Reproductive Biology and Endocrinology

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Early menopause in mothers and the risks of pre-diabetes and type 2 diabetes mellitus in female and male offspring: a population-based cohort study

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Abstract

Background Genetic factors and an unfavorable intrauterine environment may contribute to the development of metabolic disorders in offspring later in life. The present study aims to investigate and compare the risks of pre-diabetes mellitus (pre-DM), type 2 diabetes mellitus (T2DM) and abnormal glucose tolerance in female and male offspring with early maternal menopausal age versus those with normal maternal menopausal age, later in life.

Methods In this prospective population-based study, there were 1,516 females and 1,563 males with normal maternal menopausal age, as well as 213 females and 237 males with early maternal menopausal age. Unadjusted and adjusted cox regression models were used to assess the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between early maternal menopausal age with pre-DM, T2DM and abnormal glucose tolerance in offspring. Statistical analysis was performed using the STATA software package; the significance level was set at $P < 0.05$.

Results The present study revealed a higher risk of pre-DM in female offspring with early maternal menopausal age compared to females with normal maternal menopausal age (unadjusted HR (95% CI): 1.42 (0.98, 2.05); $P = 0.06$ (marginal significant) and adjusted HR (95% CI): 1.47 (1.00, 2.16); $P = 0.04$). Additionally, a higher risk of abnormal glucose tolerance among female offspring with early maternal menopausal age in adjusted model was observed (HR (95% CI): 1.13 (0.99–1.29); $P = 0.06$, marginal significant). However, no significant differences were observed in the risks of developing pre-DM and abnormal glucose tolerance in male offspring with early maternal menopausal age compared to males with normal maternal menopausal age in both unadjusted and adjusted models. No significant difference was observed in the risk of T2DM in the offspring with early maternal menopausal age compared to offspring with normal maternal menopausal age.

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Conclusions This pioneering study, characterized by a long-term follow-up, demonstrated that early maternal menopausal age is associated with an increased risk of developing pre-DM in female offspring later in life. It may be advisable to implement screening for pre-DM and glucose metabolism disorders in these female offspring.

Clinical trial number Not applicable.

Keywords Early menopause, Genetic factors, Intrauterine life, Pre-diabetes (Pre-DM), Type 2 diabetes (T2DM), Abnormal glucose tolerance, Offspring, Tehran lipid and glucose study (TLGS)

Background

Menopause is defined as the cessation of the menstrual cycle for > 12 months from the last menstruation, resulting from the loss of ovarian follicular activity. When menstruation ceases before the age of 45 years, it is defined as early menopause. Ovulation disorders lead to early depletion of the ovarian follicles and diminished ovarian reserve, resulting in early age at menopause [1]. Genome-wide association studies indicate a strong link between age at menopause and genetic factors, and heritability for menopausal age is estimated to be between 44 and 66% in mother-daughter pairs.

Cardiometabolic disorders, which are among the leading causes of global mortality and morbidity, have steadily increased over the past several decades. Family history and genetic factors are recognized as significant predictors of cardiometabolic disorders [2, 3]. A positive familial co-aggregation of cardiometabolic disorders particularly in type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), and obesity has been documented in the literature [3]. Studies indicate that individuals with a family history of these conditions may experience an increased risk due to shared genetic predispositions and environmental factors. Moreover, it has been shown that women with diminished ovarian reserve and early onset of menopause are at a higher risk of cardiometabolic disorders, including coronary heart disease (CHD), insulin resistance (IR), pre-diabetes mellitus (pre-DM), T2DM, obesity, hypertension, dyslipidemia, and MetS [4–12].

PI3K/Akt, the mammalian target of rapamycin (mTOR) and mitogen-activated protein kinases (MAPKs) signaling pathways and related genes involved in the glucose and lipid metabolism and their imbalances lead to the development of metabolic disorders such as impaired insulin secretion, IR, T2DM and obesity [13–17]. Furthermore, these molecules and signaling pathways involved in the increased primordial follicular activation in the ovaries leading to depletion of ovarian reserve and early age at menopause.

The fetal programming concept suggests that maternal nutritional imbalance and metabolic disturbances may have a persistent and intergenerational effect on the health of offspring and on the risk of diseases such as obesity, diabetes, and cardiovascular diseases (CVDs) in offspring in their later life [18].

Growing evidence suggests that numerous health problems are affected by gender. Previous researches, have shown gender-related variations in glucose homeostasis, insulin signaling, body fat distribution, and lipid metabolism [19–21]. These sex differences may be influenced by genetic background, gene expression from the X and Y chromosomes, environmental factors, sex steroid hormones, and the gut microbiome [19, 22, 23].

Most existing studies have focused on the cardiometabolic disorders in women with early menopausal age [4, 5, 7, 8, 10, 24] and based on our knowledge there is no data available on the risk of cardiometabolic disorders in offspring of women with early menopausal age, later in life.

Considering to the role of genetic factors and common pathways between metabolic disorders and early menopausal age, as well as the effects of adverse intrauterine environment on the metabolic disorders in later life, in this long-term population-based study with well-defined controls, we aimed to investigate and compare the risks of pre-DM, T2DM and abnormal glucose tolerance in female and male offspring with early maternal menopausal age versus those with normal maternal menopausal age, later in life.

Methods

Study design

The Tehran Lipid and Glucose Study (TLGS) is a long-term, ongoing research project that began in 1998. It aims to investigate the prevalence of risk factors for non-communicable diseases among 15,005 participants, both males and females, aged 3 years and older. The study involves follow-ups every 3 years (seven phases including 6 follow-ups in addition to baseline). The follow-up process involved a general physical examination, demographic, anthropometric, and metabolic evaluations, and also blood sampling. The details of the TLGS have been previously published [25].

Study population

For the purposes of the present study, we included both female and male offspring from the TLGS, whose mothers' age at menopause had been recorded. Additionally, these offspring were required to have at least one follow-up visit, to be over 20 years of age, and to be free

of pre-DM, and T2DM at baseline (at the initiation of the study). Furthermore, offspring were excluded if they were taking medications that could potentially influence their cardiometabolic parameters (such as blood sugar-lowering, blood lipid-lowering, antihypertensive medications, or medications for weight loss/gain). As a result, a total of 3,529 offspring, comprising 1,729 females and 1,800 males, met the eligibility criteria for inclusion in the present study. The offspring were categorized into 4 groups based on their mothers' menopausal age and their sex: Female offspring with normal maternal menopausal age ($n = 1{,}516$) and female offspring with early maternal menopausal age ($n = 213$), male offspring with normal maternal menopausal age ($n = 1{,}563$) and male offspring with early maternal menopausal age ($n = 237$). The study flowchart is illustrated in Fig. 1.

