)	7760 (11·9)	··	··	··	··	··
Cardiovascular diseases n (%)									
All cardiovascular diseases	1963 (12·8)	1345 (20·3)	7695 (17·8)	11 003 (16·9)	6351 (9·2)	4937 (15·9)	33844 (15·9)	45 132 (14·4)	<0·0001
Coronary artery diseases	89 (0·6)	157 (2·4)	967 (2·2)	1213 (1·9)	510 (0·7)	648 (2·1)	4118 (1·9)	5276 (1·7)	0·0018
Pulmonary embolism	75 (0·5)	72 (1·1)	408 (0·9)	555 (0·9)	199 (0·3)	201 (0·6)	1284 (0·6)	1684 (0·5)	<0·0001
Myo- endo- and pericardial	44 (0·3)	19 (0·3)	74 (0·2)	137 (0·2)	179 (0·3)	101 (0·3)	359 (0·2)	639 (0·2)	0·7940
Arrhythmias	285 (1·9)	231 (3·5)	1600 (3·7)	2116 (3·2)	1399 (2·0)	1139 (3·7)	7402 (3·5)	9940 (3·2)	0·3587
Heart failure and cardiomyopathy	195 (1·3)	133 (2·0)	543 (1·3)	871 (1·3)	255 (0·4)	329 (1·1)	1987 (0·9)	2571 (0·8)	<0·0001
Valvular diseases	109 (0·7)	90 (1·4)	330 (0·8)	529 (0·8)	232 (0·3)	182 (0·6)	1353 (0·6)	1767 (0·6)	<0·0001
Cerebrovascular	384 (2·5)	213 (3·2)	1001 (2·3)	1598 (2·5)	438 (0·6)	451 (1·5)	3511 (1·7)	4400 (1·4)	<0·0001
Hypertension	398 (2·6)	383 (5·8)	2748 (6·4)	3529 (5·4)	1642 (2·4)	1853 (6·0)	13 507 (6·4)	17 002 (5·4)	0·8590
Pulmonary n (%)									
All Pulmonary Diseases	5742 (37·5)	1771 (26·7)	8775 (20·3)	16 288 (25·0)	17 404 (25·2)	6139 (19·8)	35 535 (16·7)	59 078 (18·9)	<0·0001
Chronic lower respiratory disease	49 (0·3)	75 (1·1)	761 (1·8)	885 (1·4)	150 (0·2)	221 (0·7)	1859 (0·9)	2230 (0·7)	<0·0001
Interstitial lung disease	62 (0·4)	19 (0·3)	92 (0·2)	173 (0·3)	34 (0·0)	50 (0·2)	259 (0·1)	343 (0·1)	<0·0001
Other health related cause n (%)									
Infectious and parasitic	6498 (42·5)	1910 (28·8)	8731 (20·2)	17 139 (26·3)	12 480 (18·0)	5240 (16·9)	32 383 (15·2)	50 103 (16·0)	<0·0001
Blood and blood-forming organs	3189 (20·9)	858 (12·9)	2688 (6·2)	6735 (10·3)	1757 (2·5)	1109 (3·6)	8101 (3·8)	10 967 (3·5)	<0·0001
Thyroid and other endocrine glands	2697 (17·6)	1231 (18·5)	5844 (13·5)	9772 (15·0)	5375 (7·8)	3020 (9·7)	23 876 (11·2)	32 271 (10·3)	<0·0001
Mental illness	2348 (15·4)	1332 (20·1)	8464 (19·6)	12 144 (18·6)	11 915 (17·2)	5720 (18·4)	35 175 (16·5)	52 810 (16·9)	<0·0001
Neurological	2266 (14·8)	950 (14·3)	4844 (11·2)	8060 (12·4)	5413 (7·8)	2953 (9·5)	19 385 (9·1)	27 751 (8·9)	<0·0001
Eye	3853 (25·2)	1447 (21·8)	8790 (20·3)	14 090 (21·6)	11 017 (15·9)	5962 (19·2)	42 562 (20·0)	59 541 (19·0)	<0·0001
Ear	3003 (19·6)	710 (10·7)	4141 (9·6)	7854 (12·1)	7305 (10·6)	3035 (9·8)	20 059 (9·4)	30 399 (9·7)	<0·0001
Gastrointestinal	4420 (28·9)	2133 (32·1)	12 338 (28·5)	18891 (29·0)	16 226 (23·5)	8280 (26·6)	53 388 (25·1)	77 894 (24·9)	<0·0001
Skin	4231 (27·7)	1805 (27·2)	10 653 (24·6)	16 689 (25·6)	14 773 (21·4)	7368 (23·7)	47 375 (22·3)	69 516 (22·2)	<0·0001
Musculoskeletal	3881 (25·4)	2136 (32·2)	14 319 (33·1)	20 336 (31·2)	19 241 (27·8)	10 515 (33·8)	66 996 (31·5)	96 752 (30·9)	0,1529
kidney and genitourinary	3756 (24·6)	2617 (39·4)	24 716 (57·2)	31 089 (47·7)	18 147 (26·2)	11 030 (35·5)	87 915 (41·3)	117 092 (37·4)	<0·0001
External affliction[c]	290 (1·9)	189 (2·8)	1420 (3·3)	1899 (2·9)	476 (0·7)	673 (2·2)	5525 (2·6)	6674 (2·1)	<0·0001
Remaining intact teeth mean (SD)	22·42 (7·70)	19·75 (9·04)	20·18 (9·04)	20·40 (8·92)	22·31 (7·53)	20·00 (8·69)	20·11 (8·93)	20·46 (8·74)	0·1852
Hospital care									
Total Hospital care days mean (SD)	81·5 (126·1)	62·9 (195·1)	31·6 (98·4)	46·5 (120·4)	11·8 (95·9)	18·7 (123·8)	19·9 (100·6)	18·0 (102·2)	<0·0001

