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Preventive Medicine 208 (2026) 108578

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Generational changes in cardiometabolic disease incidence by risk factor strata in the UK Biobank

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ARTICLE INFO

Keywords:
Cardiometabolic disease
Incidence
Birth cohort
Risk factors
Age-period-cohort effect

ABSTRACT

Objective: We assessed generational changes in the incidence of coronary artery disease (CAD), acute myocardial infarction (AMI), ischemic stroke, peripheral artery disease (PAD), and type 2 diabetes (T2D) by risk factor strata.
Methods: For each disease, we included baseline (2006–2010) disease-free UK Biobank participants and prospectively calculated age-specific incidence rates across seven consecutive five-year birth-cohorts (1936–1940 to 1966–1970). We applied Age-Period-Cohort models to examine age-independent birth-cohort effects in strata by sex, genetic risks, socioeconomic status, smoking history, and body mass index.
Results: CAD, AMI, PAD, and T2D incidence declined in more recent generations among both men and women, while stroke incidence remained stable. Compared to the 1936–1940 cohort, the incidence (95%CI) in the 1950–1955 cohort was 34.0% (22.4%, 45.7%) lower for CAD and 53.5% (31.2%, 75.8%) lower for PAD in the 65–69 age group. Age-Period-Cohort models suggested birth-cohort effects in observed declines. Birth-cohort effects on CAD and PAD were most evident among individuals with normal-weight, higher socioeconomic status, and ever-smoked, while T2D declines were strongest in individuals with overweight/obesity.
Conclusions: CAD, AMI, PAD, and T2D incidences have decreased in more recent generations. However, the stable ischemic stroke incidence and diverse subgroup trends indicate disease-specific differences in preventive gains.

1. Introduction

Cardiometabolic diseases (CMD), including type 2 diabetes mellitus (T2D) and cardiovascular diseases (CVD), are common causes of mortality in Europe (Timmis et al., 2024). It has been hypothesized that a large proportion of CMD and CMD-related deaths could be prevented by adopting healthy lifestyles and reducing risk factor exposures (Wang et al., 2024). Therefore, prevention strategies, such as smoking cessation, adhering to a healthy diet, and managing hypertension, dyslipidemia, and glucose metabolism, have been widely promoted to reduce CMD risk. This has indeed led to major improvements in the reduction of smoking in Western countries and the introduction of novel risk-factor reducing medications (Fernández-Rhodes et al., 2020; Rutters et al., 2024). Following those improvements, there are studies reporting reductions in CMD-related risks across calendar periods (Conrad et al., 2024; Fallahtafti et al., 2025).

However, mixed temporal patterns across specific CMD, with some conditions declining and others increasing, have also been reported, and these patterns are challenging to interpret because they are rarely attributable to a single risk factor (Ezzati et al., 2015). Previous studies have relied on nationwide administrative/surveillance datasets that were limited by insufficient individual-level data (Sun et al., 2022; Vinter et al., 2024), which constrained the ability to identify underlying drivers and to move beyond broad ecological explanations. In addition, as age-period-cohort effects are intrinsically intertwined in trends, observed trends may reflect aging, period-related changes (diagnostic/

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https://doi.org/10.1016/j.ypmed.2026.108578
Received 28 January 2026; Received in revised form 9 April 2026; Accepted 10 April 2026
Available online 12 April 2026

coding practices), and cohort-specific exposure patterns.

These gaps are particularly important because successive birth cohorts were shaped by distinct early-life environments as well as by major social and healthcare changes; in the United Kingdom (UK), these included the establishment of the National Health Service in 1948, the end of post-war food rationing in the early 1950s, and major changes in compulsory education. Previous studies have suggested that these differences may contribute to variation in later-life disease risk across birth cohorts (Davies et al., 2018; Gracner et al., 2024). Accordingly, a generational perspective that explicitly considers the intertwined age-period-cohort effects on changes in disease incidence and subgroup heterogeneities is essential. Large-scale research cohorts, such as the UK Biobank (UKB), which includes participants spanning multiple birth cohorts and provides detailed individual-level records, can provide a valuable opportunity for such studies. Given these, this study used UKB data to assess changes in the age-specific incidence rates of CMD across consecutive birth cohorts, disentangling age-independent birth-cohort effects both in the total study population and relevant risk subgroups stratified by sex, socioeconomic status, smoking status, body mass index (BMI), and polygenetic risk scores (PRS) for CMD.