All female and male offspring were followed-up from baseline to the date of occurrence of the events, censoring, or end of the study period, whichever occurred first.

Measurements

During face-to-face interviews, a standard questionnaire was completed to collect demographic data and family medical history for all offspring (females and males) [25]. Additionally, a questionnaire was used to evaluate reproductive variables, focusing on menstrual cycle regularity, gynecological history, menopausal age, and family history of irregular menstrual cycles [26]. These interviews were conducted by trained midwives under the guidance of a gynecologist.

Offspring were asked about their level of physical activity in the past 12 months using the modifiable activity questionnaire. Physical activity status was defined as active for those with three or more days of severe-intensity activity of at least 20 min, or ≥ 5 days of moderate-intensity activity or walking at least 30 min, or ≥ 5 days of any combination of walking, moderate or severe-intensity activities, reaching at least 600 metabolic equivalent task minutes per week and less active for those not reaching to this threshold. The educational levels were divided into two categories: those with less than 12 years of formal education and those with 12 years or more of education.

The data collection process involved measuring several clinical parameters, including body mass index (BMI), fasting blood sugar (FBS), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and total cholesterol (TC), and all measurements were conducted according to the standard protocol of the TLGS. Weight and height were measured, in the standing position with calibrated equipments; BMI was calculated as weight in kilograms

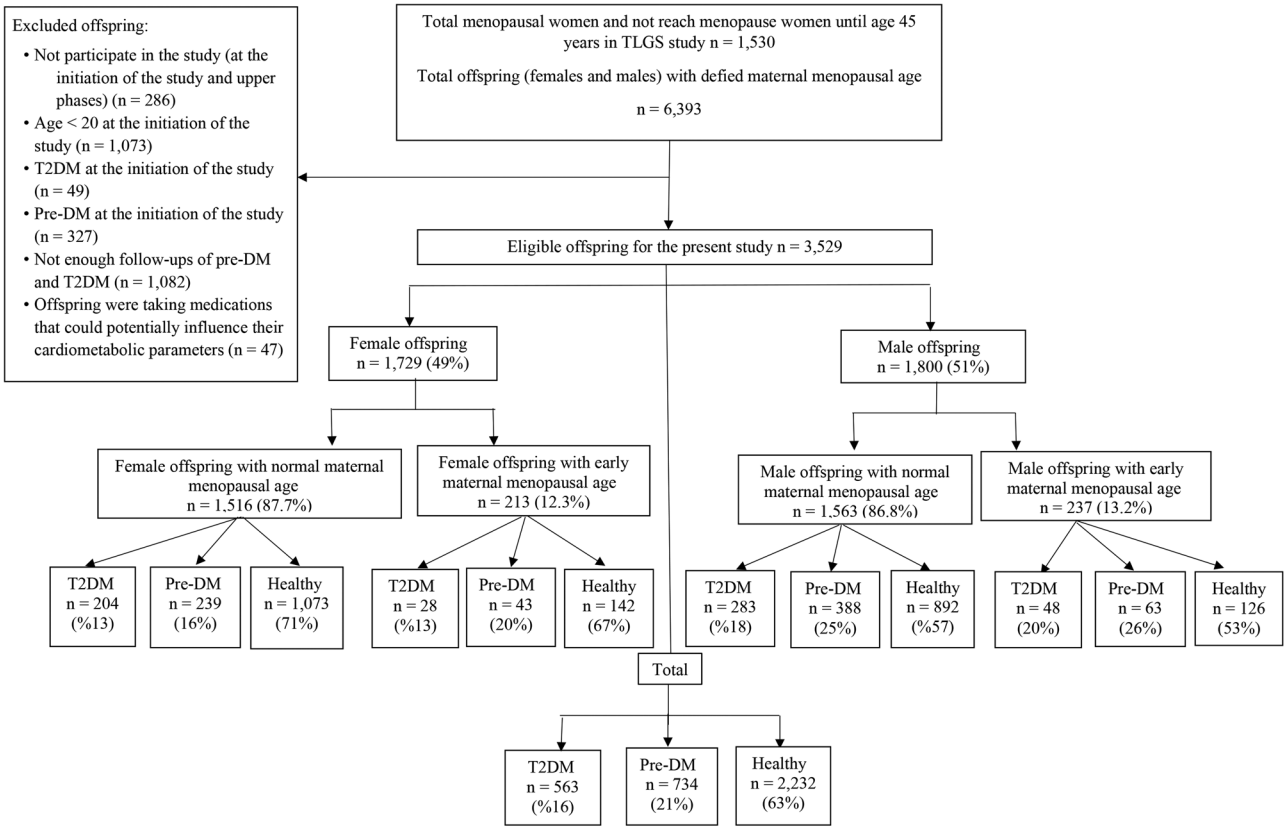

Fig. 1 Flowchart of study. *TLGS* Tehran lipid and glucose study, *T2DM* type 2 diabetes mellitus, *Pre-DM* pre-diabetes mellitus

divided by height in meters squared (kg/m^2). Blood samples were then collected from each offspring after an overnight fast. The samples were centrifuged, and the sera were separated and stored at -80 °C for future analysis. FBS was measured using the glucose oxidase method, HDL-C was measured after precipitating apolipoprotein B (APO B)-containing lipoproteins with phosphotungstic acid, TG and TC were measured using glycerol phosphate oxidase. The intra- and inter-assay coefficient variations (CVs) for FBS, HDL-C, TG and TC were all below 3%. The analyses were conducted using kits from Pars Azmon Inc. (Tehran, Iran) and a Selectra analyzer (Vital Scientific, Spankeren, Netherlands).

Definition of terms

In this study, the exposure of interest is the maternal menopausal age, while the outcome of interest is the risks of pre-DM, T2DM and abnormal glucose tolerance in offspring. Normal menopause is defined as the cessation of menstruation occurring at the age of 45 years or older, whereas early menopause is defined as occurring prior to the age of 45 years.

