# Ethnic differences in the association between age at natural menopause and risk of type 2 diabetes mellitus among postmenopausal women: a pooled analysis of individual data from 13 cohort studies

**Running title:** Age at menopause and risk of type 2 diabetes

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**Twitter summary:** Premature ovarian insufficiency (menopause <40 years) and early menopause (40-44 years) are risk factors for type 2 diabetes, with variation across ethnicity. #DiabetesRiskFactor #EthnicDifference

## Abstract

**Objective:** To investigate associations between age at natural menopause, particularly premature ovarian insufficiency (POI; natural menopause before 40 years), and incident type 2 diabetes (T2DM) and identify any variations by ethnicity.

**Research design and methods:** We pooled individual-level data of 338,059 women from 13 cohort studies without T2DM before menopause, with six ethnic groups: White (n=177,674), Chinese (n=146,008), Japanese (n=9,061), South/Southeast Asian (n=2,228), Black (n=1,838), and Mixed/Other (n=1,250). Hazard ratios (HRs) of T2DM associated with age at menopause were estimated in the overall sample and by ethnicity, with study as a random effect. For each ethnic group, we further stratified the association by birth year, education level, and BMI.

**Results:** Over nine years of follow-up, 20,064 (5.9%) women developed T2DM. Overall, POI (vs menopause at 50-51 years) was associated with an increased risk of T2DM (HR:1.31, 1.20-1.44), while there was an interaction between age at menopause and ethnicity ($p<0.0001$). T2DM risk associated with POI was higher in White (HR:1.53, 1.36-1.73), Japanese (HR:4.04, 1.97-8.27), and Chinese women born ≥1950 (HR:2.79, 2.11-3.70); while less precise, the risk estimates were consistent in South/Southeast Asian (HR:1.46, 0.89-2.40), Black (HR:1.72, 0.95-3.12), and Mixed/Other (HR:2.16, 0.83-5.57) women. A similar pattern, but smaller increased risk of T2DM was associated with early menopause overall (HR:1.16, 1.10-1.23) and for White, Japanese, and Chinese women born ≥1950.

**Conclusions:** POI and early menopause are risk factors for T2DM in postmenopausal women, with considerable variation across ethnic groups, and may need to be considered in risk assessments of T2DM among women.

## Article highlights

- Research on primary prevention of type 2 diabetes (T2DM) is largely based on data from White male populations. Very few female-specific risk factors for T2DM are considered in the current guidelines.
- This is the largest and most detailed pooled study to show premature ovarian insufficiency (POI; natural menopause before 40 years) and early menopause (40-44 years) were associated with increased risk of T2DM in White, Japanese, and Chinese women born since 1950; while less precise, POI risk estimates were consistent in other ethnic groups.
- POI and early menopause may contribute to T2DM screening or preventive strategies for postmenopausal women.

## Introduction

The estimated global prevalence of type 2 diabetes mellitus (T2DM) in adults was 10.5% (537 million) in 2021 and is expected to rise to 12.2% (783 million) by 2045 (1). The prevalence of T2DM varies substantially at regional and country levels (1), and in particular among different racial/ethnic groups (2, 3). Epidemiological studies have also demonstrated sex differences in risk, pathophysiology, and burden of T2DM (4, 5). Evidence on primary prevention and screening for prediabetes and T2DM, however, is largely based on data derived from White male populations. Very few female-specific risk factors for T2DM are considered in the current guidelines – only gestational diabetes mellitus (GDM) and polycystic ovary syndrome are well recognised (6, 7).

Early natural menopause is linked to an increased risk of cardiovascular disease (8), but the association remains unclear for T2DM. Menopause marks permanently lower oestrogen exposure and triggers adverse metabolic changes that are associated with weight gain, visceral adiposity, and insulin resistance (9), all of which are known risk factors for T2DM. Although a 2019 review and meta-analysis of 13 studies suggested that early menopause (<45 years) was associated with T2DM (10), most examined studies had a cross-sectional design (n=9), included both natural and surgical menopause (n=8), and used various menopause ages as the reference category (e.g., ≥45, 46-55, >55 years). Research has shown that the risk of T2DM is higher after surgical menopause (bilateral oophorectomy) and hysterectomy, compared to no hysterectomy/oophorectomy (11, 12). It might be expected that women with premature ovarian insufficiency (POI; amenorrhea due to loss of ovarian function before 40 years) (13) would also be at high risk, but few studies had sufficient sample size to separate POI from early menopause (10). Only three European cohort studies have examined the association of T2DM with POI (11, 14, 15), and only one of these was based on natural menopause without

interventions (15). Conversely, the review showed a tendency for a higher risk of T2DM among women with late menopause (≥55 years), with 5 of 10 studies being cross-sectional studies in China (10). More recently, however, two cohort studies of Chinese women found the associated increased risk for T2DM differed by body mass index (BMI) (16, 17). No prospective data were available for other ethnic groups. Several confounding factors may be associated with age at menopause and T2DM and contribute to ethnic differences, including BMI (17), socioeconomic position (18), and birth year (19).

The International collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE) has been developed, including variable harmonisation, to provide individual-level data from multiple cohort studies of women. In this study, we used InterLACE data from 13 studies to investigate the relationship of age at natural menopause, particularly POI (<40 years), early (40-44 years), and late (≥55 years) menopause, with incident T2DM in different ethnic groups.

## Research Design and Methods

### Ethics

Ethical approval was obtained from the Institutional Review Board or Human Research Ethics Committee at each participating institution, and all participants provided informed consent.

### Study design and participants

InterLACE is an ongoing women's health consortium, consisting of 27 observational studies. A detailed description of the study design has been published previously (20). We excluded 14 studies due to a lack of data available on diabetes (n=7) or age at diagnosis (n=3), participants being too young to have experienced menopause (born ≥1970; n=2), and no women with

menopause before age 40 due to study recruitment criteria (n=2). The present analysis used data from 13 studies that had collected information on age at menopause and diabetes, including ALWSH, HOW, MCCS, WLHS, Prospect-EPIC, NSHD, NCDS, ELSA, WHITEHALL, SABRE, UK Biobank, JNHS, and China Kadoorie Biobank. Full study names and study characteristics are listed in **Table 1**. In total, data were available for 366,331 naturally postmenopausal women. We excluded women who did not report their age at menopause (n=18,195), had type 1 diabetes or T2DM before menopause (n=4,459), or had missing data on diabetes and covariates (n=5,618) (**Fig. S1**).

**Exposure and outcome variables**

Age at natural menopause (amenorrhea for at least 12 months without interventions) was self-reported (ranged 30-60 years) and categorised as <40, 40-44, 45-49, 50-51, 52-54, and ≥55 years (8). To compare differences across ethnicity, we used the same reference category of menopause at 50-51 years.

The primary outcome was the incidence of T2DM after menopause, identified through self-reported physician-diagnosed diabetes and/or medication use (all studies) and health administrative data (four studies), including hospital admissions, emergency, or death registry. The International Classification of Disease (ICD) 10$^{th}$ Revision code E11 or 9$^{th}$ Revision code 250.X0/X2 (X=0-9) were used to identify T2DM (21). If subtype details were not available, we used ICD-10 codes E13, E14 or ICD-9 code 250 (unspecified) as diabetes diagnosed after menopause was unlikely to be type 1 or GDM. ALSWH also provided data on pharmaceutical scripts (Anatomical Therapeutic Chemical code A10: anti-diabetes therapies, such as biguanides, sulfonylureas, and insulins, with the first prescription after age 30 years) and aged

care (Aged Care Assessment Program code 403: type 2 diabetes). Age at diabetes was defined by the earliest date of the self-reported or administrative data.

**Covariates**

Ethnicity was based on self-identification in six studies (MCCS, NCDS, ELSA, WHITEHALL, SABRE, and UK Biobank; n=155,897, 46.1% of the sample). Three studies (Prospect-EPIC, JNHS, and China Biobank) did not have information on ethnicity because >95% of the participants belonged to one ethnic group at the time of recruitment due to race/ethnic homogeneity of the source population (Dutch, Japanese, and Chinese; n=163,151, 48.3%) (22, 23). The remaining four studies only had data available on the country of birth, country of residency in childhood, or language spoken at home to define ethnicity (n=18,981, 5.6%). Six ethnic groups were created: White, Chinese, Japanese, South/Southeast/other Asian, Black (African/Black Caribbean), and Mixed/Other (e.g., Hispanic, Middle Eastern, and Indigenous).