2. Methods

2.1. Study design and population

This study utilized data collected from the UKB cohort, which recruited 502,628 participants aged 40–70 years between 2006 and 2010, with written informed consent obtained via electronic signature. The details of participant selection and follow-up procedures have been described elsewhere (Sudlow et al., 2015). A total of 502,393 participants with available records and born between 1936 and 1970 were first selected. For each outcome, we further included those without a history of disease at baseline; see Table 1 for the detailed respective sample sizes. The UKB cohort has been approved by the North West Multi-Centre Research Ethics Committee and complies with UK ethical and regulatory standards. This study adheres to the principles of the Declaration of Helsinki, and data usage follows relevant UK governance frameworks.

2.2. Outcomes

CMD diagnosis was defined using the three-character *International Classification of Diseases, Tenth Revision* (ICD-10) codes according to the cohort-wide linkage of hospital inpatient records, death records, primary care records (~45%), and self-reported diagnoses (https://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=Data_providers_and_dates). The CMD of interest includes coronary artery disease (CAD), acute myocardial infarction (AMI, I21), ischemic stroke (I63), peripheral artery disease (PAD, I73), and T2D (E11). CAD was defined as the earliest occurrence of any of the following diseases: angina pectoris (I20), AMI, other acute ischemic heart diseases (I24), and chronic ischemic heart disease (I25). The dates of disease diagnoses/codes were the first recorded across all the above data sources generated by a standard algorithm from the UKB data management team (https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/first_occurrences_outcomes.pdf).

2.3. Exposures and covariates

Using birth year records, we constructed seven birth-cohorts with five-year intervals (1936–1940 to 1966–1970) as exposures. Baseline variables including sex, education level (high, medium, low, or unknown), Townsend deprivation index (TDI, low, middle-low, middle-high, or high), smoking history (never or ever), BMI category (underweight <18.5, normal between 18.5 and 24.9, overweight between 25 and 29.9, or obese $\geq$ 30 kg/m^2) based on the World Health Organization criteria (Weir and Jan, 2025), and PRS categories (high, medium, or low) were used for subgroup analyses. TDI groups and PRS categories were determined based on the mean value and interquartile range. The collection and measurements were detailed in UKB (https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=113241).

Table 1
Characteristics of eligible participants at baseline (2006–2010) across birth cohorts in the UK Biobank.

Characteristics n (%)	1936–1940 (n = 34,540)	1941–1945 (n = 103,378)	1946–1950 (n = 117,216)	1951–1955 (n = 84,072)	1956–1960 (n = 72,292)	1961–1965 (n = 62,644)	1966–1970 (n = 28,251)	Total (n = 502,393)
Sex								
Female	17,425 (50.4)	53,666 (51.9)	64,465 (55.0)	47,305 (56.3)	40,796 (56.4)	34,585 (55.2)	15,077 (53.4)	273,319 (54.4)
Male	17,115 (49.6)	49,712 (48.1)	52,751 (45.0)	36,767 (43.7)	31,496 (43.6)	28,059 (44.8)	13,174 (46.6)	229,074 (45.6)
Age								
Mean (SD)	68.4 (0.90)	65.0 (1.65)	60.3 (1.67)	55.1 (1.71)	50.1 (1.71)	45.1 (1.71)	41.4 (1.02)	56.5 (8.09)
Coronary artery disease history								
No	29,967 (86.8)	93,387 (90.3)	110,085 (93.9)	80,947 (96.3)	70,774 (97.9)	61,928 (98.9)	28,052 (99.3)	475,140 (94.6)
Yes	4573 (13.2)	9991 (9.7)	7131 (6.1)	3125 (3.7)	1518 (2.1)	716 (1.1)	199 (0.7)	27,253 (5.4)
Acute myocardial infarction history								
No	32,559 (94.3)	99,131 (95.9)	114,183 (97.4)	82,702 (98.4)	71,642 (99.1)	62,305 (99.5)	28,149 (99.6)	490,671 (97.7)
Yes	1981 (5.7)	4247 (4.1)	3033 (2.6)	1370 (1.6)	650 (0.9)	339 (0.5)	102 (0.4)	11,722 (2.3)
Stroke history								
No	34,314 (99.3)	102,843 (99.5)	116,840 (99.7)	83,864 (99.8)	72,147 (99.8)	62,566 (99.9)	28,230 (99.9)	500,804 (99.7)
Yes	226 (0.7)	535 (0.5)	376 (0.3)	208 (0.2)	145 (0.2)	78 (0.1)	21 (0.1)	1589 (0.3)
Peripheral artery disease history								
No	33,914 (98.2)	101,776 (98.5)	115,928 (98.9)	83,244 (99.0)	71,644 (99.1)	62,218 (99.3)	28,049 (99.3)	496,773 (98.9)
Yes	626 (1.8)	1602 (1.5)	1288 (1.1)	828 (1.0)	648 (0.9)	426 (0.7)	202 (0.7)	5620 (1.1)
Type 2 diabetes history								
No	32,763 (94.9)	99,178 (95.9)	113,653 (97.0)	82,074 (97.6)	71,102 (98.4)	62,029 (99.0)	28,057 (99.3)	488,856 (97.3)
Yes	1777 (5.1)	4200 (4.1)	3563 (3.0)	1998 (2.4)	1190 (1.6)	615 (1.0)	194 (0.7)	13,537 (2.7)