T2DM was defined according to the American Diabetes Association criteria as fasting plasma glucose ≥ 126 mg/dl, or 2-h plasma glucose ≥ 200 mg/dl, or using medications for a previous diagnosis of T2DM. Pre-DM referred to those with impaired fasting glucose where the fasting plasma glucose levels were 100–125 mg/dl; or impaired glucose tolerance where the 2-h plasma glucose values in the oral glucose tolerance test (OGTT) were 140–199 mg/dl. Abnormal glucose tolerance was defined as impaired fasting glucose where the fasting plasma glucose levels were 100 mg/dl or more or the use of antidiabetic medications.

Statistical analysis

Baseline demographic and clinical characteristics of female and male offspring are described and compared based on T2DM status at follow-ups. Normality of continuous variables are checked by the one-sample Kolmogorov–Smirnov test. Variables with normal distribution are presented as mean (standard deviation), and compared using the student *t* test, while those with skewed distribution are presented as median and interquartile range (IQR 25–75) and compared with Mann-Whitney test. Categorical variables are presented as numbers (n) and percentages (%) and compared by χ^2 test or Fisher exact test.

Cox proportional hazard regression model is used to assess the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of maternal menopausal age with pre-DM, T2DM, and abnormal glucose tolerance in offspring. The enter date of the first phase that offspring became over 20 years old supposed as index phase (initiation of the study). Survival time calculated as time difference between the initiation of the study and date of the occurrence of the event or last follow-up date for those didn't experience event until the end of the study (censored cases). Both unadjusted and adjusted Cox regression models were applied for the association between maternal menopausal age and the risks of pre-DM, T2DM and abnormal glucose tolerance in offspring. Potential confounding factors including sex, age, BMI, physical activity, smoking status, educational level, family history of T2DM, pre-DM, HDL-C, TC and TG were entered in adjusted models. Cumulative hazard plot is used to evaluate the difference between hazards of exposure groups in total offspring (females and males) and in separate groups of sex visually.

Additionally, cubic spline regression model was used to explore the shape of the relationship between maternal menopausal age and the log-relative hazard of pre-DM, T2DM, and abnormal glucose tolerance in offspring.

Statistical analysis was performed using the software package STATA (version 12; STATA Inc., College Station, TX, USA) and SPSS version 26. *P*-values less than 0.05 were considered statistically significant.

Results

In this study involving 3,529 eligible offspring, it was found that 734 individuals (21%) were diagnosed with pre-DM, while 563 individuals (16%) were diagnosed with T2DM during the follow-up period (Fig. 1). The median (IQR) of follow-up time for pre-DM and T2DM were 11.92 (8.26–15.80) and 18.10 (14.09–20.21) years, respectively.

The characteristics of mothers at baseline phase based on their menopausal age, as well as the characteristics of offspring at the initiation of the study, categorized by maternal menopausal age, are detailed in Tables 1 and 2.

The median (IQR) age for offspring with normal and early maternal menopausal age was 22 (21–26) and 22 (21–26) years, respectively ($P = 0.50$). The median (IQR) BMI for offspring with normal and early maternal menopausal age was 23.51 (20.79–26.66) and 23.08 (20.53–26.88) respectively ($P = 0.48$). There are no statistically significant differences between two groups of offspring with normal and early maternal menopausal age in various baseline characteristics, as shown in Table 2.

Baseline characteristics of offspring according to their last status in terms of glucose intolerance (healthy, pre-DM and T2DM) are presented in Table 3. It has been shown that offspring that experienced T2DM were older and had higher BMI than those in pre-DM and healthy groups. Also the distribution of sex, physical activity, family history of T2DM, and lipid profile were significantly different between offspring in three groups ($P < 0.05$) (Table 3).

Table 1 Characteristics of mothers at baseline phase based on their menopausal age

Variables		Menopausal age			
		Total ***n*** **= 1,530**	**Normal** ***n*** **(%) = 1,340 (87.6)**	**Early** ***n*** **(%) = 190 (12.4)**	***P***
Age, years, median (IQR)		47 (39–54)	47 (39–54)	47 (40–55)	0.5
BMI, kg/m^2, median (IQR)		28.62 (25.72–31.62)	28.61 (25.71–31.55)	28.88 (25.87–32.84)	0.2
Physical activity, n (%)	Low	1069 (69.9)	937 (69.9)	132 (69.5)	0.8
	High	461 (30.1)	403 (30.1)	58 (30.5)	
Smoking status, n (%)	Never	1456 (95.2)	1276 (95.2)	180 (94.7)	0.7
	Ever	74 (4.8)	64 (4.8)	10 (5.3)	
Educational level, n (%)	< Diploma	1468 (95.9)	1283 (95.7)	185 (97.4)	0.2
	≥ Diploma	62 (4.1)	57 (4.3)	5 (2.6)	
Family history of T2DM, n (%)	No	1074 (70.2)	948 (70.7)	126 (66.3)	0.2
	Yes	456 (29.8)	392 (29.3)	64 (33.7)	
Pre-DM, n (%)	No	1184 (77.4)	1040 (77.6)	144 (75.8)	0.5
	Yes	346 (22.6)	300 (22.4)	46 (24.2)	
HDL-C, mg/dl, median (IQR)		42 (35–53)	42 (35–53)	42 (35–49)	0.1
TC, mg/dl, median (IQR)		219 (188–250)	219 (187–250)	225 (193–256)	0.1
TG, mg/dl, median (IQR)		157 (112–222)	156 (109–217)	169 (121–240)	0.2

Values are presented as median (IQR, interquartile range), or number (n) (percentage) as appropriate

BMI body mass index, *T2DM* type 2 diabetes mellitus, *Pre-DM* pre-diabetes mellitus, *HDL-C* high density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglyceride

Total: Mothers with normal age at menopause and early age at menopause

Normal: Mothers with normal age at menopause

Early: Mothers with early age at menopause

Table 2 Characteristics of offspring at the initiation of the study based on maternal menopausal age