Based on the literature (17-19), several potential confounding factors for ethnic differences collected at cohort entry (defined as baseline) were considered: birth year (born <1940, 1940-49, and ≥1950), education level (no formal education, ≤10, 11-12, and >12 years), and BMI (using ethnicity-specific cut-offs: <18.5, 18.5-24.9, 25-29.9, and ≥30 kg/m$^2$ for White, Black, and Mixed/Other women; lower cut-offs: <18.5, 18.5-22.9, 23-27.4, and ≥27.5 kg/m$^2$ for all Asian women (24). Smoking status (never, former, and current smoker) and age at baseline (continuous) were also confounding factors in the main analysis.

Several reproductive factors that are associated with age at menopause and T2DM were also considered as potential confounders: age at menarche (≤11, 12-13, 14-15, and ≥16 years), parity (0, 1, 2, 3, and ≥4 children), and GDM (25, 26). Menopausal hormone therapy (MHT)

was also considered since women with POI and early menopause were more likely to use MHT, and MHT may have a beneficial effect on insulin resistance and T2DM, although its clinical implications are still a matter of controversy (27). Since reproductive factors were not available for all studies, they were only examined in the sensitivity analysis. **Fig. S2** shows a directed acyclic graph to illustrate the association.

**Statistical analyses**

Data from all cohorts were combined, and individual-level data were used. Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between age at menopause and incident T2DM, with study as a random effect. The proportional hazards assumption was checked using log-cumulative hazard plots and including a time-dependent covariate (covariate*time) in the Cox model. Except for birth year, no violation was found. Confounding factors were adjusted in three sequential models: age at baseline (Model 1), ethnicity, education level, smoking status (Model 2), and BMI (Model 3). To account for the time varying effect of birth year, a stratified analysis was conducted through an option of strata in the proportional hazards regression in Models 2 and 3. For women with T2DM, survival time was from birth to age at diabetes diagnosis; for women without T2DM, it was from birth to age at last follow-up.

To examine ethnic differences, we included an interaction term between age at menopause and ethnicity in the multivariable Cox model. As there was a significant interaction, we stratified the analysis by ethnicity – fitting a different model for each ethnic group. Similarly, to investigate the confounding effect of birth year, education level, and obesity in each ethnic group, we included an interaction term between age at menopause and each factor in the Cox

model and stratified the association by these factors, except for the Mixed/Other group due to the small number of diabetes cases.

**Sensitivity analyses**

Multiple sensitivity analyses were performed to test the robustness of the findings. First, because Chinese, South/Southeast Asian, Black, and Mixed/Other women reported a younger average age at menopause than White women, we used menopause at age 45-49 years as the reference in these ethnic groups. Second, since age at menarche and parity were potential confounding factors, the models were additionally adjusted for these variables in ten studies that had this information (excluding HOW, WHITEHALL, and SABRE). Third, the models were adjusted for MHT use in 12 studies (excluding China Biobank). Fourth, to rule out the influence of pre-diabetes or undiagnosed premenopausal diabetes on the timing of menopause, we further excluded T2DM cases occurring within two years of menopause (n=2,144). We excluded women with a history of GDM (n=971) in six studies with relevant information (ALSWH, HOW, WLHS, NCDS, Prospect-EPIC, and UK Biobank). Fifth, we repeated the main analysis on only the administrative data from four studies (ALSWH, WLHS, Prospect-EPIC, and UK Biobank), in which we excluded the self-reported data. Finally, to assess whether there was between-study heterogeneity and if any single study had undue influence on the overall estimates, we performed study-level analyses in ten studies with sufficient cases (excluding HOW, NSHD, and SABRE) and used random-effects meta-analysis to assess the heterogeneity (estimated by $I^2$ and p-values) in the study-level estimates (two-step method). The PHREG procedure in SAS 9.4 was used to fit the Cox proportional hazards models, and the METAN procedure in STATA 17.0 was used to perform meta-analyses.

**Data and resource availability**

The datasets that were generated for conducting this pooled analysis are not publicly available due to the data transfer agreements or restrictions under license for the current study. However, data from some studies can be assessed by submitting an application: e.g., ALSWH (https://alswh.org.au/for-data-users/applying-for-data/) and UK Biobank (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access).

## Results

### Characteristics of the study population

Overall, 338,059 postmenopausal women from 13 studies across six countries were included (**Table 1**). Over nine years of follow-up, 20,064 (5.9%) had incident T2DM, of which 44% were identified through administrative records. Six ethnic groups were identified: White (in the UK, Europe, and Australia), Chinese (99.7% from China Biobank), Japanese (98.9% from JNHS), South/Southeast Asian, Black, and Mixed/Other (all in the UK and Australia). The mean (SD) age at menopause ranged from 48.6 (4.0) years in Chinese to 50.4 (4.3) years in White women (**Table 2**). Black women had the highest prevalence of POI and early menopause (2.9% and 11.3%, respectively), followed by South/Southeast Asian women (2.8% and 10.4%), which was significantly higher than that in White women (1.8% and 7.2%). Black and South/Southeast Asian women also had a higher proportion of obesity and incident T2DM than White women. There were ethnic differences in other sociodemographic and reproductive characteristics. We also compared Chinese and Japanese women living in their countries of origin (China Biobank and JNHS) with those living in Western countries and found differences in sociodemographic and reproductive characteristics (**Table S1**). Due to the small number living in Western countries (1%), they were categorised by ethnicity in the main analysis.

### Association between age at menopause and type 2 diabetes by ethnicity

Overall, compared with menopause at age 50-51 years, POI was associated with an increased risk of T2DM after adjusting for confounders including BMI (HR:1.31, 1.20-1.44), while there was a significant interaction between age at menopause and ethnicity on T2DM (p<0.0001) (**Table 3**). The absolute risk of developing T2DM was higher among women with POI (vs menopause at age 50-51 years) in White (9.2% vs 5.5%), Japanese (9.5% vs 4.7%), South/Southeast Asian (28.6% vs 23.3%), Black (24.1% vs 18.9%), and Mixed/Other (19.2% vs 15.4%), but not in Chinese women (5.5% vs 5.4%). In the adjusted model, T2DM risk associated with POI was higher in White (HR:1.53, 1.36-1.73) and Japanese (HR:4.04, 1.97-8.27) women; while less precise (wide confidence intervals), the risk estimates were consistent in South/Southeast Asian (HR:1.46, 0.89-2.40), Black (HR:1.72, 0.95-3.12), and Mixed/Other (HR:2.16, 0.83-5.57) women. In contrast, this association was not observed in the overall Chinese women (HR:1.03, 0.89-1.18), but those born ≥1950 (HR:2.79, 2.11-3.70) had results similar to the other ethnic groups.

Women with early menopause also had an increased risk of T2DM (HR:1.16, 1.10-1.23), less than seen for POI and consistent with a dose-response. A similar pattern was evident in the variation in risk by ethnicity. We found an increased risk of T2DM in White (HR:1.27, 1.18-1.37), Japanese (HR:1.95, 1.17-3.24), and Chinese women born ≥1950 (HR:1.90, 1.59-2.27), and weak evidence for Black women (HR: 1.32, 0.88-1.96). Late menopause was not associated with a higher risk of T2DM across all ethnic groups.

**Confounding effects of sociodemographic factors and BMI**

In White women, the association between POI and T2DM was consistent across the subgroups of birth year, education level, and BMI (**Fig. 1**). However, in Chinese women there was a significant interaction between age at menopause and birth year (p<0.0001) and between age

at menopause and education level (p=0.0002). As noted above, an increased risk of T2DM associated with POI and early menopause was observed in Chinese women born ≥1950 but not in those born <1950. The association between POI and T2DM was also observed in Chinese women with higher education levels (>10 years, HR:2.46, 1.66-3.66) but not with lower education levels (**Fig. 1**). This education effect was not fully explained by younger generations having higher education levels as the increased T2DM risk was also observed in older generations with higher education (born in 1940-49 with >10 years education, HR:2.14, 1.18-3.90; born <1940 with >10 years education, HR:1.65, 0.83-3.30; results not shown). In other ethnic groups, we did not observe interactions between age at menopause and these confounding factors nor clear patterns of effect modification due to wide confidence intervals.

