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Longitudinal association of cumulative risk factors in early life, genetic risk, and healthy lifestyles during adulthood with the risk of type 2 diabetes

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Abstract

Background The combined influence of early life risk factors on the type 2 diabetes (T2D) development is not well-studied, and it is unclear whether these associations can by modified by genetic risk and healthy lifestyles in later life.

Methods We studied 148,621 participants in the UK Biobank. We calculated early-life risk scores (ERS) by summing the cumulative number of three early-life risk factors: low birth weight, maternal smoking during pregnancy, and non-breastfed as a baby. We estimated polygenic risk scores (PRS) for T2D and calculated participants' modifiable healthy lifestyle score (MHS) during adulthood.

Results A total of 7,408 incident T2D were identified. ERS showed a positive dose-response association with T2D risk. Compared with participants with 0 ERS, those with 3 ERS had the highest risk of developing T2D (hazard ratio [HR]: 1.93; 95% confidence interval [CI]: 1.65, 2.26). This association was not modified by T2D-PRS or MHS. In the joint exposure analyses, compared with participants with the lowest risk exposure (i.e., lowest ERS combined with lowest T2D-PRS/healthy lifestyle in later life), we observed highest risk of T2D among individuals with the highest ERS combined with the highest tertile of T2D-PRS (HR = 6.67, 95% CI: 5.43, 8.20) or an unhealthy lifestyle in later life (HR = 4.99, 95% CI: 3.54, 7.02), respectively.

Conclusions Early-life risk factors are associated with a higher risk of T2D in a dose-response manner, regardless of genetic risk or later-life healthy lifestyle. Therefore, identifying early-life modifiable risk factors is helpful to develop strategies of T2D prevention.

Keywords Type 2 Diabetes, Early Childhood Risk Factors, Genetic Predisposition, Healthy Lifestyle, Dose Response

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Background

The global prevalence of diabetes has risen rapidly during the last few decades, with an estimated 828 million diabetes patients in 2022 worldwide [1]. Type 2 diabetes (T2D) accounts for about 90% of all diabetes cases and imposes a significant burden due to its high mortality, disability, and poor quality of life [2]. The theory of "Developmental Origins of Health and Disease" (DOHaD) suggests that adverse experiences during early-life, including prenatal and early postnatal periods, may program an individual's metabolic development, and further lead to T2D in adulthood [3, 4]. Identifying the role of early-life risk factors, particularly those that are modifiable, will thus provide valuable insights for developing intervention strategies to prevent T2D from an early age.

Prior studies have linked early-life risk factors, such as low birth weight [5], lack of breastfeeding [6, 7], and maternal smoking during pregnancy [8], with an increased T2D risk in adulthood. However, the combined association of these early-life risk factors with the development of T2D remains less studied [9]. A combined approach reflects real-life behavioral patterns more accurately and may have a greater public health impact. Changing early-life experiences is usually difficult before individuals fully develop the capacity for independent behavior. In contrast, adherence to healthy lifestyles in later life is associated with lower risk of T2D [10, 11]. In 2022, the American Heart Association (AHA) introduced the Life's Essential 8 (LE8) [12] construct for optimal cardiovascular health, which includes 4 modifiable behavioral metrics (diet, physical activity, nicotine exposure, and sleep health) and allows generation of a composite score to evaluate cardiovascular and metabolic related healthy lifestyles [13]. However, it remains unclear whether these later-life behaviors can modify the association between early-life risk factors and T2D development.

Furthermore, the association between the early-life risk factors with T2D risk may be influenced by individual's genetic predisposition to T2D [14–16]. To our knowledge, no previous study has examined the interplay between cumulative early-life risk factors and genetic predispositions and their combined association with development of later-life T2D.

In the present study, we aimed to 1) assess the association of cumulative risk factors in early-life with development of T2D; 2) and further examine whether this association could be modified by genetic risk or later-life healthy lifestyles. We hypothesized that there is a dose-response association between cumulative early-life risk factors and later-life T2D risk, and the associations may be modified by genetic risk or later-life healthy lifestyles.