Variables		Maternal menopausal age			
		Total ***n*** **= 3,529**	**Normal** ***n*** **(%) = 3,079 (87.24)**	**Early** ***n*** **(%) = 450 (12.75)**	***P***
Age, years, median (IQR)		22 (21–26)	22 (21–26)	22 (21–26)	0.50
BMI, kg/m^2, median (IQR)		23.45 (20.75–26.70)	23.51 (20.79–26.66)	23.08 (20.53–26.88)	0.48
Sex, n (%)	Female	1729 (49)	1516 (49.2)	213 (47.3)	0.45
	Male	1800 (51)	1563 (50.8)	237 (52.7)	
*Menarche age, years, median (IQR)		13 (12–14)	13 (12–14)	13 (12–14)	0.43
Physical activity, n (%)	Low	2142 (60.7)	1859 (60.4)	283 (62.9)	0.30
	High	1387 (39.3)	1220 (39.6)	167 (37.1)	
Smoking status, n (%)	Never	2979 (84.4)	2603 (84.5)	376 (83.6)	0.59
	Ever	550 (15.60)	476 (15.5)	74 (16.4)	
Educational level, n (%)	< Diploma	2713 (76.9)	2358 (76.6)	355 (78.9)	0.27
	≥ Diploma	816 (23.1)	721 (23.4)	95 (21.1)	
Family history of T2DM, n (%)	No	2947 (83.5)	2580 (83.8)	367 (81.6)	0.23
	Yes	582 (16.5)	499 (16.2)	83 (18.4)	
Pre-DM, n (%)	No	3342 (94.7)	2911 (94.5)	431 (95.8)	0.27
	Yes	187 (5.3)	168 (5.5)	19 (4.2)	
HDL-C, mg/dl, median (IQR)		42 (35–49)	42 (35–50)	42 (35–49)	0.50
TC, mg/dl, median (IQR)		165 (145–189)	165 (145–189)	164.50 (146-187.25)	0.95
TG, mg/dl, median (IQR)		95 (69–137)	95 (69–137)	94.50 (71–133)	0.66

Values are presented as median (IQR, interquartile range), or number (n) (percentage) as appropriate

BMI body mass index, *T2DM* type 2 diabetes mellitus, *Pre-DM* pre-diabetes mellitus, *HDL-C* high density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglyceride

* In female offspring

Total: Offspring with normal and early maternal menopausal age

Normal: Offspring with normal maternal menopausal age

Early: Offspring with early maternal menopausal age

Table 3 Baseline characteristics of offspring according to their last status in terms of glucose intolerance (Healthy, Pre-DM and T2DM)

Variables		Last experienced event			
		Healthy ***n*** **(%) = 2,232 (63)**	**Pre-DM** ***n*** **(%) = 734 (21)**	**T2DM** ***n*** **(%) = 563 (16)**	***P***
Age, years, median (IQR)		22 (21–25)	23 (21–28)	24 (21–29)	< 0.001
BMI, kg/m^2, median (IQR)		22 (20–26)	24.27 (21.61–27.40)	25.02 (21.47–28.71)	< 0.001
Sex, n (%)	Female	1214 (54.4)	283 (38.6)	331 (58.8) 232 (41.2)	< 0.001
	Male	1018 (45.6)	451 (61.4)		
*Menarche age, years, median (IQR)		13 (12–14)	13 (13–14)	13 (13–14)	0.10
Physical activity, n (%)	Low	1323 (59.3)	453 (61.7)	366 (65)	0.03
	High	909 (40.7)	281 (38.3)	197 (35)	
Smoking status, n (%)	Never	1908 (85.5)	607 (82.7)	464 (82.4)	0.07
	Ever	324 (14.5)	127 (17.3)	99 (17.6)	
Educational level, n (%)	< Diploma	1716 (76.9)	558 (76.0)	439 (78.0)	0.71
	≥ Diploma	516 (23.1)	176 (24.0)	124 (22.0)	
Family history of T2DM, n (%)	No	1929 (86.4)	599 (81.6)	419 (74.4)	< 0.001
	Yes	303 (13.6)	135 (18.4)	144 (25.6)	
HDL-C, mg/dl, median (IQR)		43 (35–52)	42 (35–49)	39 (34.50–46)	< 0.001
TC, mg/dl, median (IQR)		161 (143–185)	170 (149–198)	174 (152.50–200)	< 0.001
TG, mg/dl, median (IQR)		89 (66–122)	104 (75–162)	116 (77-169.50)	< 0.001

Values are presented as median (IQR, interquartile range), or number (n) (percentage) as appropriate

BMI body mass index, *T2DM* type 2 diabetes mellitus, *Pre-DM* pre-diabetes mellitus, *HDL-C* high density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglyceride

* In female offspring

Table 4 summarizes the results of Cox proportional hazard regression analysis regarding the association between the offspring's maternal menopausal age with T2DM, pre-DM and abnormal glucose tolerance. Models are presented in total and categorized by sex in both unadjusted and adjusted models. No significant differences were observed in the risk of T2DM in the offspring with early maternal menopausal age (HR_{unadj} (95% CI): 1.03 (0.80, 1.31); $P = 0.8$) compared to offspring with normal maternal menopausal age, even by sex (females (HR_{unadj} (95% CI): 0.94 (0.63, 1.4); $P = 0.78$) and males (HR_{unadj} (95% CI): 1.08 (0.79,1.48); $P = 0.62$)); the results remained not significant after adjusting for potential confounders, including sex, age, BMI, physical activity, smoking status, educational level, family history of T2DM, pre-DM, HDL-C, TC, and TG in total offspring and same adjustment variables expect sex in models categorized by sex.

Based on the results of unadjusted model for pre-DM response, offspring with early maternal menopausal age showed a 23% marginal significant increase in the risk of pre-DM (HR_{unadj} (95% CI): 1.23 (0.97, 1.56); $P = 0.07$) compared to offspring with normal maternal menopausal age (Table 4). In addition, female offspring with early maternal menopausal age revealed a 42% marginal significant increase in the risk of pre-DM (HR_{unadj} (95% CI): 1.42 (0.98, 2.05); $P = 0.06$) compared to females with normal maternal menopausal age. While in male offspring there was no any differences (Table 4).

In adjusted cox regression model, offspring with early maternal menopausal age showed a 26% marginal significant increase in the risk of pre-DM (HR_{adj} (95% CI): 1.26 (0.99, 1.62); $P = 0.05$) compared to offspring with normal maternal menopausal age (Table 4). Additionally, female offspring with early maternal menopausal age revealed a 47% increase in the risk of pre-DM (HR_{adj} (95% CI): 1.47 (1.00, 2.16); $P = 0.04$) compared to females with normal maternal menopausal age. However, no significant difference was observed in the risk of developing pre-DM in male offspring with early maternal menopausal age (HR_{adj} (95% CI): 1.14 (0.82, 1.57); $P = 0.42$) in comparison to males with normal maternal menopausal age (Table 4).