**Sensitivity analyses**

The association between POI and T2DM remained unchanged when we used menopause at age 45-49 years as the reference among Chinese, South/Southeast Asian, Black, and Mixed/Other women (**Table S2**); even when we adjusted for reproductive confounders of age at menarche and parity (**Table S3**) or MHT use (**Table S4**). We observed slightly stronger associations across ethnic groups when we excluded diabetes cases occurring within two years of menopause (**Table S5**) and no changes to the results when we excluded GDM cases (**Table S6**). When only diabetes cases ascertained by administrative data were analysed, results were similar to the main analysis (**Table S7**). In the study-level analysis, all studies, except for China Biobank, showed a tendency for a greater T2DM risk (HRs >1) associated with POI (pooled HR:1.46, 1.14-1.78; $I^2$:65.8%, p=0.002; **Fig. S3**). Similar to the main analysis, T2DM risk was smaller across studies among women with early menopause (pooled HR:1.22, 1.07-1.36; $I^2$:54.1%, p=0.021). When we only included Chinese women born ≥1950 in the China Biobank

(**Fig. S4**), there was no significant heterogeneity for T2DM risk associated with POI (pooled HR:1.71, 1.42-1.99; $I^2$:27.0%, p=0.2).

## Conclusions

This pooled study suggests that POI and early menopause were associated with incident T2DM in the overall sample (both individual-level and study-level data), compared with menopause at age 50-51 years. T2DM risk associated with POI was higher for White, Japanese, and Chinese women born since 1950. While less precise, the POI risk estimates were consistent in South/Southeast Asian, Black, and Mixed/Other women. Early menopause was also associated with an increased risk of T2DM in White, Japanese, and younger Chinese women, but it was inconsistent in the other ethnic groups. There was no evidence of an association between late menopause and increased risk of T2DM across ethnic groups.

The existing literature on the association between early onset natural menopause, particularly POI, and T2DM risk is limited and inconclusive. Our findings were consistent with two prospective studies of European women with natural menopause (14, 15). The Rotterdam study found that women with POI and early menopause had increased risk of T2DM (over 3-fold and 2-fold, respectively), and even those with normal age at menopause (45-55 years) were at a higher risk, but it was relative to those with late menopause (>55 years) (15). The EPIC-InterAct study (which included Prospect-EPIC) reported a 30% increased risk among women with POI but not among those with early menopause (compared with menopause at age 50-54 years), and the risk estimates were similar after excluding women with a hysterectomy and/or oophorectomy (14). However, a recent cohort study of naturally menopausal women in China reported a weak association with a wide confidence interval between early menopause (≤45 years) and T2DM (OR:1.14, 0.77-1.67), compared with menopause at age 46-50 years (17).

Some individual studies included in InterLACE have previously examined this association. The China Biobank reported that POI (HR:1.14, 1.01-1.30) was modestly associated with T2DM, compared to menopause at age 45-49 years, but this analysis excluded over 18,000 women with self-reported or screening-detected diabetes at study entry, which resulted in excluding women who had developed diabetes after menopause at baseline (16). The JNHS did not observe an association between early menopause (<45 years) and T2DM (OR:0.72, 0.31-1.65), but the reference group was premenopausal women (8.6 years younger than postmenopausal women) (28). Previous studies combined POI and early menopause, compared with various menopause age or even premenopause, making it difficult to compare the results across studies. In contrast, we examined POI and early menopause separately, compared with menopause at age 50-51, and adjusted for the same confounders, which enhance the possibility of comparison across ethnic groups.

Few studies have demonstrated generational differences in the association between female reproductive factors and T2DM. Two Chinese studies (Dongfeng-Tongji cohort and China Kadoorie Biobank) reported an increased risk of T2DM in women with early menarche, pregnancy loss, and early menopause, with the association being stronger in younger generations (16, 29-31). Two Nurses' Health Study cohorts that included approximately 200,000 American nurses also showed a stronger association between early menarche and T2DM in younger (<45 years) than older (≥45 years) women (19). Our study found that well educated, younger generations of Chinese women had sociodemographic and reproductive characteristics similar to White women, and the observed association was consistent with those for White women. Older generations of Chinese women, especially those born before 1940, tended to have a much higher prevalence of POI and early menopause (4.2% and 12.6%, respectively) than younger generations, but it was not associated with incident T2DM. The

differential results among Chinese women may reflect a sociodemographic transition over time, and more evidence from low- and middle-income countries is needed. Previous research has shown that stronger associations between reproductive factors and T2DM observed in younger generations cannot be fully explained by increased adulthood obesity and suggested there may be other risk pathways beyond excessive adiposity in younger generations (19, 29).

Early onset of menopause has been suggested to increase cardiometabolic risk (8, 15), possibly due to early cessation of the protective effects of endogenous oestrogen (32). Human studies suggested that higher premenopausal oestradiol levels were associated with a lower risk of T2DM (33). Loss of oestrogen during menopause is associated with visceral adiposity, which augments the production of proinflammatory cytokines and increases circulating free fatty acids, contributing to the development of endothelial dysfunction and insulin resistance (9). However, there are arguments against the earlier view about the protective effect of oestrogen. Observational studies found that early start and longer oestrogen exposures (i.e., early menarche, late menopause, and long reproductive duration) have been linked to a higher risk of T2DM (19, 34), although our study did not find an association with late menopause. In postmenopausal women, higher levels of oestradiol were associated with increased, rather than decreased, risk of T2DM (35, 36). Thus, early loss of oestrogen may not fully explain the observed increase in diabetes risk after POI and early menopause. Other underlying conditions and genetic or environmental factors need to be considered. For example, 10-20% of women experience POI due to autoimmune diseases or genetic abnormalities, such as Turner Syndrome, which may partially explain the association as women with Turner Syndrome have an excess risk of obesity and impaired glucose tolerance (13). More research is needed to unravel the biological mechanisms through which the timing of menopause and hormone changes influence adiposity, insulin resistance, and diabetes risk.

The strengths of our study include the prospective design, long duration of follow-up, and large sample size from 13 studies across different geographical regions. Given this, our results should be generalisable to populations of White and East Asian (Chinese and Japanese) women. Individual-level data enabled us to examine the association across ethnic groups and among cohorts recruited with different approaches, in different birth decades.

Several limitations should be acknowledged. First, South/Southeast Asian, Black, and Mixed/Other groups were relatively small, leading to a lack of statistical power. These women were migrants living in the UK and Australia and could have different characteristics compared to women living in their countries of origin. Results for these ethnic groups should be interpreted with caution and may be less generalisable. In addition, most of the Japanese women were nurses with a lower prevalence of POI and early menopause, so the magnitude of risk may not be applicable to the general population of Japanese women. Second, most of the women in this study were postmenopausal at baseline (mean age 58 years) and retrospectively reported their age at menopause, which may be prone to recall bias. However, the validity and reproducibility of self-reported age at menopause are fairly good (37), and misclassification is less likely to occur among women with POI or early menopause, since women would notice if their periods stopped much earlier than expected (25). Third, we adjusted the associations for reproductive factors and excluded GDM in sensitivity analyses, but we cannot rule out the possibility of residual confounding, such as genetic factors. However, the Rotterdam study showed that the association between early menopause and T2DM was independent of shared genetic factors, endogenous sex hormones, as well as potential mediators, including lipids and insulin levels (15). Fourth, despite the prospective design, we could not identify women who may have had pre-diabetes and undiagnosed diabetes before menopause, rendering the

possibility of reverse causality. However, when we excluded diabetes cases occurring within two years of menopause, we observed slightly stronger associations between earlier menopause and T2DM across ethnic groups. Finally, while 56% of diabetes cases were self-reported, the four studies that used linked health records showed a moderate to substantial level of agreement (kappa 54%-72%) between the administrative and self-reported data. In the sensitivity analysis using only diabetes cases ascertained by administrative data, results were similar to the main analysis.

Given the high prevalence of T2DM in postmenopausal women (over 15% for women aged ≥55 years) (1), our findings have important clinical and public health implications. Approximately 5-10% of women experience menopause before age 45 in high-income countries (25), and the prevalence of early menopause or POI is even higher in low and middle-income countries (38). Strategies to reduce the modifiable risk factors for POI or early menopause are important, such as smoking cessation and maintaining a healthy weight (39, 40). This evidence is not only to identify those at-risk women but also inform practice that these women (particularly POI) need close monitoring and active management of metabolic risk factors to have better health.