Abbreviation: SD, standard deviation. Note: Participants with a history of disease of interest were excluded from the separate prospective analysis.

2.4. Statistical analysis

All data were collected from individuals from baseline (2006–2010) until the first registration of a diagnosis code of the target diseases, loss to follow-up, death, or the end of the study period (July 31, 2023), whichever came first for each CMD analysis. We first built individual Lexis objects, using age at enrolment as the entry and the age at index diagnosis or censoring as the exit, then split the life-lines into five-year age bands (40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, and 80–84 years) to aggregate person-years and cases. We subsequently calculated age-specific incidence rates (per 1000 person-years) with 95% confidence interval (CI) for each disease and each eligible birth cohort. Participants remained in the risk set after developing other conditions, so the age-specific incidence rates reflect the total real-world burden for each cohort and disease. Because stroke diagnosis is subject to the competing risk of death, we additionally estimated age- and birth-cohort-specific cumulative incidence for stroke under a competing-risks framework (R package: cmprsk). Considering that incident measurements and data collection may have been significantly impacted by the COVID-19 pandemic due to factors such as limited healthcare access, reduced hospital visits, increased competing mortality risks, and delays in data reporting, the follow-up in the main analyses reported below was censored in 2020 (Jansen et al., 2024). Additionally, sensitivity analyses were performed with censoring at the study's end time in 2023 for CVD.

We applied Age-Period-Cohort (APC) analysis models with natural splines (five degrees of freedom) to disentangle the time-varying effects of birth cohort (Carstensen, 2007). Accordingly, we reformatted our aggregated data into the required four-column APC input format. With the median birth year among cases as the reference, age effects were presented as age-specific incidence rates (per 1000 person-years) for the reference cohort, and birth-cohort effects as incidence rate ratios relative to this reference. Given the limited calendar-time window (~10–14 years), we constrained the period linear component to have zero mean and zero slope. Under these common identification constraints, the non-identifiable linear drift is fixed, and period effects were presented as incidence rate ratios to the median diagnosis year of all cases. As local non-linear features can be sensitive to smoothing and parameterization, we focus on overall age and cohort patterns rather than local inflections. Each effect was estimated while adjusting for the other two. All data analyses were conducted using R version 4.4.0.

3. Results

3.1. Characteristics of study participants

A total of 502,393 participants (54.4% women) were selected, as described in Table 1, stratified by birth cohort (1936–1940 to 1966–1970). The mean age at baseline (standard deviation) in the different birth cohorts, measured between 2006 and 2010, ranged from 41.4 (1.0) years to 68.4 (0.9) years. Table 1 also reports the number of participants who were disease-free at baseline and included in each prospective analysis, with sample sizes ranging from 475,140 to 500,804 across the different outcomes.

Detailed individual characteristics and risk factors stratified by birth cohort are presented in online supplementary Table S1. There were similar distributions of alcohol consumption frequencies, PRS for CAD, PRS for T2D, and insulin usage across birth cohorts. However, in addition to a younger mean age, the most recent birth cohort showed lower proportions of overweight or obese individuals, a higher number of non-smokers, and greater proportions of well-educated participants. Additionally, more recent birth cohorts had a lower proportion of individuals using medications for cholesterol and blood pressure management at baseline.

3.2. Age-specific incidence rate by birth-cohorts

In general, the incidence of CAD increased with age but was lower for same-aged individuals in more recent birth cohorts. For example, the CAD incidence showed an absolute decrease of 34.0% (95% CI: 22.4%, 45.7%) in the 65–69 age group, and 22.7% (95% CI: 16.7%, 28.6%) in the 70–74 age group between the most recent birth cohort and the birth cohort of 1936–1940 (Fig. 1A). A decrease in AMI incidence across birth cohorts was also observed, but the absolute changes were small, and considerable decreases were only observed in certain age groups (Fig. S1A). For example, AMI incidence decreased between the 1941–1945 and 1956–1960 cohorts in the 65–69 age group with 16.4% (95% CI: 5.7%, 27.2%).