No significant differences were observed in the risk of abnormal glucose tolerance in the offspring with early maternal menopausal age (HR_{unadj} (95% CI): 1.05 (0.96, 1.14); $P = 0.23$) compared to offspring with normal maternal menopausal age, even by sex (females (HR_{unadj} (95% CI): 1.09 (0.96, 1.24); $P = 0.16$) and males (HR_{unadj} (95% CI): 1.01 (0.91, 1.12); $P = 0.79$)) (Table 4).

In adjusted cox regression model, no significant difference was observed in the risk of abnormal glucose tolerance in the offspring with early maternal menopausal age compared to offspring with normal maternal menopausal age (HR_{adj} (95% CI): 1.06 (0.98, 1.16); $P = 0.11$). In adjusted model, female offspring with early maternal menopausal age showed a 13% marginal significant increase in the risk of abnormal glucose tolerance (HR_{adj} (95% CI): 1.13 (0.99, 1.29); $P = 0.06$) compared to females with normal maternal menopausal age. However, no significant difference was observed in the risk of abnormal glucose tolerance in male offspring with early maternal menopausal age

Table 4 Association between maternal menopausal age and hazard ratio of the T2DM, pre-DM, and abnormal glucose tolerance in total offspring and based on their sex

Response event	Models	Variables	Total offspring		Female offspring		Male offspring	
			HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
T2DM								
	Unadjusted	Early maternal menopausal age, (ref: Normal)	1.03 (0.80, 1.31)	0.80	0.94 (0.63, 1.4)	0.78	1.08 (0.79,1.48)	0.62
	Adjusted	Early maternal menopausal age, (ref: Normal)	1.16 (0.89, 1.5)	0.25	1.07 (0.7, 1.64)	0.74	1.15 (0.83, 1.6)	0.39
		Sex, (ref: Female)	1.24 (1.01, 1.52)	0.03	-	-	-	-
		Age, years	1.06 (1.04, 1.07)	< 0.001	1.04 (1.01, 1.06)	< 0.001	1.09 (1.06, 1.11)	< 0.001
		BMI, kg/m^2	1.02 (1.00, 1.04)	0.008	1.03 (1.00, 1.06)	< 0.001	1.02 (0.99, 1.04)	0.11
		Physical activity (ref: Low)	0.94 (0.78, 1.14)	0.55	0.95 (0.69, 1.29)	0.74	0.91 (0.72, 1.17)	0.48
		Smoking status (ref: No)	1.057 (0.82, 1.35)	0.65	0.59 (0.14, 2.39)	0.46	0.97 (0.75, 1.26)	0.85
		Educational level (ref: Under diploma)	0.85 (0.68, 1.05)	0.14	1.13 (0.81, 1.59)	0.44	0.70 (0.52, 0.93)	0.01
		Family history of T2DM (ref: No)	1.70 (1.38, 2.09)	< 0.001	1.89 (1.36, 2.63)	< 0.001	1.63 (1.24, 2.14)	< 0.001
		Pre-DM (ref: No)	3.73 (2.86, 4.87)	< 0.001	4.85 (3.28, 7.19)	< 0.001	2.46 (1.66, 3.63)	< 0.001
		HDL-C, mg/dl	0.99 (0.98, 1.004)	0.23	0.99 (0.97, 1.00)	0.26	0.99 (0.98, 1.01)	0.79
		TC, mg/dl	1.00 (0.99, 1.00)	0.13	1.00 (0.99, 1.00)	0.11	1.00 (0.99, 1.00)	0.94
		TG, mg/dl	1.00 (1.00, 1.00)	< 0.001	1.00 (1.00, 1.00)	0.01	1.00 (1.00, 1.00)	< 0.001
Pre-DM								
	Unadjusted	Early maternal menopausal age, (ref: Normal)	1.23 (0.97, 1.56)	0.07	1.42 (0.98, 2.05)	0.06	1.15 (0.85, 1.56)	0.35
	Adjusted	Early maternal menopausal age, (ref: Normal)	1.26 (0.99, 1.62)	0.05	1.47 (1.00, 2.16)	0.04	1.14 (0.82, 1.57)	0.42
		Sex, (ref: Female)	1.86 (1.5, 2.3)	< 0.001	-	-	-	-
		Age, years	1.05 (1.03, 1.06)	< 0.001	1.04 (1.02, 1.06)	< 0.001	1.05 (1.03, 1.08)	< 0.001
		BMI, kg/m^2	1.01 (0.99, 1.03)	0.18	1.04 (1.00, 1.08)	0.03	1.00 (0.97, 1.02)	0.97
		Physical activity (ref: Low)	1.02 (0.85, 1.23)	0.78	0.95 (0.69, 1.32)	0.78	1.05 (0.83, 1.32)	0.67
		Smoking status (ref: No)	0.88 (0.69, 1.12)	0.30	0.28 (0.04, 2.07)	0.21	0.90 (0.7, 1.15)	0.41
		Educational level	0.87 (0.7, 1.09)	0.23	0.90 (0.62, 1.3)	0.60	0.85 (0.64, 1.13)	0.27
		Family history of T2DM (ref: No)	1.27 (1.01, 1.59)	0.03	1.46 (1.00, 2.12)	0.04	1.16 (0.87, 1.55)	0.30
		HDL-C, mg/dl	1.00 (0.98, 1.01)	0.93	1.00 (0.98, 1.01)	0.77	0.99 (0.98, 1.01)	0.71
		TC, mg/dl	0.99 (0.99, 1.00)	0.50	1.00 (0.99, 1.00)	0.92	0.99 (0.99, 1.00)	0.32
		TG, mg/dl	1.00 (1.00, 1.01)	< 0.001	1.00 (1.00, 1.00)	0.08	1.00 (1.00, 1.00)	0.001
Abnormal glucose tolerance (Pre-DM + T2DM)	Unadjusted	Early maternal menopausal age, (ref: Normal)	1.05 (0.96, 1.14)	0.23	1.09 (0.96, 1.24)	0.16	1.01 (0.91, 1.12)	0.79
	Adjusted	Early maternal menopausal age, (ref: Normal)	1.06 (0.98, 1.16)	0.11	1.13 (0.99, 1.29)	0.06	1.02 (0.92, 1.14)	0.61
		Sex, (ref: Female)	1.43 (1.25, 1.63)	< 0.001	-	-	-	-
		Age, years	1.01 (1.00, 1.02)	0.002	1.00 (0.99, 1.02)	0.45	1.02 (1.00, 1.03)	0.009
		BMI, kg/m^2	1.05 (1.03, 1.06)	< 0.001	1.07 (1.05, 1.09)	< 0.001	1.03 (1.02, 1.05)	< 0.001
		Physical activity (ref: Low)	1.11 (0.98, 1.25)	0.08	0.99 (0.81, 1.21)	0.94	1.18 (1.01, 1.37)	0.03
		Smoking status (ref: No)	0.90 (0.77, 1.06)	0.22	0.72 (0.30, 1.76)	0.48	0.91 (0.77, 1.07)	0.26
		Educational level	0.99 (0.86, 1.13)	0.90	1.09 (0.88, 1.36)	0.40	0.95 (0.79, 1.13)	0.56
		Family history of T2DM (ref: No)	1.19 (1.03, 1.36)	0.01	1.27 (1.01, 1.58)	0.03	1.13 (0.95, 1.35)	0.14
		HDL-C, mg/dl	1.01 (1.00, 1.01)	0.001	1.01 (1.00, 1.02)	0.002	1.01 (1.00, 1.01)	0.02
		TC, mg/dl	0.99 (0.99, 1.00)	0.01	0.99 (0.99, 1.00)	0.24	0.99 (0.99, 0.99)	0.01
		TG, mg/dl	1.00 (1.00, 1.00)	< 0.001	1.00 (1.00, 1.00)	< 0.001	1.00 (1.00, 1.00)	< 0.001