Methods

Study population

The UK Biobank is a large population-based multicenter prospective cohort study in the United Kingdom [17]. From 2006 to 2010, more than 0.5 million participants aged 40–69 years, registered with the UK National Health Service and lived less than 25 miles with 1 of the 22 research assessment centers across the UK were enrolled. Researchers interviewed participants at the enrollment visit and collected their information through questionnaires, health records, anthropometry, and biological samples, and further followed up to obtain their health-related outcomes. Further details of the UK Biobank study design and population have been reported previously [18]. The study has been approved by the North West Multicenter Research Ethical Committee (REC reference for UK Biobank 21/NW/0157), and all participants provided written informed consent. This study was conducted as part of UK Biobank Project Number 173828.

Of 502,389 participants at enrollment, we excluded participants who were multiple births (n=12,120), had diabetes other than T2D at enrollment (n=22,458), were lost to follow up (n=1,223), had a mismatch between genetic sex and self-reported gender (n=322), leaving a total of 466,266 participants. We further excluded participants who did not have information on early-life risk factors (n=255,667), or had missing data on the polygenic risk scores (PRS) for T2D (n=6,248), or healthy-lifestyle factors during adulthood (n=55,730), leaving 148,621 participants in the final analysis (See Additional file 2: Figure S1).

Exposures assessment

Early-life risk factors

In this study, we selected three early-life modifiable factors (birth weight, maternal smoking around birth, and breastfeeding) that have each been reported in prior UK Biobank studies to be associated with T2D development [6–8, 19]. At the enrollment visit, participants reported information on the early-life factors using touchscreen questionnaires. Participants reported information on maternal smoking status during pregnancy and breastfeeding status with the following questions: "Did your mother smoke regularly around the time when you were born?" and "Were you breastfed when you were a baby?". We defined the risk factors as "yes" for maternal smoking and "no" for breastfeeding. Participants were asked to enter their birth weight in kilograms. We defined low birth weight as a risk factor (<2.5 kg), with birth weight ≥2.5 kg serving as the reference group. We combined normal and high birth weight as the reference group because a previous meta-analysis study had illustrated an

"L-shape" relation between birth weight and T2D risk [5], and in UK Biobank participants, high birth weight was associated with a lower risk of T2D [19]. We developed an early-life risk factor score (ERS) by calculating the cumulative number of the risk factors for each individual. The ERS ranges from 0 to 3, with a higher score representing more disadvantaged experiences. In addition, we further constructed weighted early-life risk factors, using the equation: ($\beta_1 \times$ factor 1 + $\beta_2 \times$ factor 2 + $\beta_3 \times$ factor 3) × (3/sum of the β coefficients). Here, β_1, β_2, and β_3 denoted the estimates of β coefficients for breastfeeding, maternal smoking around birth, and birth weight, respectively.

Modifiable Healthy Lifestyle Factors during Adulthood

In the current study, four modifiable behavioral lifestyle factors were selected according to the AHA's LE8 construct to compute a modifiable healthy lifestyle score (MHS) during adulthood for each participant. The four lifestyle factors include diet, physical activity, nicotine exposure, and sleep health. The lifestyle information was obtained from the UK Biobank questionnaires at the enrollment visit. The detailed scoring process of the four components was provided in Additional file 1: Table S1-S2. In brief, each lifestyle metric was given a score between 0 and 100, with a higher score indicating a healthier lifestyle. We divided the healthy lifestyle scores into 3 categories based on AHA's guidelines: healthy (80–100), moderate (50–79), and unhealthy (0–49) [13].

Assessment of T2D and T2D Polygenic risk scores

We identified T2D individuals with both prevalent T2D at baseline and new incident T2D during the follow up. Participants' prevalent T2D at baseline was determined through the hospitalization records, death registration, self-reported medical history and medication use, blood glucose (random glucose ≥11.1 mmol/L), and glycated hemoglobin (≥6.5%). Incident T2D was determined by hospital inpatient records from the Hospital Episode Statistics for England, Scottish Morbidity Record data for Scotland, and the Patient Episode Database for Wales and was identified based on International Classification of Diseases, Tenth Revision (ICD-10) codes (E11) [20]. And all participants enrolled in the UK Biobank study were followed up. We tracked the incidence of newly diagnosed T2D among participants who were free of T2D at baseline during the follow-up period. Additionally, the UK Biobank provided detailed records on participants' use of diabetes medications, mortality data, and the endpoint of follow-up (September 30, 2021, for centers in England; February 28, 2018, for centers in Wales; and July 31, 2021, for centers in Scotland). We did not exclude individuals with T2D at baseline because T2D is most likely to happen after early-life experiences; thus, excluding these participants may underestimate the association between ERS and the risk of T2D.