The incidence of PAD was decreased considerably over the generations (Fig. 1B). For instance, in the 65–69 and 70–74 years age groups, the PAD incidences in the most recent birth cohort decreased by 53.5% (95% CI: 31.2%, 75.8%) and 30.3% (95% CI: 18.7%, 42.0%), respectively, when compared to the 1936–1940 birth cohort. Whereas the incidence of ischemic stroke increased with age, it did not show a clear trend across birth cohorts, as shown in Fig. 1C and Fig. S1C & D. Fig. 1D shows that the incidence of T2D increased with age but decreased in more recent birth cohorts within each age group. Specifically, in the 65–69 age group, T2D incidence decreased by 37.1% (95% CI: 24.5%, 49.6%), and in the 70–74 age group, by 29.1% (95% CI: 22.5%, 35.7%) when comparing the most recent birth cohort to the 1936–1940 birth cohort.

3.3. Age-period-cohort effects on incidence

The APC models showed a strong age effect for all CMD incidences (Fig. 2 and supplementary Fig. S1B), with incidences increasing with age after adjusting for the period effect, in both men and women. There was a strong, age-independent birth-cohort effect on CAD incidence. The CAD incidence in birth-cohorts after the reference birth year (1946 for women, 1948 for men) was lower, as shown in Fig. 2A. The AMI incidence showed no cohort effect in women, but a subtle decrease in men compared with the reference year of 1948 (supplementary Fig. S1B).

The APC analysis further showed a strong, age-independent birth-cohort effect in PAD incidence, with decreasing incidence in more recent birth-cohorts in both men (reference birth year: 1946) and women (reference birth year: 1948), depicted in Fig. 2B. In line with the results above, the analysis also provided no evidence for a birth cohort effect on ischemic stroke incidence stratified by sex (Fig. 2C). As shown in Fig. 2D, the APC analysis demonstrated strong evidence of a positive effect of age and an age-independent negative effect of birth cohort for T2D incidence, after adjusting for period effects, in both men (reference birth year: 1948) and women (reference birth year: 1948).

3.4. Stratified and sensitivity analyses

For CAD, AMI, PAD, and T2D incidence, generational decreases were observed across all strata, but the strength and slope of these decreases varied across subgroups, as shown in Fig. 3. Stratification by PRS showed consistent decreases in CAD incidence across risk strata (Fig. S2A). Specific decreases in T2D incidence among those with medium-to-high genetic susceptibility were observed (Fig. S2B). When stratified by smoking histories, downward birth cohort effects were observed for CAD, PAD, and T2D incidences in both ever- and never-smokers, whereas the effect on AMI incidence was observed only among ever-smokers (Fig. 3). Consistent cohort declines in CAD, PAD, and T2D incidences were found across all TDI strata (Fig. 3). In contrast, the birth cohort effect in incidences was predominantly observed among individuals with higher education (Fig. 3). In addition, reductions in CAD, AMI, and PAD incidences were most pronounced among individuals with normal weight, while T2D incidence decreased primarily among overweight or obese participants. Sensitivity analyses that