T2DM type 2 diabetes mellitus, *Pre-DM* pre-diabetes mellitus, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *HDL-C* high density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglyceride

(HR_{adj} (95% CI): 1.02 (0.92, 1.14); $P = 0.61$) in comparison to males with normal maternal menopausal age (Table 4).

Figure 2 illustrates the cumulative hazard plot for the occurrence of pre-DM event during follow-ups among all offspring, as well as stratified by sex (female and male). This figure indicates that offspring whose mothers experienced early menopausal age had a higher hazard of developing pre-DM compared to those with mothers who had

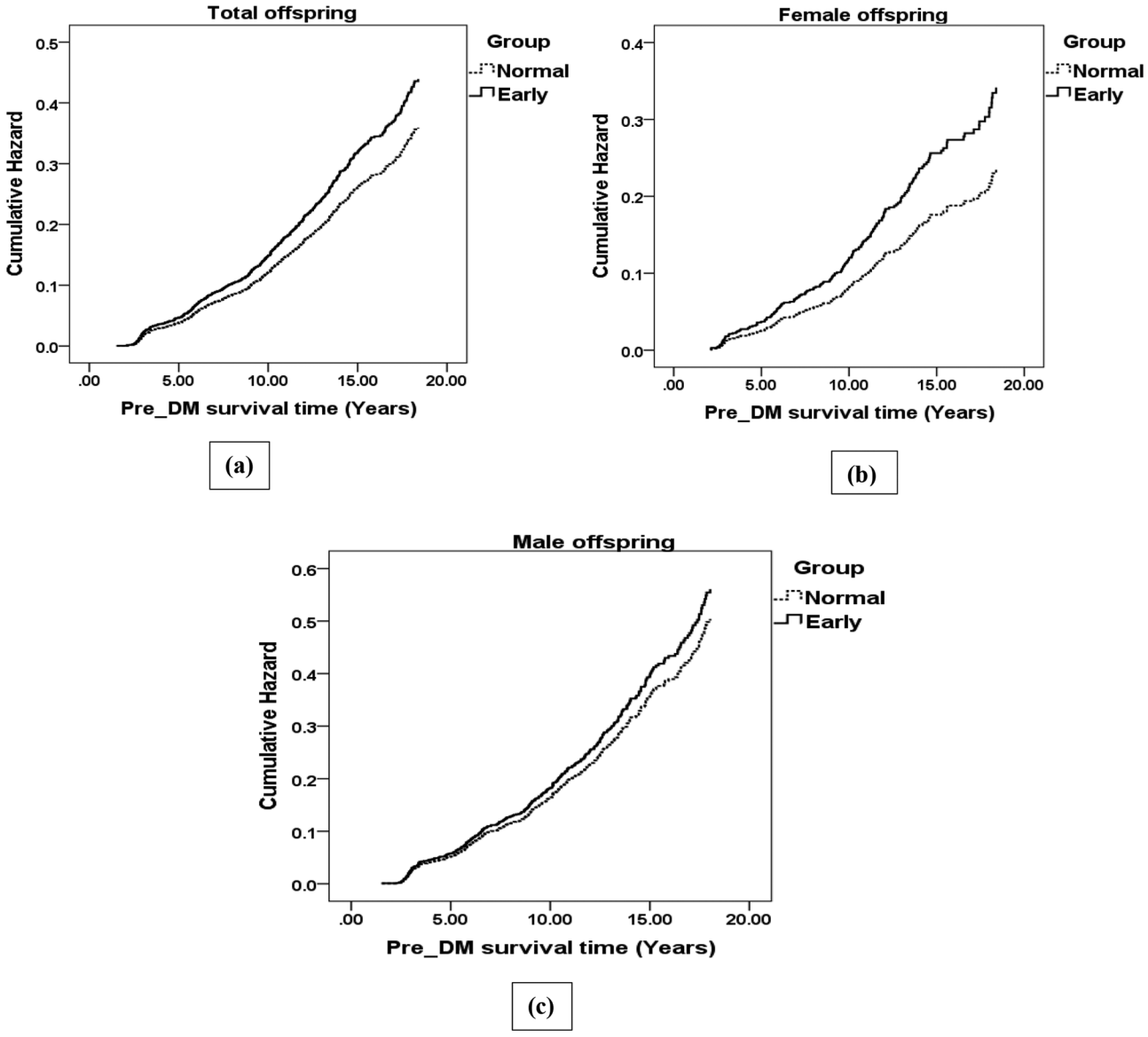

Fig. 2 (a-c) Cumulative hazard function plot. Hazard changes of pre-DM within survival time between groups (total offspring, female and male offspring with early maternal menopausal age vs. total offspring, female and male offspring with normal maternal menopausal age). Adjusted for age, BMI, physical activity, smoking status, educational level, family history of T2DM, HDL-C, TC, TG, and sex. Sex is not adjusted in adjusted models separated for females and males. (**a**): Total offspring, (**b**): Female offspring, and (**c**): Male offspring. *T2DM* type 2 diabetes mellitus, *Pre-DM* pre-diabetes mellitus, *BMI* body mass index, *HDL-C* high density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglyceride

normal menopausal age, both in the total offspring population and within sex-specific groups. Notably, this difference is more pronounced in female offspring. Conversely, while male offspring show a greater increase in pre-DM hazard over the follow-up period than females, this trend is consistent across both exposure groups (normal and early maternal menopausal ages (Fig. 2-c vs. 2-b); in male offspring (2-c); however it is significantly higher in female offspring with early maternal menopausal age than females with normal maternal menopausal age (Fig. 2-b).