A standard polygenic risk score (PRS) for type 2 diabetes (T2D-PRS) (UK Biobank Data-Field 26285) has been utilized as a metric to quantify genetic predisposition for T2D. This standard PRS was derived by conducting a meta-analysis across multiple external Genome-Wide Association Study (GWAS) datasets and applying it uniformly to all participants within the UK Biobank. Detailed information regarding access to these PRS data and GWAS resources can be found in an earlier study [21]. Individualized PRS values were calculated by summing the posterior effect size of each variant weighted by its allele dosage across the entire genome. The standard T2D-PRS has been utilized in previous UK Biobank studies [22, 23], and has demonstrated a significantly improved predictive performance than other PRS models [24]. For analytical purposes, individuals were categorized based on their T2D-PRS scores into three PRS groups: low risk (tertile 1), medium risk (tertile 2), and high risk (tertile 3). Higher tertiles correspond to greater genetic risk of developing type 2 diabetes.

Covariates

We considered following sociodemographic, biological and behavioral characteristics as covariates based on directed acyclic graphs, including age (continuous in years), sex (male; female), ethnicity (White; Asian; Black; Mixed/other), educational attainment, household income (<18,000; 18,000-30,999; 31,000-51,999; >52,000 £/year), Townsend deprivation index (TDI), a measure of neighborhood-level deprivation (continuous), region (England; Scotland; Wales), alcohol drinking status (never; former; current), year of birth (1934-1940; 1941-1950; 1951-1960; 1961-1970), family history of diabetes (yes; no), and body mass index (<25; 25 to <30; ≥30 kg/m^2), the amount of smoking (never; former; current), the amount of drinking (three or four times a week and more; once a month to twice a week; special occasions only; never). Education attainment was classified into three categories: high (College or University degree), medium (A levels/AS levels or equivalent, NVQ, HND, HNC, or equivalent, and other professional qualifications), and low (CSEs or equivalent, O levels/GCSEs or equivalent, or none of the above). Genetic ancestry, indicating genetic similarities indicating the geographic origins of common ancestors, was classified into two categories: European and non-European.

Statistical analysis

Baseline characteristics of participants were described as numbers (proportions) for categorical variables and

mean (± standard deviation [SD]) for continuous variables, according to ERS categories, T2D-PRS tertiles, MHS categories, and T2D status. Differences in characteristics were compared using Chi-square test for categorical variables and ANOVA for continuous variables.

Cox proportional hazards regression models were fitted to examine the associations of ERS with the risk of T2D, accounting for left, right, and interval censoring, with ERS as a categorical variable and using individuals with 0 early-life risk factors as the reference group. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed. Linear trends were tested by treating the ERS as a continuous variable. Participants' age was selected as the time scale, with follow-up time calculated from birth until time of T2D event, or age at enrollment (those with prevalent T2D at baseline but without diagnostic age), or right censored. We conducted following models: Model 1: an unadjusted model; Model 2: adjusted for sex; Model 3: further adjusted for age, TDI, birth year, ethnicity, household income, educational attainment, and region based on Model 2; Model 4: further adjusted for family history of diabetes based on Model 3. To examine whether the association were modified by the genetic risk or adulthood lifestyles, we conducted stratified analyses, according to participants' T2D-PRS level (tertile 1; tertile 2; tertile 3) and MHS level (unhealthy; moderate; healthy), respectively. To test the interactions between early-life risk factors and T2D-PRS, and MHS, cross-product of the two terms (e.g., early-life risk factors and PRS) were included in the fully adjusted Cox model. In joint analyses, we used individuals with 0 early-life risk factor combined with low tertile of T2D-PRS or healthy adulthood lifestyle as the referent, respectively.