In conclusion, this is the largest and most detailed study demonstrating that women with POI or early menopause had an increased risk of T2DM after menopause, with considerable ethnic variations. These results provide insights into the aetiology of T2DM, which could inform ethnic-specific implementation of primary prevention. The findings suggest POI and early menopause may contribute to the factors considered for diabetes screening or preventive strategies for postmenopausal women.

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## Conflict of interest statements

No potential conflicts of interest relevant to this article were reported**.** Where authors are identified as personnel of the International Agency for Research on Cancer or WHO, the authors alone are responsible for the views expressed in this Article, and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer or WHO.

## Author contributions

HFC and GDM conceptualised the research question and study design. HFC conducted statistical analyses and wrote the manuscript. AJD and GDM critically reviewed the statistical methods and edited the manuscript. RH, DK, KH, YTS, DCG, JEC, DJA, PD, EJB, SVE, RM, MKS, SS, EW contributed study data and provided critical revision of the manuscript for intellectual content. All authors approved the final manuscript. GDM is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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- The Department of Health Tasmania, and the Tasmanian Data Linkage Unit, for the Public Hospital Admitted Patient Episodes and Tasmanian Emergency Department Presentations Data Collections.

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## References


1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.

2. Cheng YJ, Kanaya AM, Araneta MRG, Saydah SH, Kahn HS, Gregg EW, et al. Prevalence of Diabetes by Race and Ethnicity in the United States, 2011-2016. JAMA. 2019;322(24):2389-98.

3. Pham TM, Carpenter JR, Morris TP, Sharma M, Petersen I. Ethnic Differences in the Prevalence of Type 2 Diabetes Diagnoses in the UK: Cross-Sectional Analysis of the Health Improvement Network Primary Care Database. Clin Epidemiol. 2019;11:1081-8.

4. Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocr Rev. 2016;37(3):278-316.

5. Huebschmann AG, Huxley RR, Kohrt WM, Zeitler P, Regensteiner JG, Reusch JEB. Sex differences in the burden of type 2 diabetes and cardiovascular risk across the life course. Diabetologia. 2019;62(10):1761-72.

6. U. S. Preventive Services Task Force, Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, et al. Screening for Prediabetes and Type 2 Diabetes: US Preventive Services Task Force Recommendation Statement. JAMA. 2021;326(8):736-43.

7. American Diabetes Association Professional Practice Committee. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S17-S38.

8. Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruinsma F, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. Lancet Public Health. 2019;4(11):e553-e64.

9. Slopien R, Wender-Ozegowska E, Rogowicz-Frontczak A, Meczekalski B, Zozulinska-Ziolkiewicz D, Jaremek JD, et al. Menopause and diabetes: EMAS clinical guide. Maturitas. 2018;117:6-10.

10. Anagnostis P, Christou K, Artzouchaltzi AM, Gkekas NK, Kosmidou N, Siolos P, et al. Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: a systematic review and meta-analysis. Eur J Endocrinol. 2019;180(1):41-50.

11. Appiah D, Winters SJ, Hornung CA. Bilateral oophorectomy and the risk of incident diabetes in postmenopausal women. Diabetes Care. 2014;37(3):725-33.

12. Luo J, Manson JE, Urrutia RP, Hendryx M, LeBlanc ES, Margolis KL. Risk of Diabetes After Hysterectomy With or Without Oophorectomy in Postmenopausal Women. Am J Epidemiol. 2017;185(9):777-85.

13. European Society for Human Reproduction Embryology Guideline Group on POI. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31(5):926-37.

14. Brand JS, van der Schouw YT, Onland-Moret NC, Sharp SJ, Ong KK, Khaw KT, et al. Age at menopause, reproductive life span, and type 2 diabetes risk: results from the EPIC-InterAct study. Diabetes Care. 2013;36(4):1012-9.

15. Muka T, Asllanaj E, Avazverdi N, Jaspers L, Stringa N, Milic J, et al. Age at natural menopause and risk of type 2 diabetes: a prospective cohort study. Diabetologia. 2017;60(10):1951-60.

16. Wang M, Gan W, Kartsonaki C, Guo Y, Lv J, Chen Z, et al. Menopausal status, age at natural menopause and risk of diabetes in China: a 10-year prospective study of 300,000 women. Nutr Metab (Lond). 2022;19(1):7.

17. Jiang J, Cui J, Wang A, Mu Y, Yan Y, Liu F, et al. Association Between Age at Natural Menopause and Risk of Type 2 Diabetes in Postmenopausal Women With and Without Obesity. J Clin Endocrinol Metab. 2019;104(7):3039-48.

18. Whitty CJ, Brunner EJ, Shipley MJ, Hemingway H, Marmot MG. Differences in biological risk factors for cardiovascular disease between three ethnic groups in the Whitehall II study. Atherosclerosis. 1999;142(2):279-86.

19. He C, Zhang C, Hunter DJ, Hankinson SE, Buck Louis GM, Hediger ML, et al. Age at menarche and risk of type 2 diabetes: results from 2 large prospective cohort studies. Am J Epidemiol. 2010;171(3):334-44.

20. Mishra GD, Chung HF, Pandeya N, Dobson AJ, Jones L, Avis NE, et al. The InterLACE study: Design, data harmonization and characteristics across 20 studies on women's health. Maturitas. 2016;92:176-85.

21. Eastwood SV, Mathur R, Atkinson M, Brophy S, Sudlow C, Flaig R, et al. Algorithms for the Capture and Adjudication of Prevalent and Incident Diabetes in UK Biobank. PLoS One. 2016;11(9):e0162388.

22. IBC 50K CAD Consortium. Large-scale gene-centric analysis identifies novel variants for coronary artery disease. PLoS Genet. 2011;7(9):e1002260.

23. Chen Z, Chen J, Collins R, Guo Y, Peto R, Wu F, et al. China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. Int J Epidemiol. 2011;40(6):1652-66.

24. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157-63.

25. Mishra GD, Pandeya N, Dobson AJ, Chung HF, Anderson D, Kuh D, et al. Early menarche, nulliparity and the risk for premature and early natural menopause. Hum Reprod. 2017;32(3):679-86.

26. Pandeya N, Huxley RR, Chung HF, Dobson AJ, Kuh D, Hardy R, et al. Female reproductive history and risk of type 2 diabetes: A prospective analysis of 126 721 women. Diabetes Obes Metab. 2018;20(9):2103-12.

27. Mauvais-Jarvis F, Manson JE, Stevenson JC, Fonseca VA. Menopausal Hormone Therapy and Type 2 Diabetes Prevention: Evidence, Mechanisms, and Clinical Implications. Endocr Rev. 2017;38(3):173-88.

28. Lee JS, Hayashi K, Mishra G, Yasui T, Kubota T, Mizunuma H. Independent association between age at natural menopause and hypercholesterolemia, hypertension, and diabetes mellitus: Japan nurses' health study. J Atheroscler Thromb. 2013;20(2):161-9.

29. Yang L, Li L, Peters SAE, Clarke R, Guo Y, Chen Y, et al. Age at Menarche and Incidence of Diabetes: A Prospective Study of 300,000 Women in China. Am J Epidemiol. 2018;187(2):190-8.

30. Shen L, Song L, Li H, Liu B, Zheng X, Zhang L, et al. Association between earlier age at natural menopause and risk of diabetes in middle-aged and older Chinese women: The Dongfeng-Tongji cohort study. Diabetes Metab. 2017;43(4):345-50.

31. Peters SAE, Yang L, Guo Y, Chen Y, Bian Z, Sun H, et al. Pregnancy, pregnancy loss and the risk of diabetes in Chinese women: findings from the China Kadoorie Biobank. Eur J Epidemiol. 2020;35(3):295-303.

32. Mendelsohn ME. Protective effects of estrogen on the cardiovascular system. Am J Cardiol. 2002;89(12A):12E-7E; discussion 7E-8E.

33. Park SK, Harlow SD, Zheng H, Karvonen-Gutierrez C, Thurston RC, Ruppert K, et al. Association between changes in oestradiol and follicle-stimulating hormone levels during the menopausal transition and risk of diabetes. Diabet Med. 2017;34(4):531-8.

34. LeBlanc ES, Kapphahn K, Hedlin H, Desai M, Parikh NI, Liu S, et al. Reproductive history and risk of type 2 diabetes mellitus in postmenopausal women: findings from the Women's Health Initiative. Menopause. 2017;24(1):64-72.