We also evaluated the shape of relationship between continuous maternal menopausal age and risk of pre-DM by cubic spline regression model. As shown in Fig. 3, the curve generated using the cubic spline regression model demonstrated a higher risk of pre-DM in offspring with early maternal menopausal age compared to those with normal maternal menopausal age (Fig. 3). Additionally, the shapes of relationship between continuous maternal menopausal age and risks of T2DM and abnormal glucose tolerance in offspring are presented in supplementary file 1.

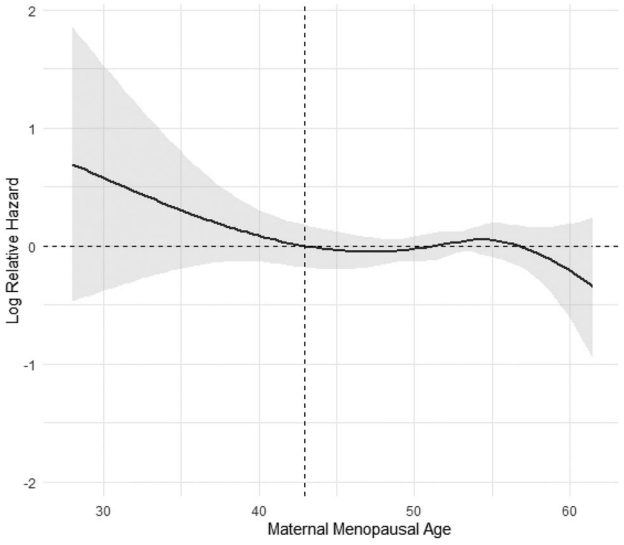

Fig. 3 Nonlinear relationship between maternal menopausal age and log relative hazard of pre-diabetes mellitus (pre-DM) in offspring by cubic spline regression model

Discussion

In this large, population-based study with over two decades of follow-up, it was demonstrated that the risk of pre-DM was statistically significantly higher among female offspring whose mothers experienced early menopausal age compared to those with mothers who had a normal menopausal age. Additionally, a higher risk (marginal significant) of abnormal glucose tolerance among female offspring with early maternal menopausal age in adjusted model was observed. However, no significant differences were observed in the risks of developing pre-DM and abnormal glucose tolerance in male offspring with early maternal menopausal age compared to males with normal maternal menopausal age in both unadjusted and adjusted models. This finding suggests that the influential effect of maternal menopausal age on the risks of pre-DM and abnormal glucose tolerance are varied by sex. Conversely, there were no significant differences in the risk of developing T2DM between offspring with mothers who had early menopausal age and those with mothers who had normal menopausal age, regardless of sex.

There is currently a lack of evidence to directly compare our findings with previous studies. While existing research has explored various aspects of maternal health and its impact on offspring outcomes in short- and long-term, no study have specifically addressed how maternal menopausal age can affect the risks of pre-DM, T2DM and abnormal glucose tolerance in offspring in long-term. This gap highlights the novel contribution of this study in investigating this particular association of early maternal menopausal age and the risk of glucose metabolism disorders in offspring.

In the current study, we observed an elevated risks of pre-DM and abnormal glucose tolerance among female offspring of women who experienced early menopause. This increased risk may be attributed to several factors, including genetic predispositions and adverse conditions during intrauterine development. Genetic factors may play a significant role in the transmission of metabolic vulnerabilities from mother to offspring, potentially influencing the offspring's susceptibility to pre-DM. Additionally, adverse intrauterine environments, which can be shaped by maternal health and hormonal profiles during pregnancy, may contribute to the developmental origins of metabolic disorders.

A worse cardiometabolic profile and increased risks of IR, diabetes, hypertension, weight gain, dyslipidemia and CVDs have been observed in women with poor ovarian reserve and early menopause compared to women with normal menopausal age [4–12, 27–29]. Genetic factors may play a role in the development of cardiometabolic disorders within families. It has been reported that individuals with a first-degree relative with a cardiometabolic disorder had a higher risk of the same disorder [3]. Familial aggregation of impaired fasting blood glucose, IR, T2DM, obesity, and MetS have been observed [30–37]. Based on accumulated evidences, some signaling pathways and their relevant genes including transforming growth factor-β (TGF-β/SMAD), PI3K/AKT, mTOR, and MAPKs, which involved in early menopausal age, are required for normal metabolism as well. Dysregulation in these pathways is implicated in the onset and progression of some human diseases, including metabolic disorders such as IR, diabetes, decreased insulin sensitivity, MetS, hypertension, dyslipidemia, obesity, and CVDs [15, 16, 38–41].

The prenatal environment is a crucial developmental period that has a profound impact on future metabolic and health outcomes. It is suggested that an unfavorable intrauterine environment through intrauterine growth retardation, small for gestational age, and epigenetic changes in genes involved in energy balance regulation, lipid metabolism, insulin signaling, proinflammatory factors, and pancreas islet beta cell's development may make individuals more susceptible to CVDs, metabolic (such as IR, obesity, MetS) and endocrine disorders in later life [42–47].

Cardiometabolic disorders such as MetS, T2DM, and hypertension exhibit sexual dimorphism in their development [48], which could be partially attributed to variations in hypothalamic neurocircuitry and the expression of androgen receptor (AR) in the hypothalamus. The hypothalamus a critical brain region plays a vital role in regulating energy and glucose homeostasis and it is influenced by testosterone, leading to differences in reproductive behavior and physiology between genders [49]. As

revealed in our present study and supported by previous studies, sex differences affect pre-DM conditions including impaired fasting glucose and impaired glucose tolerance. Notably, women have been found to have a higher prevalence of impaired glucose tolerance compared to men [20, 21, 50–52]. One study demonstrated that the prevalence of pre-DM decreases with age in males, while it increases in females [53]. This finding demonstrates a complex interplay between age and sex in the development of pre-DM conditions. In a cohort study, it was reported that girls had higher HOMA-IR than boys during the prepubertal ages [54]. Triglycerides are considered as a major risk factor for T2DM in women, although they are less influential in men [55, 56]. Our previous studies, along with a cohort study conducted by Huang and colleagues revealed that elevated maternal androgen levels were associated with a greater likelihood of MetS in adult offspring, with a pronounced effect observed in female offspring but not for male [57–59].