>5 years after index days mean (SD)	16·2 (94·3)	24·0 (174·7)	15·1 (77·6)	16·3 (95·9)	10·1 (93·6)	14·6 (116·5)	12·2 (78·1)	12·0 (86·2)	<0·0001
Total ICU care hours mean (SD)	15·1 (116·9)	7·8 (69·6)	3·4 (43·1)	6·6 (70·4)	1·5 (26·6)	1·8 (24·7)	2 (30·8)	1·9 (29·4)	<0·0001
>5 years after index hours mean (SD)	4·3 (73·6)	3·9 (54·7)	2·2 (36·5)	2·9 (49·6)	1·3 (25·1)	1·6 (22·9)	1·6 (28·1)	1·6 (27·0)	<0·0001
Medical leave days Mean (SD)									
Total sick leave + disability pension	343·1 (1309·3)	626·4 (1680·0)	623·9 (1605·5)	558·3 (1553·8)	241·5 (1038·4)	465·7 (1465·0)	528·8 (1524·7)	459 (1430·1)	<0·0001
Sick leave >180 days· No (%)	802 (5·2)	897 (13·5)	8090 (18·7)	9789 (15·0)	4644 (6·7)	3835 (12·3)	29343 (13·8)	37 822 (12·1)	<0·0001
Years in study n (%)									
0-5	6061 (39·6)	1889 (28·5)	10642 (24·6)	18 592 (28·5)	7507 (10·8)	3063 (9·9)	41930 (19·7)	52 500 (16·8)	<0·0001
6-10	1597 (10·4)	692 (10·4)	6248 (14·4)	8537 (13·1)	7200 (10·4)	3159 (10·2)	30358 (14·3)	40 717 (13·0)	0·5496
11-20	2347 (15·3)	1087 (16·4)	6962 (16·1)	10 396 (16·0)	13 233 (19·1)	5904 (19·0)	35422 (16·7)	54 559 (17·4)	<0·0001
21-30	2161 (14·1)	865 (13·0)	5175 (12·0)	8201 (12·6)	13 556 (19·6)	5150 (16·6)	26 900 (12·6)	45 606 (14·6)	<0·0001
31-40	1544 (10·1)	882 (13·3)	6306 (14·6)	8732 (13·4)	11 296 (16·3)	5492 (17·7)	33 374 (15·7)	50 162 (16·0)	<0·0001
41-50	924 (6·0)	805 (12·1)	5742 (13·3)	7471 (11·5)	10 239 (14·8)	5431 (17·5)	31 581 (14·8)	47 251 (15·1)	<0·0001
51-60	499 (3·3)	335 (5·0)	2033 (4·7)	2867 (4·4)	5333 (7·7)	2442 (7·9)	12 357 (5·8)	20 132 (6·4)	<0·0001
>61	160 (1·0)	83 (1·3)	133 (0·3)	376 (0·6)	825 (1·2)	430 (1·4)	753 (0·4)	2008 (0·6)	0·0612
Mortality									
All-cause mortality n (%)	5531 (36·2)	1763 (26·6)	4390 (10·2)	11 684 (17·9)	1063 (1·5)	985 (3·2)	5970 (2·8)	8018 (2·6)	<0·0001
Female No (%)	2469 (44·6)	687 (39·0)	2438 (55·5)	5594 (47·9)	310 (29·2)	423 (44·1)	4460 (74·7)	5193 (64·8)	<0·0001
Age mean (SD)	9·7 (9·7)	23·6 (13·2)	35·69 (17·8)	21·5 (18·3)	37·3 (16·7)	49·9 (17·0)	55·1(16·1)	52·1 (17·4)	<0·0001
years after index mean (SD)	3·6 (8·1)	7·0 (13·1)	7·0 (13·1)	8·0 (14·0)	29·9 (16·0)	33·1 (16·9)	33,0 (16·0)	32·6 (16·2)	<0·0001
>5 years- after index mean age (SD)	13·5 (10·0)	23·6 (13·2)	35·7 (17·8)	25·3 (17·7)	38,0 (16·2)	49·9 (17·0)	55·1 (16·1)	52·2 (17·2)	<0·0001
Cancer specific mortality n (%)	3211 (21·0)	1029 (15·5)	2157 (5·0)	6397 (9·8)	19 (0·0)	27 (0·1)	229 (0·1)	275 (0·1)	<0·0001
Mean age (SD)	8·0 (6·1)	19·3 (5·4)	25·9 (9)	15·8 (10·8)	57·0 (9·4)	62·1 (12·6)	65·1 (11·1)	64·3 (11·3)	<0·0001
Years after index mean (SD)	2·0 (3·9)	2·7 (5·3)	4·2 (8·6)	2·8 (6·2)	48·2 (9)	45·3 (12·2)	42·8 (10·9)	43·4 (11)	<0·0001
>5 years after index mean age (SD)	18·1 (9·2)	28·8 (10·5)	38·4 (14·6)	30 (15·4)	57 (9·4)	62·1 (12·6)	65·5 (10·4)	64·6 (10·8)	<0·0001
Cardiovascular mortality n (%)	433 (2·8)	199 (3·0)	620 (1·4)	1252 (1·9)	216 (0·3)	303 (1·0)	1810 (0·9)	2329 (0·7)	<0·0001
Mean age (SD)	14·2 (15·9)	36·5 (20·4)	49·6 (18·7)	35·3 (24·1)	45·1 (17)	56·5 (13·9)	60 (13·1)	58·1 (14·3)	<0·0001
Years after index mean (SD)	7·7 (14·3)	19·9 (20·2)	27·6 (18·5)	19·5 (19·6)	37·3 (15·7)	39·7 (13·9)	37·7 (13·1)	37·9 (13·4)	<0·0001
>5 years after index mean age (SD)	33·1 (19·5)	52·3 (14·5)	57·1 (13·8)	52·4 (17·4)	46·9 (15·1)	56·9 (13·5)	60·6 (12·3)	58·9 (13·3)	<0·0001
External affliction[c] (%)	99 (0·6)	74 (1·1)	366 (0·8)	539 (0·8)	492 (0·7)	315 (1·0)	1394 (0·7)	2201 (0·7)	<0·0001
Mean age (SD)	24·8 (13·5)	33·9 (14·2)	41·3 (13·8)	37·2 (15·2)	30·5 (13·1)	37·1 (13·9)	40·9 (13·7)	38 (14·2)	0·2796
Years after index mean (SD)	17·5 (12·6)	17·2 (14·1)	19·1 (13·7)	18·6 (13·5)	23·4 (13·4)	20·4 (13·9)	18·8 (13·8)	20·1 (13·8)	0·0225
>5 years after index mean age (SD)	29·5 (11)	39·7 (12·6)	45·4 (12·1)	41·8 (13·4)	31·7 (12·5)	40·4 (12·6)	44·7 (12·4)	40·9 (13·6)	0·1977

p-values apply between all CAYAs and all controls, regardless of age group. Abbreviations: CAYA= child, adolescent, and young adult. IQR=interquartile range. SD=standard deviation. CNS= central nervous system. ¨=not applicable. n=numbers

a. As a Swedish citizen, you are registered as unmarried at birth, and this is changed to married and thereafter divorced or widowed in later life.

b. Subsequent malignancy: > 5 years after index date, for controls primary cancer after index date.

c. Injuries, poisonings, suicide, and other consequences of external causes.