35. Ding EL, Song Y, Manson JE, Rifai N, Buring JE, Liu S. Plasma sex steroid hormones and risk of developing type 2 diabetes in women: a prospective study. Diabetologia. 2007;50(10):2076-84.

36. Kalyani RR, Franco M, Dobs AS, Ouyang P, Vaidya D, Bertoni A, et al. The association of endogenous sex hormones, adiposity, and insulin resistance with incident diabetes in postmenopausal women. J Clin Endocrinol Metab. 2009;94(11):4127-35.

37. den Tonkelaar I. Validity and reproducibility of self-reported age at menopause in women participating in the DOM-project. Maturitas. 1997;27(2):117-23.

38. Golezar S, Ramezani Tehrani F, Khazaei S, Ebadi A, Keshavarz Z. The global prevalence of primary ovarian insufficiency and early menopause: a meta-analysis. Climacteric. 2019;22(4):403-11.

39. Zhu D, Chung HF, Pandeya N, Dobson AJ, Cade JE, Greenwood DC, et al. Relationships between intensity, duration, cumulative dose, and timing of smoking with age at menopause: A pooled analysis of individual data from 17 observational studies. PLoS Med. 2018;15(11):e1002704.

40. Zhu D, Chung HF, Pandeya N, Dobson AJ, Kuh D, Crawford SL, et al. Body mass index and age at natural menopause: an international pooled analysis of 11 prospective studies. Eur J Epidemiol. 2018;33(8):699-710.

**Table 1.** Characteristics of 13 cohort studies with information on age at natural menopause and type 2 diabetes in the InterLACE consortium

| Study | Country | No. of women | Median (IQR) | | Ethnicity, n (%) | | | | | | T2DM |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Age at baseline | Age at last follow-up | White | Chinese | Japanese | South/ Southeast Asian | Black | Mixed/ Other* | % by linked records† |
| Australian Longitudinal Study on Women's Health (ALSWH) | Australia | 6,946 | 47 (46-48) | 71 (69-72) | 6,670 (96.0) | 28 (0.4) | 5 (0.1) | 150 (2.2) | 14 (0.2) | 79 (1.1) | 76.6% |
| Healthy Ageing of Women Study (HOW) | Australia | 314 | 55 (53-57) | 62 (60-66) | 299 (95.2) | 0 | 0 | 2 (0.6) | 0 | 13 (4.1) | 0% |
| Melbourne Collaborative Cohort Study (MCCS) | Australia | 12,524 | 59 (53-64) | 68 (62-73) | 12,524 (100) | 0 | 0 | 0 | 0 | 0 | 0% |
| Women's Lifestyle and Health Study (WLHS) | Sweden | 11,071 | 46 (43-48) | 64 (61-66) | 11,071 (100) | 0 | 0 | 0 | 0 | 0 | 73.0% |
| Prospect–EPIC Utrecht (Prospect–EPIC) | Netherlands | 8,615 | 57 (52-62) | 74 (70-78) | 8,615 (100) | 0 | 0 | 0 | 0 | 0 | 80.9% |
| MRC National Survey of Health and Development (NSHD) | UK | 650 | 47‡ | 54 | 650 (100) | 0 | 0 | 0 | 0 | 0 | 0% |
| National Child Development Study (NCDS) | UK | 2,367 | 50‡ | 55 | 2,325 (98.2) | 0 | 0 | 15 (0.6) | 8 (0.3) | 19 (0.8) | 0% |
| English Longitudinal Study of Aging (ELSA) | UK | 3,529 | 59 (52-67) | 67 (61-76) | 3,458 (98.0) | 1 (0.0) | 0 | 25 (0.7) | 19 (0.5) | 26 (0.7) | 0% |
| Whitehall II Study (WHITEHALL) | UK | 1,595 | 47 (41-52) | 63 (59-69) | 1,419 (89.0) | 0 | 0 | 0 | 0 | 176 (11.0) | 0% |
| Southall And Brent Revisited (SABRE) | UK | 441 | 56 (53-60) | 61 (56-72) | 258 (58.5) | 0 | 0 | 63 (14.3) | 120 (27.2) | 0 | 0% |
| UK Biobank (UK Biobank) | UK | 135,471 | 60 (56-64) | 73 (68-77) | 130,385 (96.3) | 408 (0.3) | 91 (0.1) | 1,973 (1.5) | 1,677 (1.2) | 937 (0.7) | 90.9% |
| Japan Nurses' Health Study (JNHS) | Japan | 8,965 | 51 (46-55) | 56 (53-60) | 0 | 0 | 8,965 (100) | 0 | 0 | 0 | 0% |
| China Kadoorie Biobank (China Biobank) | China | 145,571 | 58 (54-65) | 58 (54-65) | 0 | 145,571 (100) | 0 | 0 | 0 | 0 | 0% |
| Overall | | 338,059 | 58 (53-64) | 67 (58-73) | 177,674 (52.6) | 146,008 (43.2) | 9,061 (2.7) | 2,228 (0.7) | 1,838 (0.5) | 1,250 (0.4) | 44.4% |

T2DM: type 2 diabetes mellitus.

* Mixed/Other included mixed, Hispanic, Middle Eastern, indigenous, and islander.

† Four studies provided health administrative data – presenting the percentage of type 2 diabetes cases identified by linked health records.

‡ NSHD (1946 British Birth Cohort) and NCDS (1958 British Birth Cohort) first collected information on women's health in 1993 (aged 47) and 2008 (aged 50), respectively, so we used age 47 and 50 as baseline age in the analysis.