Sex hormones partially mediate the differences in metabolic status between sexes, including glucose homeostasis, insulin signaling, fat accumulation, and lipid metabolism [19]. In addition, sex differences in physiology between men and women may arise from differences in sex chromosomes. Genes expressed on the X chromosome can have a substantial effect on metabolic parameters. These genes contribute to various aspects, including body weight and adiposity [60–62]. Notably, excess abdominal adiposity and the elevated risks of IR and T2DM have been observed in men with Klinefelter syndrome, who possess two X chromosomes, therefore metabolic dysfunction is promoted by an additional X chromosome [63, 64]. Moreover, XX animals with 2 X chromosomes show increased fasting insulin levels, IR, elevated liver triglycerides, higher expression of fatty acid oxidation enzymes, and increased fat mass when exposed to a high-fat diet [60]. One study conducted on mice revealed extensive gene-by-sex regulation in IR [23]. Furthermore, the other study on mice revealed that XX mice fed by high fat/high carbohydrate produced higher concentration of insulin to maintain normal glucose levels in comparison to XY mice [60]. Some genes on the X chromosome could contribute to phenotypic differences between males and females, impacting metabolic outcomes [65].

There are several other mechanisms that could contribute to the observed sex differences in the development of chronic diseases. These may include Resistin functions as a pro-inflammatory molecule, and gut microbiota [66–70].

Strengths and limitations of the study

Our study has several notable strengths. To the best of our knowledge, our study is the first population-based prospective cohort study evaluated the risks of pre-DM, T2DM and abnormal glucose tolerance in female and male offspring with early maternal menopausal age versus those with normal maternal menopausal age, later in their life. The population-based design of this cohort study likely mitigates concerns regarding selection bias that are often associated with clinical based studies. In addition, our adjustment of the potential confounders produced valuable results. The inter observer and/or intra-assay variability for assessment of glucose concentration in our data is likely to be minimal because all assessments were done at the same laboratory. Moreover, as an ongoing study, it allows us to monitor the participants for further events. Conversely, our study also has several limitations that should be acknowledged. Notably, we did not assess lifestyle modifications, including dietary habits, which may significantly influence adverse cardiometabolic outcomes. The omission of these factors limits our ability to fully understand the interplay between lifestyle and metabolic health in the offspring of women with varying menopausal ages. Additionally, we did not evaluate the ovarian reserve status of mothers during their pregnancy. Understanding the ovarian reserve may help elucidate the biological mechanisms through which maternal health influences the risk of developing conditions such as pre-DM, T2DM and abnormal glucose tolerance in later life. Consequently, we did not incorporate the timing of offspring puberty onset into our primary analysis, as it was not available for male offspring and 20% of female offspring. However, we acknowledge the potential significance of puberty onset as a mediating factor and suggest that future studies with more comprehensive data on this variable could provide valuable insights into its role in the relationship between maternal menopausal age and glucose intolerance in offspring.

Future research should aim to incorporate these critical variables to enhance our understanding of the multifaceted relationships between maternal factors, lifestyle choices, and cardiometabolic health outcomes in offspring. Addressing these limitations will contribute to a more comprehensive understanding of the determinants of metabolic disorders across generations.

Conclusions

In conclusion, this pioneer study with a long-term follow-up showed that female offspring of women who experienced early menopause have an increased risk of developing pre-DM in their adult life compared to females with normal maternal menopausal age. As the precise pathophysiological links are not entirely understood and many aspects still require elucidation, an integrated description of the genetic, epigenetic, and environmental influences involved in the concomitant

development of diseases are still needed to shed new light on the interlinks between early maternal menopausal age and cardiometabolic disorders in offspring. Female offspring of women who experienced early menopause may benefit from early screening for glucose metabolism disorders. Given the established association between maternal menopausal age and the metabolic health of offspring, it is imperative to consider the potential intergenerational risk factors that may predispose these individuals to developing metabolic disorders. Early screening could facilitate the timely identification of at-risk individuals, allowing for the implementation of preventive measures and lifestyle modifications aimed at reducing the incidence of diabetes and its associated comorbidities.

Abbreviations

Pre-DM	Pre-diabetes mellitus
T2DM	Type 2 diabetes mellitus
HRs	Hazard ratios
CIs	Confidence intervals
TLGS	Tehran Lipid and Glucose Study
MetS	Metabolic syndrome
CHD	Coronary heart disease
IR	Insulin resistance
PI3K/Akt	Phosphatidylinositol 3-kinase/protein kinase B
mTOR	Mammalian target of rapamycin
MAPKs	Mitogen-activated protein kinases
CVDs	Cardiovascular diseases
BMI	Body mass index
FBS	Fasting blood sugar
HDL-C	High-density lipoprotein cholesterol
TG	Triglycerides
TC	Total cholesterol
APO B	Apolipoprotein B
CVs	Coefficient variations
OGTT	Oral glucose tolerance test
IQR	Inter-quartile range
AR	Androgen receptor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-025-01405-z.

Supplementary Material 1

Acknowledgements

This article is based on data obtained from the disease registry entitled 'Designing the Tehran Registry Program for Premature Ovarian Insufficiency (TRPPOI)' and the project approved by the ethics committee under code number IR.SBMU.ENDOCRINE.REC.1403.116. The project was supported by the Deputy of Research and Technology of Shahid Beheshti University of Medical Sciences (http://dregistry.sbmu.ac.ir).

Author contributions

M.N., F.RT., and F.A. contributed to the study conception and design.M.N., M. M. and F.R.T. material preparation, data collection and analysis. M.N., F. R.T., M.S.Gh. Naz., and M. F. involved in reviewing the manuscript and critical discussion. The first draft of the manuscript was written by Mahsa Noroozzadeh and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This study funded by the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Grant number: 1-43012543).

Data availability

All relevant data presented in this study are included in the article. Any other data that support the findings discussed here are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

This study was conducted in compliance with the principles outlined in the Declaration of Helsinki and received ethical approval from the institutional ethics review board of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran, under approval number IR.SBMU.ENDOCRINE.REC.1403.116. All participants were provided with comprehensive information regarding the study, and written informed consent was obtained from each participant.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 1 February 2025 / Accepted: 26 April 2025
Published online: 22 May 2025

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