Figure1a

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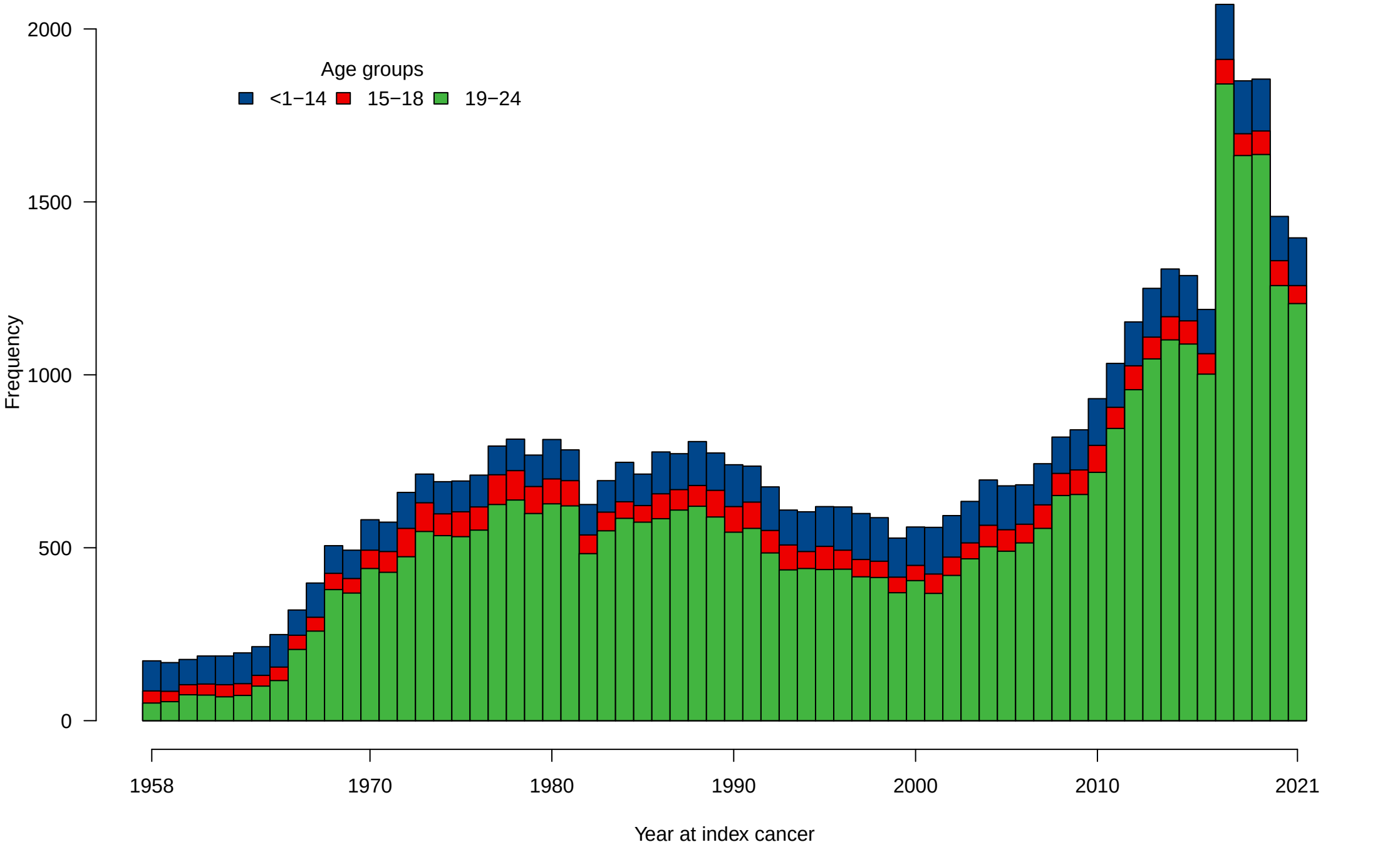

Figure 1b

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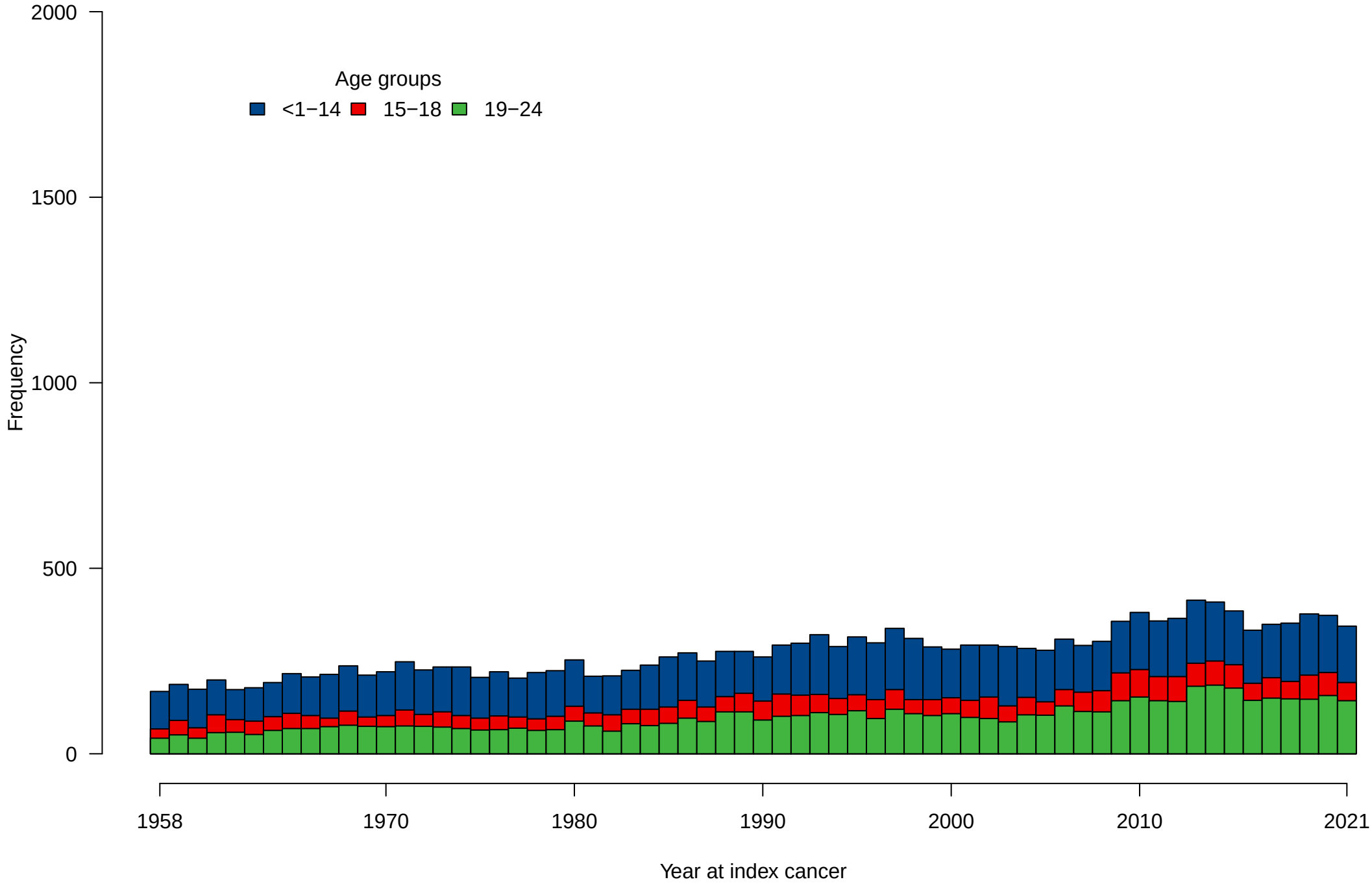