**Table 2.** Baseline characteristics of postmenopausal women according to ethnicity

| Baseline characteristics | Overall (n=338,059) | White (n=177,674) | Chinese (n=146,008) | Japanese (n=9,061) | South/Southeast Asian (n=2,228) | Black (n=1,838) | Mixed/Other (n=1,250) |
|---|---|---|---|---|---|---|---|
| Median (IQR) age at baseline, years | 58 (53-64) | 59 (53-63) | 58 (54-65) | 51 (46-55) | 57 (52-62) | 56 (52-62) | 55 (50-60) |
| Birth year | | | | | | | |
| Born before 1940 | 53315 (15.8) | 22975 (12.9) | 29927 (20.5) | 85 (0.9) | 74 (3.3) | 145 (7.9) | 109 (8.7) |
| Born 1940-49 | 159783 (47.3) | 95998 (54.0) | 58340 (40.0) | 3367 (37.2) | 941 (42.2) | 619 (33.7) | 518 (41.4) |
| Born 1950 or later | 124961 (37.0) | 58701 (33.0) | 57741 (39.5) | 5609 (61.9) | 1213 (54.4) | 1074 (58.4) | 623 (49.8) |
| Education level | | | | | | | |
| No formal education | 63569 (18.8) | 9325 (5.2) | 53985 (37.0) | 0 (0) | 133 (6.0) | 70 (3.8) | 56 (4.5) |
| ≤10 years | 160937 (47.6) | 82418 (46.4) | 76499 (52.4) | 7 (0.1) | 753 (33.8) | 790 (43.0) | 470 (37.6) |
| 11-12 years | 36816 (10.9) | 24520 (13.8) | 11495 (7.9) | 157 (1.7) | 282 (12.7) | 189 (10.3) | 173 (13.8) |
| >12 years | 76737 (22.7) | 61411 (34.6) | 4029 (2.8) | 8897 (98.2) | 1060 (47.6) | 789 (42.9) | 551 (44.1) |
| Smoking status | | | | | | | |
| Never smoker | 246047 (72.8) | 99975 (56.3) | 135198 (92.6) | 6640 (73.3) | 2010 (90.2) | 1478 (80.4) | 746 (59.7) |
| Former smoker | 63218 (18.7) | 58981 (33.2) | 2371 (1.6) | 1149 (12.7) | 149 (6.7) | 236 (12.8) | 332 (26.6) |
| Current smoker | 28794 (8.5) | 18718 (10.5) | 8439 (5.8) | 1272 (14.0) | 69 (3.1) | 124 (6.8) | 172 (13.8) |
| Body mass index | | | | | | | |
| Underweight | 10169 (3.0) | 1610 (0.9) | 8015 (5.5) | 501 (5.5) | 26 (1.2) | 5 (0.3) | 12 (1.0) |
| Normal weight | 168888 (50.0) | 75408 (42.4) | 52828 (36.2) | 5262 (58.1) | 360 (16.2) | 334 (18.2) | 483 (38.6) |
| Overweight | 113331 (33.5) | 64808 (36.5) | 61855 (42.4) | 2850 (31.5) | 966 (43.4) | 643 (35.0) | 466 (37.3) |
| Obese | 45671 (13.5) | 35848 (20.2) | 23310 (16.0) | 448 (4.9) | 876 (39.3) | 856 (46.6) | 289 (23.1) |
| Mean ± SD, $kg/m^2$ | 25.3±4.6 | 26.5±4.9 | 23.9±3.6 | 22.4±2.8 | 27.1±4.9 | 30.3±6.0 | 27.1±5.2 |
| Age at menarche (n=331,348; 11 studies)† | | | | | | | |
| ≤11 years | 34073 (10.3) | 31277 (18.2) | 832 (0.6) | 1236 (13.8) | 295 (14.5) | 221 (13.5) | 212 (20.5) |
| 12-13 years | 99656 (30.1) | 76612 (44.6) | 16441 (11.3) | 4704 (52.4) | 840 (41.2) | 609 (37.3) | 450 (43.6) |
| 14-15 years | 101072 (30.5) | 54078 (31.5) | 42687 (29.3) | 2779 (30.9) | 672 (33.0) | 566 (34.6) | 290 (28.1) |
| ≥16 years | 96547 (29.1) | 9777 (5.7) | 85954 (58.9) | 267 (3.0) | 230 (11.3) | 239 (14.6) | 80 (7.8) |
| Mean ± SD, years | 14.3±2.3 | 13.0±1.6 | 15.9±2.0 | 12.9±1.4 | 13.3±1.7 | 13.6±1.9 | 12.9±1.7 |
| Number of children (n=335,215; 12 studies)† | | | | | | | |
| 0 | 30713 (9.2) | 28320 (16.0) | 461 (0.3) | 1238 (14.2) | 283 (13.1) | 197 (11.2) | 214 (17.7) |
| 1 | 45612 (13.6) | 21561 (12.2) | 22446 (15.5) | 896 (10.3) | 269 (12.5) | 250 (14.2) | 190 (15.7) |
| 2 | 127211 (38.0) | 77382 (43.8) | 44098 (30.5) | 3970 (45.7) | 837 (38.8) | 484 (27.6) | 440 (36.3) |
| 3 | 75745 (22.6) | 34734 (19.7) | 37634 (26.0) | 2290 (26.3) | 500 (23.2) | 357 (20.3) | 230 (19.0) |
| ≥4 | 55934 (16.7) | 14721 (8.3) | 40040 (27.7) | 299 (3.4) | 268 (12.4) | 469 (26.7) | 137 (11.3) |
| Mean ± SD, children | 2.4±1.4 | 2.0±1.2 | 2.9±1.5 | 1.9±1.0 | 2.2±1.3 | 2.6±1.8 | 2.0±1.4 |
| MHT use (n=191,318; 12 studies)† | | | | | | | |
| Never | 125878 (65.8) | 112940 (63.9) | 340 (77.8) | 8588 (96.5) | 1694 (76.2) | 1509 (82.3) | 807 (69.2) |
| Ever | 65440 (34.2) | 63819 (36.1) | 97 (22.2) | 312 (3.5) | 528 (23.8) | 325 (17.7) | 359 (30.8) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Age at natural menopause | | | | | | | |
| <40 years | 7354 (2.2) | 3122 (1.8) | 4005 (2.7) | 84 (0.9) | 63 (2.8) | 54 (2.9) | 26 (2.1) |
| 40-44 years | 28653 (8.5) | 12838 (7.2) | 14914 (10.2) | 354 (3.9) | 232 (10.4) | 207 (11.3) | 108 (8.6) |
| 45-49 years | 108049 (32.0) | 42661 (24.0) | 60954 (41.8) | 2722 (30.0) | 740 (33.2) | 596 (32.4) | 376 (30.1) |
| 50-51 years | 80612 (23.9) | 42959 (24.2) | 33641 (23.0) | 2782 (30.7) | 544 (24.4) | 380 (20.7) | 306 (24.5) |
| 52-54 years | 76175 (22.5) | 47611 (26.8) | 24875 (17.0) | 2640 (29.1) | 405 (18.2) | 345 (18.8) | 299 (23.9) |
| ≥55 years | 37216 (11.0) | 28483 (16.0) | 7619 (5.2) | 479 (29.1) | 244 (11.0) | 256 (13.9) | 135 (10.8) |
| Mean ± SD, years | 49.6±4.3 | 50.4±4.3 | 48.6±4.0 | 50.1±3.2 | 49.0±4.5 | 49.2±4.8 | 49.5±4.4 |
| Incident type 2 diabetes | | | | | | | |
| No | 317995 (94.1) | 167006 (94.0) | 138056 (94.6) | 8605 (95.0) | 1749 (78.5) | 1486 (80.8) | 1093 (87.4) |
| Yes | 20064 (5.9) | 10668 (6.0) | 7952 (5.4) | 456 (5.0) | 479 (21.5) | 352 (19.2) | 157 (12.6) |
| Identified by linked records (4 studies)‡ | 8905 (44.4) | 8064 (75.6) | 33 (0.4) | 2 (0.4) | 419 (87.5) | 282 (80.1) | 105 (66.9) |
| Identified by self-report only | 11159 (55.6) | 2604 (24.4) | 7919 (99.6) | 454 (99.6) | 60 (12.5) | 70 (19.9) | 52 (33.1) |

IQR: interquartile range; SD: standard deviation; MHT: menopausal hormone therapy.

* White included White women living in the UK (77.9%), Europe (11.1%), and Australia (11.0%).
Chinese included Chinese women living in China (99.7%) and those living in the UK and Australia (0.3%).
Japanese included Japanese women living in Japan (98.9%) and those living in the UK and Australia (1.1%).
South/Southeast Asian included South Asian (n=1,777), Southeast Asian (n=317), and other Asian (n=134) living in the UK (93.2%) and Australia (6.8%).
Black included African or Caribbean women living in the UK (99.2%) and Australia (0.8%).
Mixed/Other included mixed, Hispanic, Middle Eastern, indigenous, and islander living in the UK (92.6%) and Australia (7.4%).

† WHITEHALL and SABRE did not collect data on age at menarche, HOW did not have data on number of children, and China Biobank did not have data on MHT use.

‡ Four studies (ALSWH, WLHS, Prospect–EPIC, and UK Biobank) provided diabetes data from health administrative records.

**Table 3.** The association between age at natural menopause and risk of type 2 diabetes in the overall sample and each ethnic group