Seven sensitivity analyses were performed to test the robustness of the association between ERS and T2D risk: 1) we assessed the association between weighted ERS and the risk of T2D; 2) we explored the association between ERS, PRS, MHS and T2D, the association between ERS and PRS on T2D, and the association between ERS and MHS on T2D stratified by sex; 3)we further adjusted for BMI, the amount of drinking, the amount of smoking, and genetic ancestry; 4) we explored the associations between ERS and T2D risk without considering left-censoring by excluding participants with prevalent T2D at baseline; 5) when examining the effect of low birth weight, we used individuals with normal birth weight (2.5-4 kg) as the reference instead of the combination of normal and high birth weight (≥2.5 kg), to exclude the potential effect of high birthweight; 6) we excluded participants who died without T2D in follow-up; 7) we examined the 8 combinations of the three early-life factors with T2D risk.

All analyses were performed using SAS version 9.4. All values were two-sided and a $P < 0.05$ was considered statistically significant.

Results

Characteristics of participants

The mean age of participants at study enrollment was 55.4 years (SD: 8.1; range: 40.2–72.0). The number of left-censored, interval-censored, and right-censored individuals were 3,368, 4,040, and 141,213, respectively. A total of 7,408 T2D events were identified at baseline (*N*=3,368) or during the year of follow up of a median of 12.5 years (*N*=4,040) and the median age at T2D event was 64.7 years (range: 24.5–83.8). The prevalence of T2D in our study in 4.98%, with higher prevalence of T2D in males (6.11%) than females (4.25%), which was similar in the general population in UK [25]. The baseline characteristics of the 148,621 participants by ERS categorizes are presented in Table 1. Compared with participants with lower ERS, those with higher ERS tended to be younger, more likely to be male, White, had lower household income, higher TDI, lower qualification of education, tended to live in Scotland and Wales, be born in 1961-1970, had higher levels of BMI and T2D-PRS, and more likely to have a family history of diabetes. The characteristics of participants stratified by T2D-PRS, MHS, and T2D categorizes are presented in Additional file 1: Table S3-S5, respectively. The characteristics of participants who were included and excluded were shown in Additional file 1: Table S6. The included participants were younger, more likely to be females and White, had higher household income, lower TDI and higher education attainment, and they were also more likely to be current drinkers, had less family history of diabetes and lower BMI.

ERS and T2D risk

Table 2 presents the association between ERS and the risk of T2D. In the unadjusted model, ERS was positively associated with risk of T2D in a dose-response manner (P for trend < 0.001). Compared to participants with no early-life risk factors, those who had 1-3 risk factors had a 14% (HR: 1.14; 95% CI:1.08, 1.20), 25% (HR: 1.25; 95% CI:1.16, 1.34), and 85% (HR: 1.85; 95% CI:1.58, 2.16) increased risk of T2D, respectively. Further adjustments for sex, age, TDI, birth year, ethnicity, household income, education, assessment regions, and family history of diabetes did not alter this positive association. In the fully-adjusted model, individuals with 1–3 early-life risk factors had a 16% (HR: 1.16; 95% CI:1.10, 1.22), 26% (HR: 1.26; 95% CI:1.17, 1.36), and 93% (HR: 1.93; 95% CI:1.65, 2.26) higher risk of T2D, compared with individuals who had no early-life risk factors.

Table 1 Characteristics of participants of UK Biobank according to early-life risk score