Figure 2

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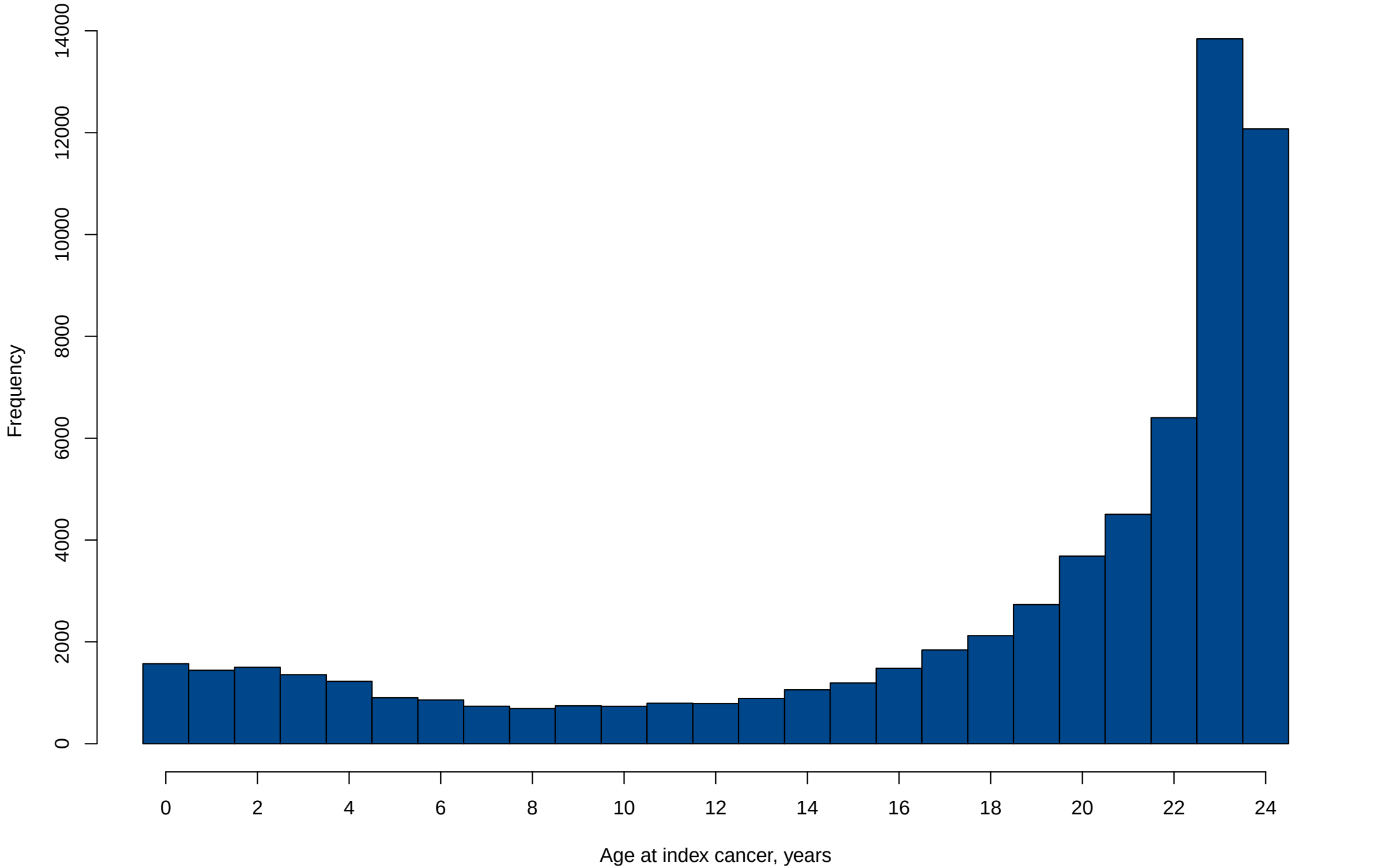

Figure 3

Diseases	CAYAs	Controls	OR (95% CI)
Subsequent and new malignancy			
Malignant neoplasms	3673	6110	3.00 (2.88 to 3.13)
Lip, oral cavity, and pharynx	118	163	3.48 (2.72 to 4.44)
Esophagus, stomach and small intestine	43	40	5.16 (3.28 to 8.15)
Colon	40	78	2.46 (1.64 to 3.65)
Liver and gallbladder	33	60	2.64 (1.67 to 4.11)
Pancreas	28	78	1.72 (1.08 to 2.69)
Other gastrointestinal	21	4	25.22 (8.51 to 101.06)
Mouth, airways, and lungs	102	118	4.16 (3.16 to 5.46)
Bone, connective, and soft tissue	143	19	36.23 (22.34 to 61.82)
Skin	1151	4779	1.16 (1.09 to 1.24)
Breast	50	155	1.55 (1.10 to 2.14)
Female reproductive	82	130	3.03 (2.27 to 4.03)
Cervix	8	15	2.56 (0.94 to 6.43)
Prostate	19	37	2.47 (1.34 to 4.40)
Testis	23	6	18.41 (7.29 to 55.25)
Kidney and bladder	48	93	2.48 (1.71 to 3.55)
CNS	411	66	30.11 (23.15 to 39.62)
Thyroid and other endocrine glands	115	39	14.18 (9.78 to 20.95)
Lymphoma	386	81	23.01 (18.06 to 29.64)
Leukemia	363	49	35.78 (26.46 to 49.24)
Benign meningioma	243	225	5.20 (4.32 to 6.26)
All other specified neoplasms	418	150	13.46 (11.14 to 16.34)
Cardiovascular diseases			
All cardiovascular diseases	11003	45132	1.21 (1.18 to 1.23)
Coronary artery diseases	1213	5276	1.11 (1.04 to 1.18)
Pulmonary embolism	555	1684	1.59 (1.44 to 1.75)
Myo−, endo− and pericardial	137	639	1.03 (0.85 to 1.24)
Arrhythmias	2116	9940	1.02 (0.97 to 1.07)
Heart failure and cardiomyopathy	871	2571	1.64 (1.51 to 1.77)
Valvular diseases	529	1767	1.44 (1.30 to 1.59)
Cerebrovascular	1598	4400	1.76 (1.66 to 1.87)
Hypertension	3529	17002	1.00 (0.96 to 1.03)
Pulmonary			
All Pulmonary Diseases	16288	59078	1.43 (1.40 to 1.46)
Chronic lower respiratory disease	885	2230	1.92 (1.77 to 2.08)
Interstitial lung disease, incl. fibrosis	173	343	2.43 (2.01 to 2.92)
Other health−related cause			
Infectious and parasitic	17139	50103	1.87 (1.83 to 1.91)
Blood and blood−forming organs	6735	10967	3.17 (3.07 to 3.28)
Endocrine, nutritional and metabolic diseases	9772	32271	1.53 (1.50 to 1.57)
Mental and behavioral disorders	12144	52810	1.13 (1.10 to 1.15)
Nervous system	8060	27751	1.45 (1.41 to 1.49)
Eye and adnexa	14090	59541	1.17 (1.15 to 1.20)
Ear and mastoid process	7854	30399	1.27 (1.24 to 1.31)
Digestive system	18891	77894	1.23 (1.21 to 1.25)
Skin and subcutaneous tissue	16689	69516	1.21 (1.18 to 1.23)
Musculoskeletal system and connective tissue	20336	96752	1.01 (1.00 to 1.03)
Genitourinary system	31089	117092	1.53 (1.50 to 1.55)
External causes	1899	6674	1.38 (1.31 to 1.45)