| Age at natural menopause (years) | Sample N | Person-years | T2DM n | Absolute risk (%) | IR /$10^3$ p-ys | BMI at baseline Mean ± SD | Model 1* HR (95% CI) | Model 2† HR (95% CI) | Model 3‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| **Overall (n=338,059)** | | | | | | | | | |
| <40 | 7354 | 463108 | 549 | 7.5 | 1.19 | 25.1±5.0 | 1.35 (1.24-1.48) | 1.31 (1.20-1.43) | 1.31 (1.20-1.44) |
| 40-44 | 28653 | 1826195 | 1855 | 6.5 | 1.02 | 25.0±4.8 | 1.18 (1.12-1.25) | 1.15 (1.09-1.21) | 1.16 (1.10-1.23) |
| 45-49 | 108049 | 6779749 | 6262 | 5.8 | 0.92 | 24.9±4.5 | 1.11 (1.07-1.15) | 1.09 (1.05-1.13) | 1.09 (1.05-1.13) |
| 50-51 | 80612 | 5255262 | 4561 | 5.7 | 0.87 | 25.2±4.5 | Ref | Ref | Ref |
| 52-54 | 76175 | 5082476 | 4363 | 5.7 | 0.86 | 25.7±4.6 | 0.96 (0.92-1.00) | 0.98 (0.94-1.02) | 0.95 (0.91-0.99) |
| ≥55 | 37216 | 2623157 | 2474 | 6.6 | 0.94 | 26.4±4.8 | 0.98 (0.94-1.03) | 0.99 (0.94-1.04) | 0.94 (0.89-0.98) |
| **White (n=177,674)** | | | | | | | | | |
| <40 | 3122 | 212214 | 286 | 9.2 | 1.35 | 27.1±5.5 | 1.86 (1.64-2.10) | 1.71 (1.51-1.93) | 1.53 (1.36-1.73) |
| 40-44 | 12838 | 890921 | 944 | 7.4 | 1.06 | 26.8±5.1 | 1.42 (1.32-1.53) | 1.35 (1.25-1.45) | 1.27 (1.18-1.37) |
| 45-49 | 42661 | 2949763 | 2693 | 6.3 | 0.91 | 26.5±5.0 | 1.23 (1.16-1.30) | 1.20 (1.13-1.27) | 1.16 (1.10-1.23) |
| 50-51 | 42959 | 3027406 | 2353 | 5.5 | 0.78 | 26.3±4.8 | Ref | Ref | Ref |
| 52-54 | 47611 | 3371900 | 2622 | 5.5 | 0.78 | 26.5±4.8 | 0.99 (0.93-1.04) | 1.00 (0.95-1.06) | 0.97 (0.92-1.03) |
| ≥55 | 28483 | 2069473 | 1770 | 6.2 | 0.86 | 26.9±4.9 | 1.01 (0.95-1.07) | 1.02 (0.96-1.09) | 0.95 (0.89-1.01) |
| **Chinese (n=146,008)** | | | | | | | | | |
| <40 | 4005 | 237892 | 219 | 5.5 | 0.92 | 23.5±3.7 | 0.97 (0.84-1.12) | 0.99 (0.86-1.14) | 1.03 (0.89-1.18) |
| 40-44 | 14914 | 881962 | 794 | 5.3 | 0.90 | 23.4±3.6 | 0.98 (0.90-1.06) | 0.99 (0.91-1.08) | 1.03 (0.95-1.12) |
| 45-49 | 60954 | 3568550 | 3136 | 5.1 | 0.88 | 23.8±3.6 | 0.99 (0.94-1.05) | 1.00 (0.94-1.06) | 1.01 (0.95-1.07) |
| 50-51 | 33641 | 1987149 | 1832 | 5.4 | 0.92 | 24.0±3.6 | Ref | Ref | Ref |
| 52-54 | 24875 | 1484307 | 1433 | 5.8 | 0.97 | 24.4±3.6 | 0.99 (0.92-1.06) | 0.98 (0.91-1.05) | 0.94 (0.88-1.01) |
| ≥55 | 7619 | 478974 | 538 | 7.1 | 1.12 | 24.4±3.8 | 0.98 (0.89-1.08) | 0.98 (0.89-1.08) | 0.94 (0.85-1.03) |
| **Chinese born ≥1950 (n=57,741)** | | | | | | | | | |
| <40 | 1433 | 69685 | 57 | 4.0 | 0.82 | 23.7±3.5 | 2.74 (2.07-3.63) | 2.75 (2.08-3.63) | 2.79 (2.11-3.70) |
| 40-44 | 5756 | 290957 | 186 | 3.2 | 0.64 | 23.5±3.4 | 1.84 (1.54-2.19) | 1.84 (1.54-2.20) | 1.90 (1.59-2.27) |
| 45-49 | 26622 | 1381530 | 693 | 2.6 | 0.50 | 23.8±3.4 | 1.26 (1.11-1.43) | 1.26 (1.11-1.43) | 1.28 (1.12-1.45) |
| 50-51 | 14404 | 765349 | 369 | 2.6 | 0.48 | 24.1±3.4 | Ref | Ref | Ref |
| 52-54 | 8848 | 481671 | 236 | 2.7 | 0.49 | 24.4±3.4 | 0.85 (0.72-1.00) | 0.85 (0.72-1.00) | 0.82 (0.69-0.96) |
| ≥55 | 678 | 38462 | 20 | 2.9 | 0.52 | 25.0±3.6 | 0.70 (0.45-1.10) | 0.70 (0.44-1.10) | 0.64 (0.41-1.01) |
| **Japanese (n=9,061)** | | | | | | | | | |
| <40 | 84 | 4213 | 8 | 9.5 | 1.90 | 21.9±3.6 | 3.82 (1.87-7.80) | 3.81 (1.86-7.80) | 4.04 (1.97-8.27) |
| 40-44 | 354 | 18460 | 17 | 4.8 | 0.92 | 22.1±3.1 | 1.99 (1.20-3.30) | 1.97 (1.19-3.28) | 1.95 (1.17-3.24) |
| 45-49 | 2722 | 148917 | 136 | 5.0 | 0.91 | 22.2±2.9 | 1.41 (1.11-1.79) | 1.41 (1.11-1.80) | 1.39 (1.09-1.77) |
| 50-51 | 2782 | 157715 | 130 | 4.7 | 0.82 | 22.3±2.8 | Ref | Ref | Ref |
| 52-54 | 2640 | 154279 | 135 | 5.1 | 0.88 | 22.6±2.8 | 0.87 (0.69-1.11) | 0.88 (0.69-1.12) | 0.85 (0.66-1.08) |
| ≥55 | 479 | 29433 | 30 | 6.3 | 1.02 | 23.0±2.9 | 0.83 (0.56-1.24) | 0.83 (0.56-1.24) | 0.72 (0.48-1.08) |
| **South/Southeast Asian (n=2,228)** | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| <40 | 63 | 3907 | 18 | 28.6 | 4.61 | 28.1±5.3 | 1.64 (1.00-2.69) | 1.55 (0.95-2.55) | 1.46 (0.89-2.40) |
| 40-44 | 232 | 14917 | 49 | 21.1 | 3.28 | 27.4±4.6 | 1.07 (0.77-1.49) | 1.06 (0.76-1.48) | 1.04 (0.75-1.45) |
| 45-49 | 740 | 48982 | 151 | 20.4 | 3.08 | 26.9±5.1 | 0.93 (0.74-1.18) | 0.93 (0.74-1.18) | 0.96 (0.76-1.22) |
| 50-51 | 544 | 36659 | 127 | 23.3 | 3.46 | 27.2±5.0 | Ref | Ref | Ref |
| 52-54 | 405 | 27912 | 82 | 20.2 | 2.94 | 27.0±4.7 | 0.79 (0.60-1.04) | 0.80 (0.61-1.06) | 0.81 (0.62-1.08) |
| ≥55 | 244 | 17417 | 52 | 21.3 | 2.99 | 26.9±4.4 | 0.75 (0.54-1.04) | 0.74 (0.53-1.02) | 0.75 (0.54-1.04) |
| **Black (n=1,838)** | | | | | | | | | |
| <40 | 54 | 3348 | 13 | 24.1 | 3.88 | 30.9±6.0 | 1.85 (1.02-3.35) | 1.83 (1.01-3.32) | 1.72 (0.95-3.12) |
| 40-44 | 207 | 12907 | 39 | 18.8 | 3.02 | 31.1±7.3 | 1.32 (0.89-1.96) | 1.29 (0.87-1.92) | 1.32 (0.88-1.96) |
| 45-49 | 596 | 38804 | 108 | 18.1 | 2.78 | 30.3±6.0 | 1.09 (0.81-1.47) | 1.11 (0.82-1.51) | 1.12 (0.83-1.52) |
| 50-51 | 380 | 25804 | 72 | 18.9 | 2.79 | 30.2±5.4 | Ref | Ref | Ref |
| 52-54 | 345 | 23597 | 59 | 17.1 | 2.50 | 30.1±6.1 | 0.87 (0.62-1.23) | 0.89 (0.63-1.25) | 0.92 (0.65-1.30) |
| ≥55 | 256 | 18275 | 61 | 23.8 | 3.34 | 30.0±5.3 | 1.10 (0.78-1.56) | 1.09 (0.77-1.55) | 1.14 (0.80-1.61) |
| **Mixed/Other (n=1,250)** | | | | | | | | | |
| <40 | 26 | 1534 | 5 | 19.2 | 3.26 | 27.8±6.5 | 2.16 (0.85-5.47) | 2.15 (0.84-5.52) | 2.16 (0.83-5.57) |
| 40-44 | 108 | 7028 | 12 | 11.1 | 1.71 | 26.8±4.7 | 0.73 (0.39-1.38) | 0.72 (0.38-1.36) | 0.71 (0.37-1.35) |
| 45-49 | 376 | 24733 | 38 | 10.1 | 1.54 | 26.9±5.5 | 0.70 (0.46-1.08) | 0.70 (0.46-1.08) | 0.71 (0.46-1.10) |
| 50-51 | 306 | 20529 | 47 | 15.4 | 2.29 | 27.3±4.8 | Ref | Ref | Ref |
| 52-54 | 299 | 20481 | 32 | 10.7 | 1.56 | 27.2±5.2 | 0.59 (0.38-0.93) | 0.59 (0.38-0.93) | 0.59 (0.37-0.93) |
| ≥55 | 135 | 9585 | 23 | 17.0 | 2.40 | 27.2±4.9 | 0.89 (0.54-1.47) | 0.87 (0.52-1.44) | 0.87 (0.53-1.45) |

BMI: body mass index; SD: standard deviation; T2DM: type 2 diabetes; IR: incidence rate (per 1000 person-years); HR: hazard ratio; CI: confidence interval.