Characteristics	Early-life risk score (*n*=148,621)				*P*-Value
	0 (*n*=72,306)	1 (*n*=55,572)	2 (*n*=18,593)	3 (*n*=2,150)	
Age, years	55.2±8.0	53.9±8.1	52.7±7.9	53.0±7.8	<0.001
Sex					<0.001
Male	29,475 (40.76)	21,807 (39.24)	6,686 (35.96)	574 (26.70)	
Female	42,831 (59.24)	33,765 (60.76)	11,907 (64.04)	1,576 (73.30)	
Ethnicity					<0.001
White	69,323 (95.87)	54,438 (97.96)	18,328 (98.57)	2,128 (98.98)	
Asian	1,218 (1.68)	447 (0.80)	62 (0.33)	1 (0.05)	
Black	929 (1.28)	169 (0.30)	29 (0.16)	2 (0.09)	
Mixed/other	836 (1.16)	518 (0.93)	174 (0.94)	19 (0.88)	
Household income, GBP (£)					<0.001
<18,000	11,457 (15.85)	8,862 (15.95)	3,176 (17.08)	430 (20.00)	
18,000–30,999	17,505 (24.21)	13,514 (24.32)	4,505 (24.23)	557 (25.91)	
31,000–51,999	20,990 (29.03)	16,571 (29.82)	5,650 (30.39)	640 (29.77)	
52,000–100,000	17,391 (24.05)	13,088 (23.55)	4,268 (22.95)	447 (20.79)	
≥100,000	4,963 (6.86)	3,537 (6.36)	994 (5.35)	76 (3.53)	
TDI	−1.73±2.84	−1.57±2.92	−1.30±3.06	−1.08±3.20	<0.001
Education					<0.001
Low qualification	25,428 (35.17)	21,745 (39.13)	7,720 (41.52)	940 (43.72)	
Medium qualification	36,937 (51.08)	27,282 (49.09)	8,991 (48.36)	1,014 (47.16)	
High qualification	9,941 (13.75)	6,545 (11.78)	1,882 (10.12)	196 (9.12)	
Region					<0.001
England	64,029 (88.55)	48,242 (86.81)	15,925 (85.65)	1,806 (84.00)	
Scotland	3,889 (5.38)	3,283 (5.91)	1,146 (6.16)	138 (6.42)	
Wales	4,388 (6.07)	4,047 (7.28)	1,522 (8.19)	206 (9.58)	
Birth year					<0.001
1934–1940,	3,622 (5.01)	1,999 (3.60)	452 (2.43)	63 (2.93)	
1941–1950	27,174 (37.58)	18,599 (33.47)	5,274 (28.37)	598 (27.81)	
1951–1960	25,934 (35.87)	19,892 (35.80)	6,900 (37.11)	844 (39.26)	
1961–1970	15,576 (21.54)	15,082 (27.14)	5,967 (32.09)	645 (30.00)	
Drinking					0.047
Current	67,455 (93.29)	52,045 (93.65)	17,432 (93.76)	1,980 (92.09)	
Ex-drinker	2,029 (2.81)	1,740 (3.13)	621 (3.34)	90 (4.19)	
Non-drinker	2,822 (3.90)	1,787 (3.22)	540 (2.90)	80 (3.72)	
Family diabetes					0.020
No	57,265 (79.20)	43,916 (79.03)	14,531 (78.15)	1,711 (79.58)	
Yes	15,041 (20.80)	11,656 (20.97)	4,062 (21.85)	439 (20.42)	
BMI, kg/m^2					<0.001
<25	27,709 (38.32)	19,809 (35.65)	6,203 (33.36)	679 (31.58)	
25–30	30,171 (41.73)	23,076 (41.52)	7,661 (41.20)	871 (40.51)	
≥30	14,426 (19.95)	12,687 (22.83)	4,729 (25.43)	600 (27.91)	
PRS for T2D					<0.001
Tertile 1	24506 (33.89)	18366 (33.05)	5835 (31.38)	636 (29.58)	
Tertile 2	24054 (33.27)	18330 (32.98)	6239 (33.56)	718 (33.40)	
Tertile 3	23746 (32.84)	18876 (33.97)	6519 (35.06)	796 (37.02)	
MHS					<0.001
Unhealthy (0–49)	4,136 (5.72)	4,024 (7.24)	1,603 (8.62)	206 (9.58)	
Moderate (50–79)	33,433 (46.24)	26,528 (47.74)	9,074 (48.80)	1,022 (47.53)	
Healthy (80–100)	34,737 (48.04)	25,020 (45.02)	7,916 (42.58)	922 (42.88)	