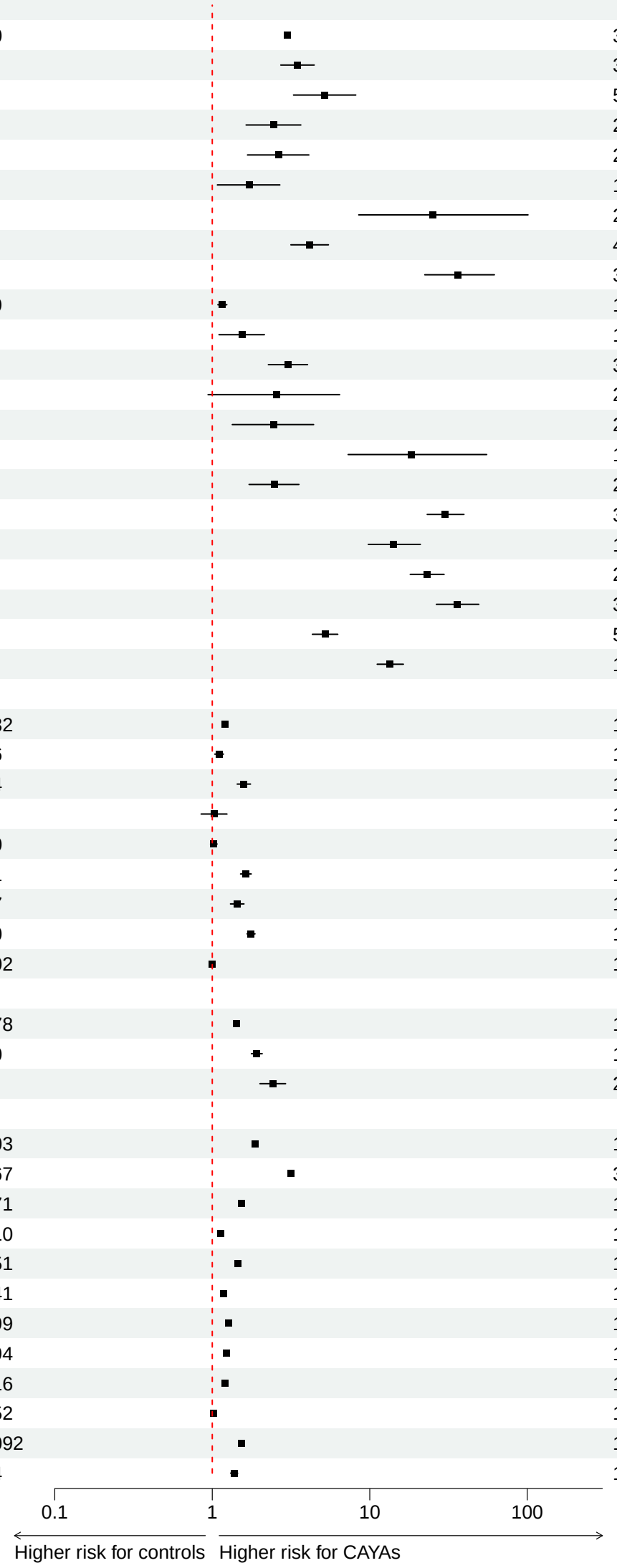

Figure 4a

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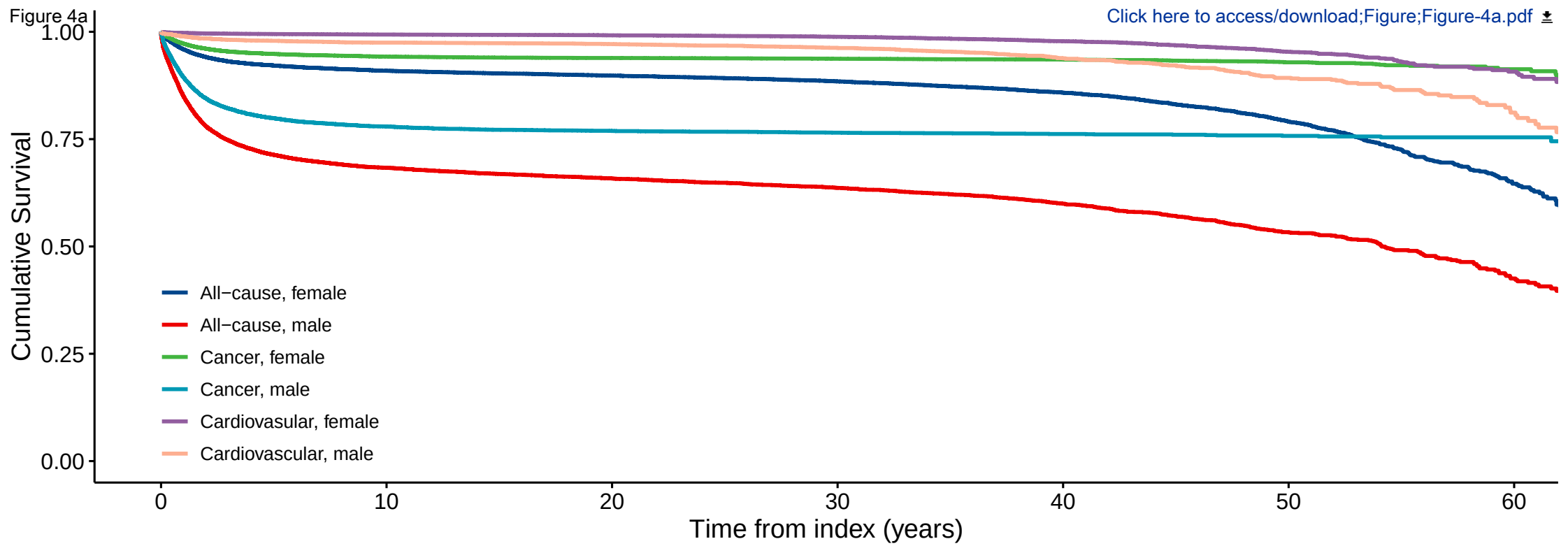
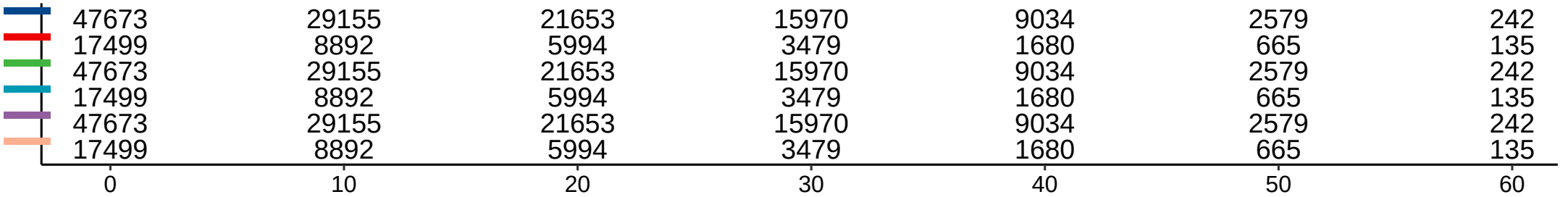


Number at risk



Cumulative number of events

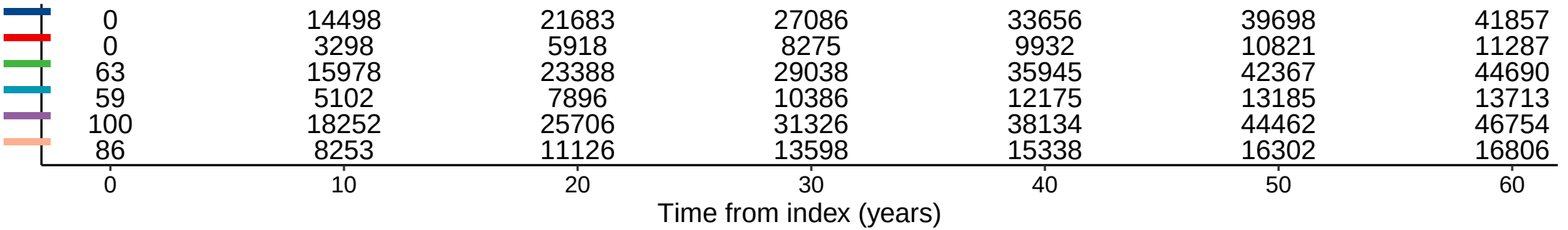


Figure 4b

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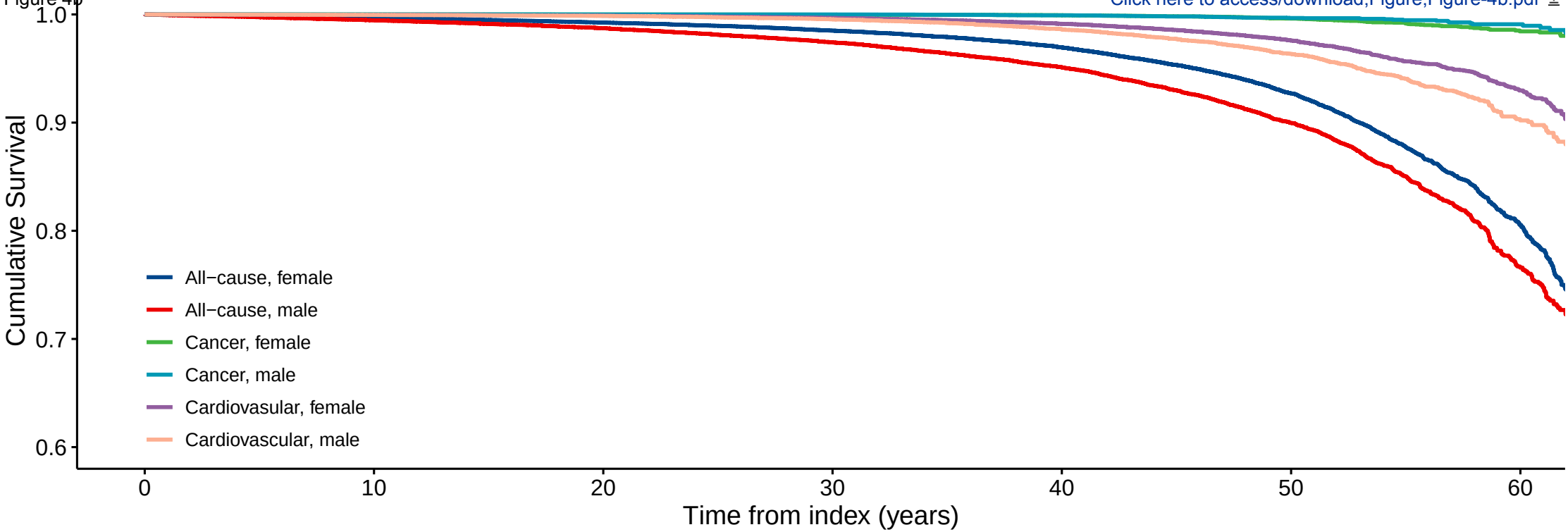


Number at risk

All−cause, female	232644	158202	119557	89355	52138	15719	1285
All−cause, male	80291	61536	45602	30214	17256	6421	733
Cancer, female	232644	158202	119557	89355	52138	15719	1285
Cancer, male	80291	61536	45602	30214	17256	6421	733
Cardiovasular, female	232644	158202	119557	89355	52138	15719	1285
Cardiovascular, male	80291	61536	45602	30214	17256	6421	733

0 10 20 30 40 50 60

Time from index (years)