* Cox proportional hazard models were used to estimate HR and 95% CI in the overall sample and then separately for each ethnicity (each ethnic group was a different model), with study as a random effect. Model 1 was adjusted for age (continuous) at baseline.

† Model 2 was adjusted for age (continuous) at baseline, ethnicity (only in the overall sample), education level, and smoking status, and stratified by birth year (as a strata variable).

‡ Model 3 included all covariates in Model 2 and BMI (using ethnicity-specific cut-offs: <18.5, 18.5-24.9, 25-29.9, ≥30 kg/m$^2$ for White, Black, and Mixed/Other; <18.5, 18.5-22.9, 23-27.4, ≥27.5 kg/m$^2$ for Chinese, Japanese, and South/Southeast Asian).

| Ethnicity | Case/<40y | Case/50-51y | HR (95%CI) |
|---|---|---|---|
| **White** | | | |
| Overall | 286/3122 | 2353/42959 | 1.53 (1.36, 1.73) |
| Born before1940 | 71/505 | 486/5685 | 1.46 (1.13, 1.87) |
| Born 1940-49 | 138/1372 | 1358/22106 | 1.46 (1.22, 1.73) |
| Born 1950 or later | 77/1245 | 509/15168 | 1.84 (1.45, 2.35) |
| No formal education | 50/258 | 241/2184 | 1.69 (1.25, 2.30) |
| ≤10 yrs education | 157/1667 | 1275/19855 | 1.43 (1.21, 1.69) |
| >10 yrs education | 79/1197 | 837/20920 | 1.68 (1.33, 2.12) |
| Under/normal weight | 45/1269 | 384/19454 | 1.92 (1.41, 2.62) |
| Overweight | 78/1054 | 797/15367 | 1.42 (1.12, 1.79) |
| Obese | 163/799 | 1172/8138 | 1.50 (1.27, 1.76) |
| **Chinese** | | | |
| Overall | 219/4005 | 1832/33641 | 1.03 (0.89, 1.18) |
| Born before1940 | 76/1252 | 626/6512 | 0.68 (0.53, 0.86) |
| Born 1940-49 | 86/1320 | 837/12725 | 0.99 (0.79, 1.24) |
| Born 1950 or later | 57/1433 | 369/14404 | 2.79 (2.11, 3.70) |
| No formal education | 81/1861 | 547/11603 | 0.87 (0.69, 1.09) |
| ≤10 yrs education | 110/1858 | 1064/18235 | 1.09 (0.89, 1.32) |
| >10 yrs education | 28/286 | 221/3803 | 2.46 (1.66, 3.66) |
| Under/normal weight | 75/1868 | 502/13740 | 1.11 (0.87, 1.41) |
| Overweight | 98/1589 | 879/14508 | 0.97 (0.79, 1.20) |
| Obese | 46/548 | 451/5393 | 1.04 (0.77, 1.41) |
| **Japanese** | | | |
| Overall | 8/84 | 130/2782 | 4.04 (1.97, 8.27) |
| Born before 1950 | 2/14 | 53/1072 | 2.53 (0.61, 10.4) |
| Born 1950 or later | 6/70 | 77/1710 | 5.21 (2.26, 12.0) |
| Under/normal weight | 5/62 | 60/1795 | 4.59 (1.83, 11.5) |
| Overweight/obese | 3/22 | 70/987 | 3.10 (0.97, 9.89) |
| **South/Southeast Asian** | | | |
| Overall | 18/63 | 127/544 | 1.46 (0.89, 2.40) |
| Born before 1950 | 9/24 | 78/255 | 1.42 (0.71, 2.85) |
| Born 1950 or later | 9/39 | 49/289 | 1.65 (0.80, 3.41) |
| No or ≤10 yrs education | 11/39 | 63/214 | 1.15 (0.61, 2.19) |
| >10 yrs education | 7/24 | 64/330 | 1.80 (0.82, 3.94) |
| Under/normal weight | 0/6 | 11/88 | N/A |
| Overweight | 6/25 | 45/245 | 1.75 (0.74, 4.14) |
| Obese | 12/32 | 71/211 | 1.52 (0.82, 2.83) |
| **Black** | | | |
| Overall | 13/54 | 72/380 | 1.72 (0.95, 3.12) |
| Born before 1950 | 5/16 | 39/169 | 1.80 (0.71, 4.62) |
| Born 1950 or later | 8/38 | 33/211 | 1.79 (0.82, 3.92) |
| No or ≤10 yrs education | 4/18 | 37/180 | 1.41 (0.50, 4.00) |
| >10 yrs education | 9/36 | 35/200 | 2.04 (0.97, 4.27) |
| Under/normal weight | 2/10 | 4/62 | 3.98 (0.67, 23.8) |
| Overweight | 5/16 | 24/143 | 3.11 (1.17, 8.28) |
| Obese | 6/28 | 44/175 | 1.04 (0.44, 2.46) |

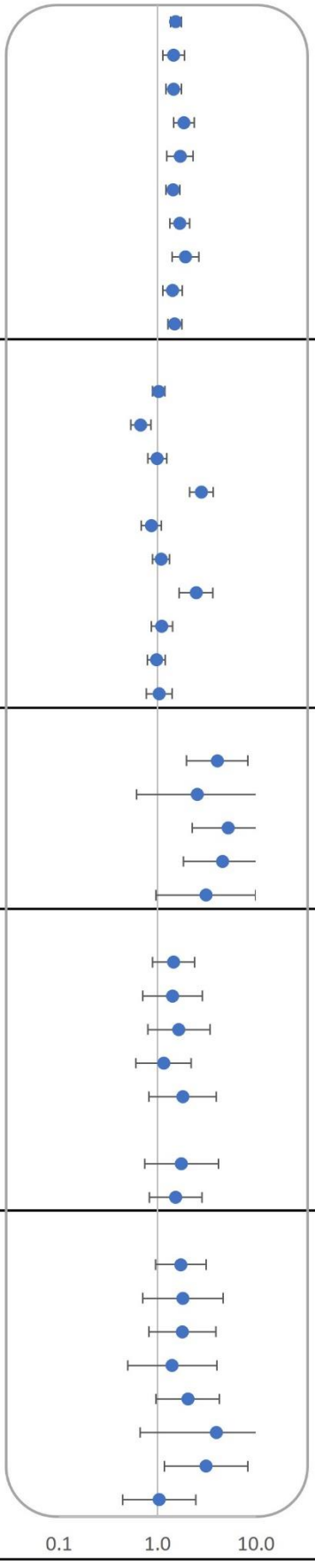

**Figure 1.** Forest plot for the association between POI <40 years (vs menopause at age 50-51 years) and risk of type 2 diabetes in each ethnic group, stratified by birth years, education levels, and obesity status.

Some categorises of birth year, education level, and obesity were combined due to small sample sizes. The stratified analysis was not performed for the Mixed/Other group due to limited sample. Ethnicity-specific body mass index (BMI) cut-offs <18.5, 18.5-24.9, 25-29.9, ≥30 kg/m$^2$ for White and Black and <18.5, 18.5-22.9, 23-27.4, ≥27.5 kg/m$^2$ for Chinese, Japanese, and South/Southeast Asian were used to define underweight, normal weight, overweight, and obese, respectively. There were no variations in education levels among Japanese as most of them were nurses, so stratification by education was not performed in Japanese. Hazard ratios (HRs) were fully adjusted for age (continuous) at baseline, education level, smoking status, and BMI, and stratified by birth year (as a strata variable), with study as a random effect. A base-10 log scale was used for the x-axis.