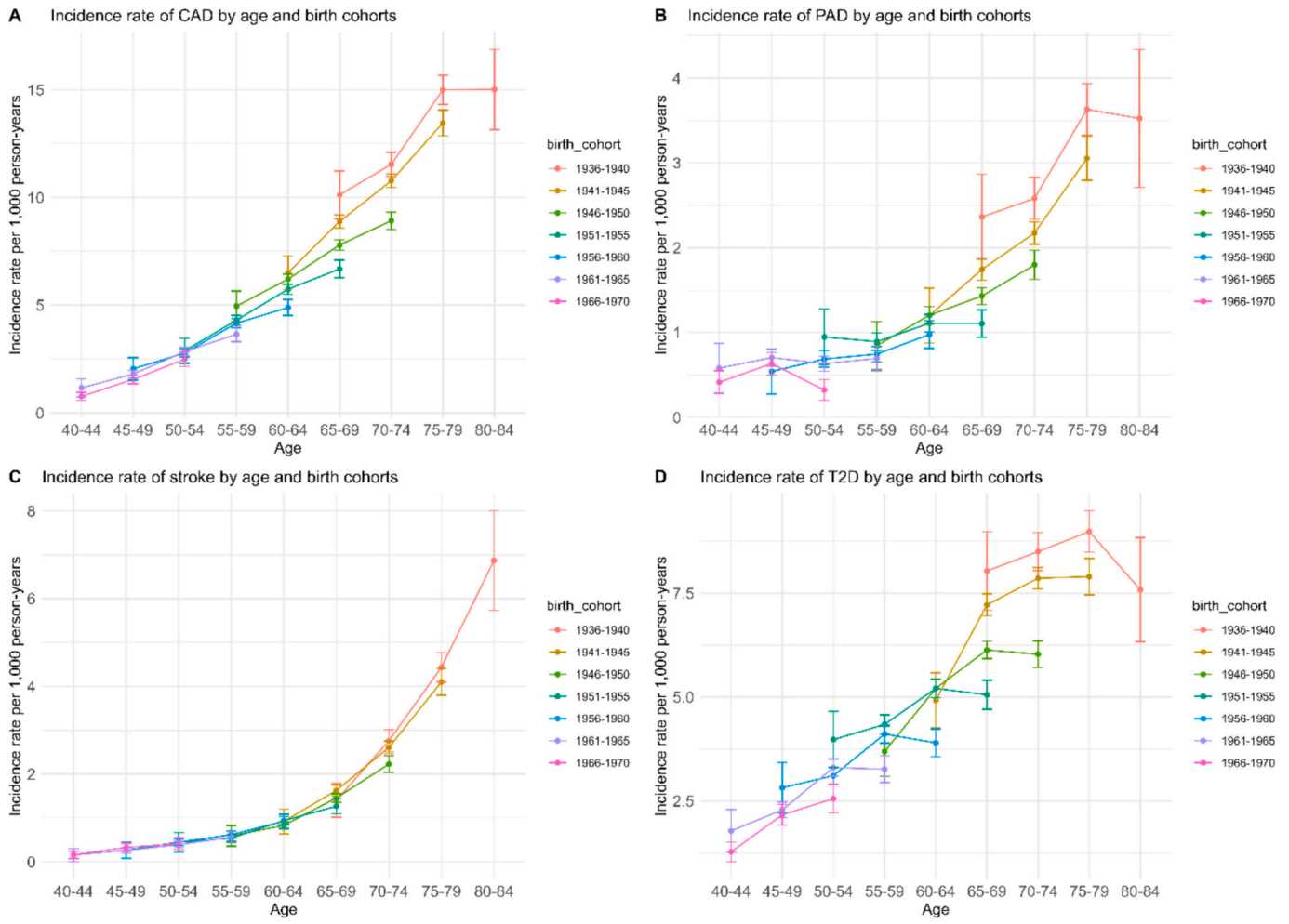

Fig. 1. Age-specific incidence rates per 1000 person-years of cardiometabolic diseases among UK Biobank participants, from baseline (2006–2010) through 2020. Observed incidence rate by age groups per birth cohort, with error bar, of four cardiometabolic diseases. (A) The overall coronary artery disease (CAD) incidence decreased across all age groups and decreased significantly among the older birth cohorts. (B) Peripheral artery disease (PAD) incidence decreased slightly across birth cohorts in the aged groups. (C) Stable stroke incidence by age groups across birth cohorts. (D) Type 2 diabetes (T2D) incidence significantly decreased across birth cohorts.

censored follow-up in 2023 showed decreasing incidence trends for all four CVD outcomes, as illustrated in the supplementary Fig. S3. Stroke incidence exhibited a modest decrease in older generations in the sensitivity analysis (supplementary Fig. S3), which was stable when excluding the COVID-19 pandemic period.

4. Discussion

This study observed a decrease in age-specific incidence rates of CAD, AMI, PAD, and T2D within UKB participants born between 1936 and 1970, while the incidence of ischemic stroke remained stable across birth cohorts. Our analysis also revealed strong evidence of cohort effects in the decreasing CMD incidences, after accounting for age and period effects. Further stratified analyses demonstrated varying generational benefits of reduced disease incidence across risk subgroups.

The observed decrease in CAD incidence is consistent with the findings from previous studies in the UK setting and global reports (Conrad et al., 2024; Meirhaeghe et al., 2020; Vancheri et al., 2022). Nathalie et al., using data from the UK general practice registers between 2000 and 2019, reported a 30% decrease in CAD incidence (Conrad et al., 2024). An analysis across 20 Western European countries reported a 36% decline in ischemic heart disease incidence and a 60% decline in mortality between 1990 and 2019 (Vancheri et al., 2022). The decreasing trend of AMI was less pronounced than that of overall CAD in this study, which aligns with previous research where some reported upward trends in AMI incidence, while others found it remained stable (Arora et al., 2019; Guo et al., 2018; Okoth et al., 2022). The observed reductions in CAD incidence are likely to be explained by the success in smoking cessation, the introduction of novel risk-reducing medication, and decades of efforts in prevention (Lewington et al., 2007; Mannsverk et al., 2016). Although no evidence for causality can be retrieved from this study, we found coincidental reductions in the prevalence of ever-smoked and increased use of medication for cholesterol-lowering in recent UKB birth cohorts at baseline.