Cumulative number of events

All−cause, female	0	73847	111877	141320	177452	212515	226259
All−cause, male	0	18372	33914	48803	61213	71428	76787
Cancer, female	0	74459	113076	143280	180447	216775	231151
Cancer, male	0	18754	34687	50075	63018	73822	79509
Cardiovasular, female	0	74397	112909	142915	179748	215693	229889
Cardiovascular, male	0	18720	34608	49881	62631	73208	78762

0 10 20 30 40 50 60

Time from index (years)

Figure 5a

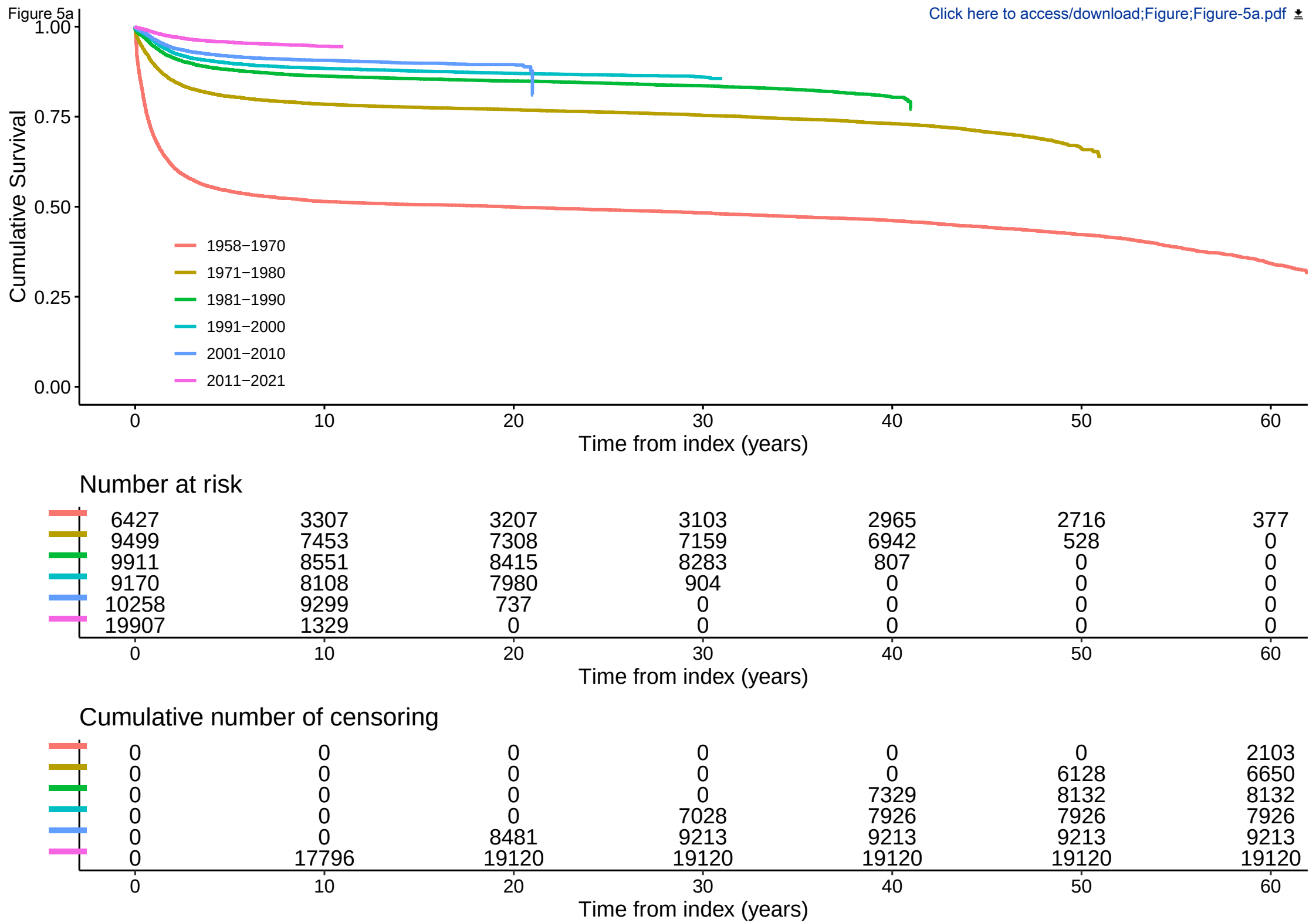


Figure 5b

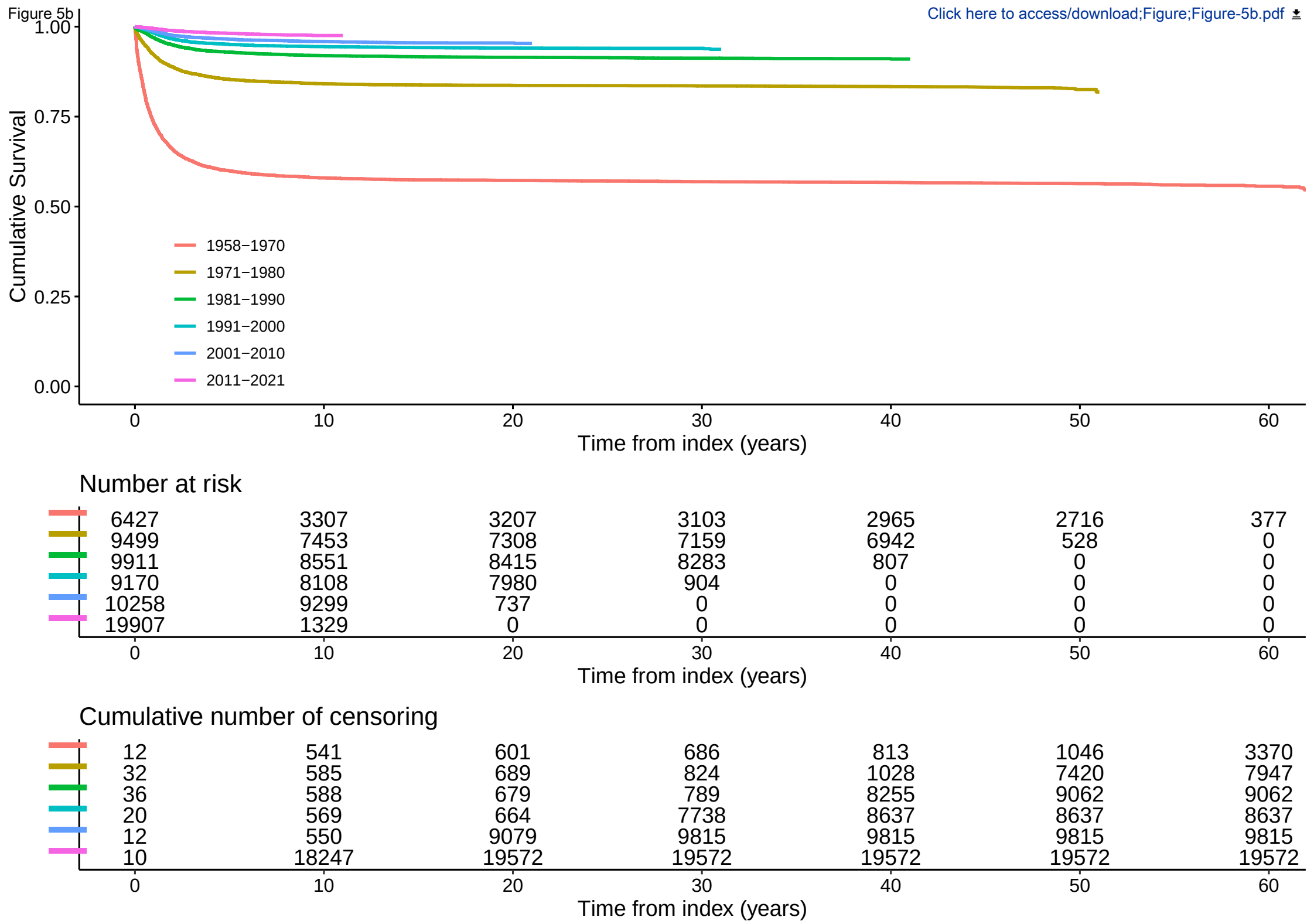
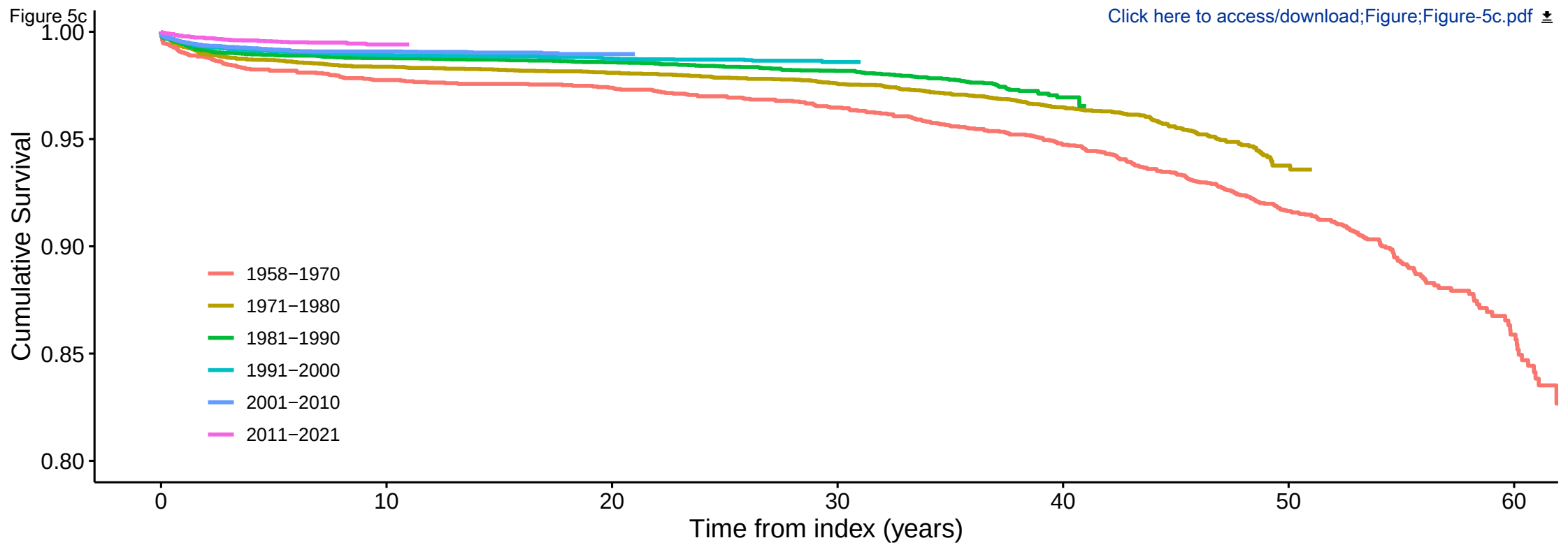
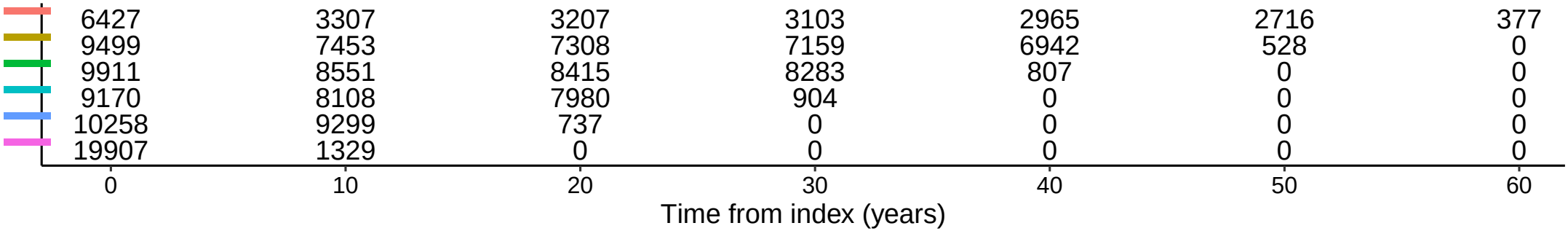


Figure 5c



Number at risk



Cumulative number of censoring

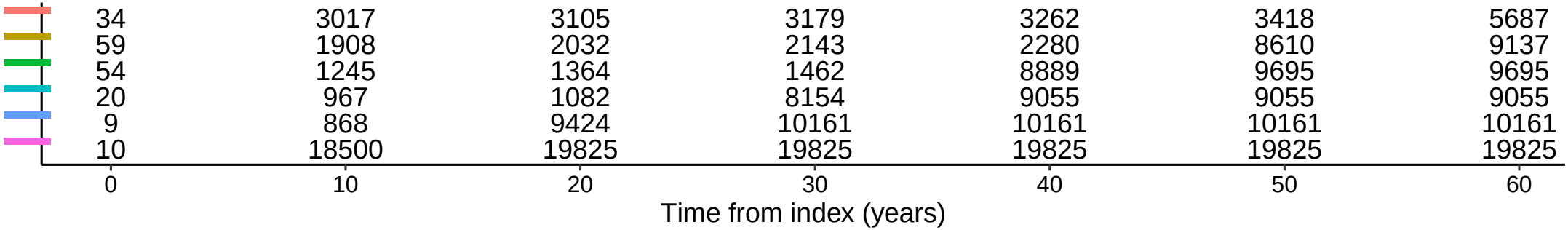


Figure 6