Abbreviation: *GBP* Great Britain Pound, *TDI* Townsend Deprivation Index, *BMI* Body mass index, *PRS* Polygenic risk score, *T2D* Type 2 diabetes, *MHS* Modifiable healthy lifestyle score

Table 2 The associations of early-life risk score with T2D in adulthood

T2D	Early-life risk score, HR (95% CI)				*P*-trend
	0	1	2	3	
Model 1	Ref (1.0)	1.14 (1.08, 1.20)	1.25 (1.16, 1.34)	1.85 (1.58, 2.16)	<0.001
Model 2	Ref (1.0)	1.15 (1.09, 1.21)	1.28 (1.19, 1.37)	1.97 (1.68, 2.30)	<0.001
Model 3	Ref (1.0)	1.15 (1.10, 1.21)	1.26 (1.17, 1.36)	1.90 (1.63, 2.22)	<0.001
Model 4	Ref (1.0)	1.16 (1.10, 1.22)	1.26 (1.17, 1.36)	1.93 (1.65, 2.26)	<0.001

Abbreviation: *HR* Hazard ratio, *CI* Confidence interval, *T2D* Type 2 diabetes. Model 1: crude model; Model 2: adjusted for sex; Model 3: adjusted for Model 2+age, Townsend Deprivation Index, birth year, ethnicity, household income, education, region; Model 4: Model 3+family history of diabetes

ERS, T2D-PRS and T2D risk

As presented in Additional file 1: Table S7, higher T2D-PRS was associated with higher T2D risk (Tertile 3 vs. Tertile 1: HR: 3.28; 95% CI: 3.07, 3.50). Although ERS was only positively associated with T2D risk in those with low (tertile 1) and high levels (tertile 3) of T2D-PRS (See Additional file 2: Figure S2), we observed no significant interaction between ERS and T2D-PRS on the risk of T2D (*P* for interaction = 0.360). In the joint exposure analysis, we observed consistently positive monotonic increases in the risk of T2D with increasing number of early-life risk factors among all PRS levels in the fully adjusted model, with the highest risk was observed among individuals exposed to highest number of early-life risk factors (ERS=3) and high T2D-PRS (tertile 3) (HR =6.67, 95% CI:5.43, 8.20), compared with individuals with no early-life risk factors (ERS=0) and low T2D-PRS (tertile 1) (Figure 1).

ERS, MHS and T2D risk

As shown in Additional file 1: Table S8, participants with higher MHS were at a lower risk of T2D. Participants with healthy lifestyle during adulthood had a 53% (HR: 0.47; 95% CI:0.44, 0.51) reduction in T2D risk, compared to those with an unhealthy lifestyle. In the stratified analysis, we observed ERS was associated with increased risk of T2D risk among all MHS levels (See Additional file 2: Figure S3). No significant interaction between ERS and MHS was observed (*P* for interaction = 0.113). In the joint analysis, we observed similar trends, with the highest risk was observed among individuals with the highest number of early-life risk factors (ERS=3) and unhealthy lifestyle during adulthood (HR: 4.99; 95% CI:3.54, 7.02), compared with their counterparts (Figure 2).