The decreasing trend of PAD incidence in this study has also been reported by previous studies (Goodall et al., 2021; Søgaard et al., 2023). The increased attention to the timely and appropriate treatment of thrombosis, inflammation, dyslipidemia, and microvascular disease may have contributed to the decrease in PAD incidence (Bonaca et al., 2021). The absence of a trend in ischemic stroke incidence was consistent with a previous study in the UK (Conrad et al., 2024; Vinter et al., 2024), which may be hypothesized to be due to risk factors we did not include, such as hypertension. A systematic review reported that the high burden of stroke may be attributed to the poor and inadequate hypertension prevention and management of high systolic blood pressure (Collaborators, 2021). A study also reported that over 50% of hypertension is uncontrolled, and 55.2% of them are unaware or aware but untreated (Choudhry et al., 2022). In addition, stroke diagnosis is

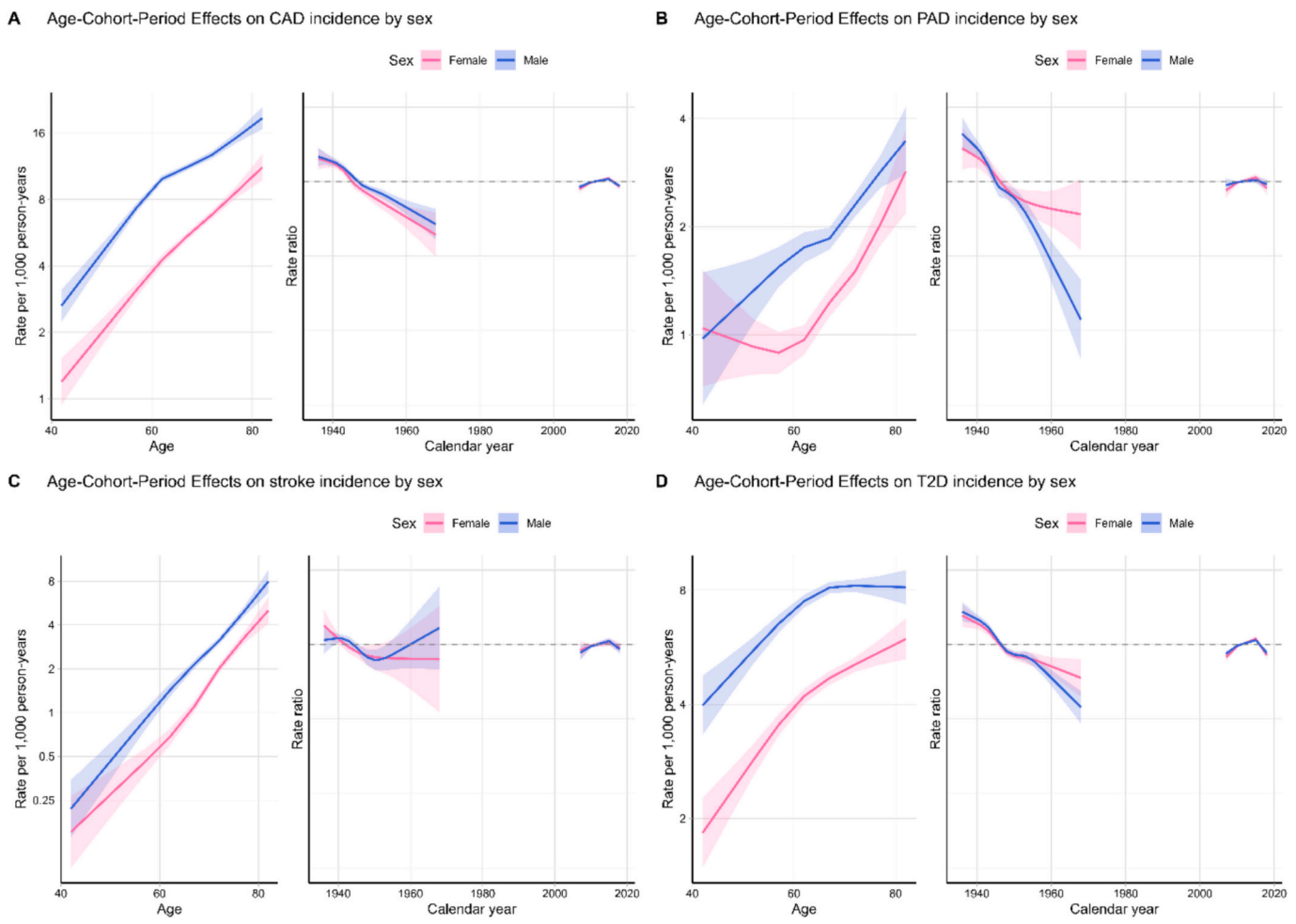

Fig. 2. Sex-stratified age-cohort-period effects on cardiometabolic diseases among UK Biobank participants, from baseline (2006–2010) through 2020.
(A) Age-cohort-period effects on coronary artery disease (CAD) by sex. (B) Age-cohort-period effects on peripheral artery disease (PAD) by sex. (C) Age-cohort-period effects on stroke by sex. (D) Age-cohort-period effects on type 2 diabetes (T2D) by sex. Age effects are expressed as age-specific rates per 1000 person-years conditional on the reference cohort and period. Birth cohort effects are expressed as incidence rate ratios relative to the reference cohort. Period effects are expressed as rate ratios relative to the age–cohort prediction. The dotted line corresponds to a rate ratio of 1. Shaded areas around the lines show 95% confidence intervals.

subject to the competing risk of death from CVD. Improvements in CVD survival among younger generations may increase the time spent at risk for stroke, thereby inflating the absolute number of observed stroke events and making cohort-specific patterns appear more similar.

We anticipated an increasing trend in T2D incidence as a result of the increased BMI burden, which is an important risk factor for T2D (Krüger et al., 2025). However, the decreasing trend of T2D incidence in more recent generations observed in this study may also be reasonable. As reported in previous studies, while the prevalence of overweight and obesity continues to increase, the T2D incidence has been observed to also decrease during recent decades in other epidemiological studies (Knudsen et al., 2022; Overbeek et al., 2024). Improvements in weight management and cardiometabolic risk-factor control following the identification of overweight/obesity may have contributed to the observed trends. Nevertheless, the underlying drivers are likely multifactorial, such as earlier attention to dysglycaemia and more systematic prevention and follow-up of gestational diabetes.

Interestingly, we observed that the incidence of CMD across generations is different among subgroups by PRS, smoking, and socioeconomic inequalities. These associations are complex and multifactorial, suggesting that the effectiveness of prevention may vary substantially across subpopulations. Notably, CAD and T2D showed differing patterns of generational decrease across PRS strata, underscoring the potential interaction between genetic susceptibility and environmental changes. As large-scale shifts in environment and lifestyle continue to shape disease risk, whereas genetic risk is unlikely to change, our findings highlight the need to consider gene-environment interactions and subgroup-specific dynamics in a generational perspective. The directions of generational trends of each CMD remained robust, with no substantial changes observed in sensitivity analyses. The observed small decline in stroke among the aged generations in older age groups may be attributable to differences in increasing competing mortality risks and data reporting during the COVID-19 period (Ho et al., 2024).

Some limitations need to be addressed. First, the incidence is based on diagnostic criteria, screening practices, availability, and accuracy of diagnostic tests in place at a particular time and must therefore be interpreted within this context in the UKB. Then, due to the descriptive nature of this study, we cannot infer causal evidence for the contributions of the observed trends, and the findings from the competing risk model and ACP analyses should be interpreted with caution (Bell, 2020; Gregson et al., 2024). Considering the limited follow-up time of about 14 years, we lack an opportunity to assess the long-term incidences in younger generations; the effects and trends are mainly derived from the older participants. Finally, because the UKB is a relatively healthy volunteer cohort using a limited number of assessment centers, the regional distribution of participants is not uniform across the UK, and the generalizability of the absolute incidence rates is not possible. Nevertheless, this selection tends to be relatively consistent across birth