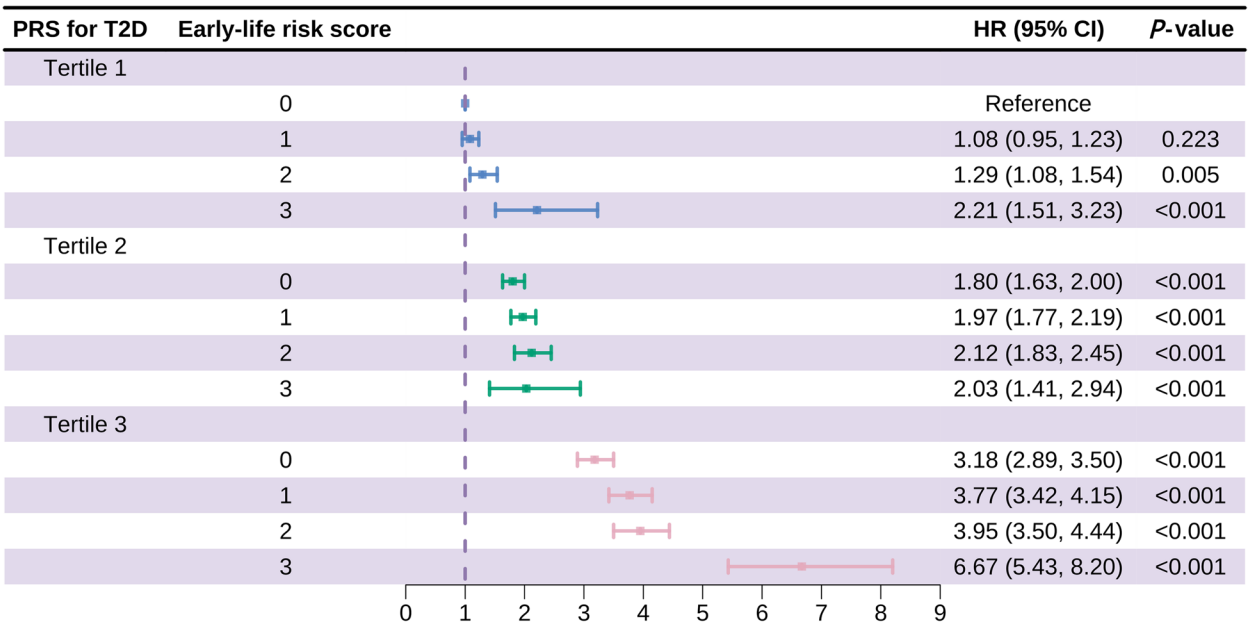

Fig. 1 Combined association of early-life risk score and PRS with T2D risk in adulthood. Abbreviation: T2D, Type 2 diabetes; PRS, Polygenic risk score; HR, Hazard ratio; CI, Confidence interval. Models were adjusted for sex, age, Townsend Deprivation Index, birth year, ethnicity, household income, education, region, and family history of diabetes

Secondary results

We found higher weighted ERS was associated with higher T2D risk in adulthood in Additional file 1: Table S9 [Tertile 3 (T3) vs. Tertile 1 (T1), HR (95% CI): 1.29 (1.23, 1.36)]. We did not observe significant sex differences in all sex-stratified analyses in Additional file 1: Table S10 to S12, and Additional file 2: Figure S4 to S5. Further adjustment for the amount of smoking and drinking showed substantial attenuation in HRs (See Additional file 1: Table S13). After adjusting for BMI (See Additional file 1: Table S13), genetic ancestry (See Additional file 1: Table S14) or limiting analysis to participants with new incident T2D during the follow up (See Additional file 1: Table S15) did not change the results. Similar attenuated associations were observed when using normal birth weight (2.5-4.0 kg) instead normal/high birth weight combination (≥2.5 kg) as reference (See Additional file 1: Table S16). The positive associations between ERS and T2D risk could be still observed when excluding participants who died without T2D in follow-up (See Additional file 1: Table S17). For the specific combinations of the three early-life risk factors, all six combinations, except for having only non-breastfeeding, showed an increased risk of T2D, compared to having none of the three risk factors (See Additional file 1: Table S18).

Discussion

In this large population-based cohort study, we observed a dose-response association between higher ERS and an increased risk of T2D in later life. Moreover, this association remains consistent across major subgroups and sensitivity analyses, and was not significantly modified by genetic risk and later-life healthy lifestyles.

Developments in the life course epidemiology of T2D offer new perspectives for primordial prevention strategies, especially for early-life period [26]. Previous studies have reported that individual early-life risk factors, including low birth weight [19], non-breastfed [6, 7], and maternal smoking around birth [8, 14], were associated with higher risks of T2D. Our study addressed the knowledge gap of the existing literature by demonstrating a dose-response association between cumulative exposure to these early-life risk factors and lifelong T2D risk. We noted that additional adjustment for amount of smoking or drinking led to substantial attenuation of the association between ERS and T2D. One possible reason could be the clustering of unhealthy lifestyles within families, and the offspring of mothers who have unhealthy lifestyles (e.g. smoking) during pregnancy are more likely to smoke and drink themselves, thus have higher risk of T2D. A previous study has reported high birth weight was associated with a lower risk of T2D in UK Biobank participants [19], which may explain the attenuation when we used the participants with normal birth weight (2.5-4.0 kg) as the reference instead of participants with normal to high birth weight combination (≥2.5 kg) as the reference group. From a mechanistic perspective, intrauterine metabolic development reprogramming and abnormal intestinal flora colonization might potentially account for this association. Meanwhile, it is undeniable that early-life risk factors were also a reflection and microcosm of the household health literacy, which could influence the