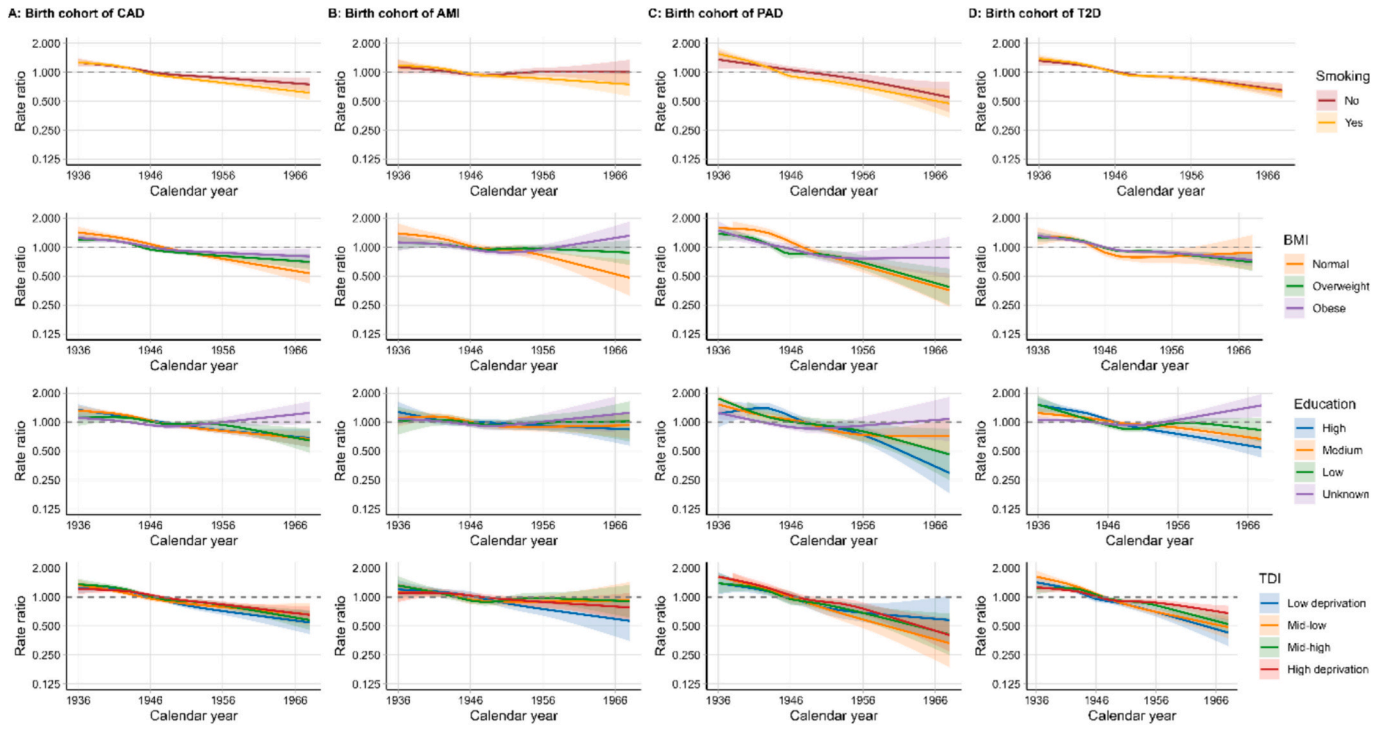

Fig. 3. Cohort effects on disease incidence across risk factor strata among UK Biobank participants, from baseline (2006–2010) through 2020.
Each line represents the cohort effect stratified by smoking history, body mass index (BMI), education level, and Townsend Deprivation Index (TDI). Each row represents different diseases, including (A) coronary artery disease (CAD), (B) acute myocardial infarction (AMI), (C) peripheral artery disease (PAD), and (D) type 2 diabetes (T2D). Birth cohort effects are expressed as incidence rate ratios relative to the reference median year of birth. The dotted line corresponds to a rate ratio of 1. Shaded areas around the lines show 95% confidence intervals.

cohorts. As a result, the birth-cohort differences observed within the cohort are unlikely to be driven by cohort-specific selection and therefore remain meaningful for internal comparisons.

5. Conclusion

In conclusion, our findings indicate substantial generational decreases in CAD, AMI, PAD, and T2D incidence over the past decades. In contrast, the stable ischemic stroke incidence and diverse trends across risk subgroups indicate disease-specific differences in preventive gains.

CRediT authorship contribution statement

Denghui Hu: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Diana van Heemst:** Writing – review & editing, Supervision, Conceptualization. **J. Wouter Jukema:** Writing – review & editing, Methodology. **Saskia le Cessie:** Writing – review & editing, Methodology. **Ko Willems van Dijk:** Writing – review & editing, Supervision, Conceptualization. **Raymond Noordam:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

Funding

Denghui Hu was supported by a fellowship from the China Scholarship Council (CSC; no. 202406210047). The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The present study was accepted under proposal number 56340. We acknowledge the contribution of all participants in the UK Biobank study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2026.108578.

Data availability

The data of this study are available from the UK Biobank project site, subject to registration and application processes.

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