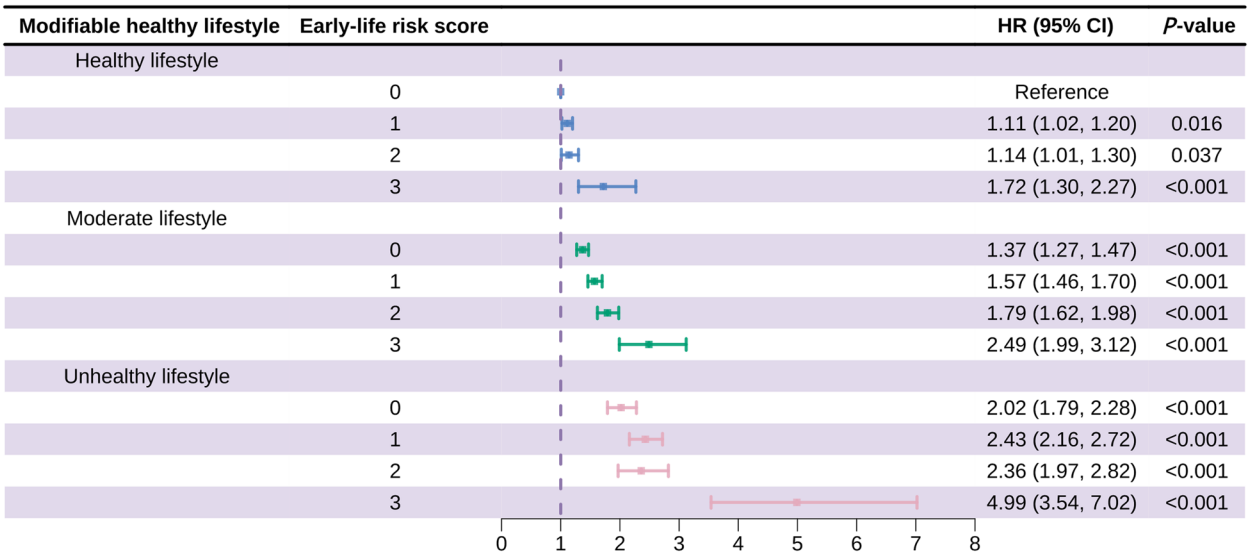

Fig. 2 Combined association of early-life risk score and modifiable healthy lifestyle with T2D risk in adulthood. Abbreviation: T2D, Type 2 diabetes; HR, Hazard ratio; CI, Confidence interval. Models were adjusted for sex, age, Townsend Deprivation Index, birth year, ethnicity, household income, education, region, and family history of diabetes

development of T2D. And unhealthy lifestyles tend to cluster within families. Previous studies have reported that early-life risk factors in the first 1,000 days of life were cumulatively associated with T2D risk factors of obesity and metabolic risk during childhood and adolescence [27, 28]. Recent studies based on UK Biobank reported that individuals exposed to both maternal smoking and non-breastfed were at higher risks of adult-onset T2D [9] and hypertension [29], compared with those exposed to isolated risk factor. Taken together, our findings support the "accumulation of risk" hypothesis in life course epidemiology, which suggests that metabolic system damage increases with the accumulation of various exposures over a lifetime [26]. Thus, targeting multiple T2D-related risk factors early in the life course may represent a more effective intervention strategy to prevent T2D.

Apart from early-life risk factors, adulthood lifestyle, as a modifiable risk factor, could not be ignored. Previous studies have demonstrated the association between genetic risk and adulthood lifestyle with T2D in observational [30–32] and intervention studies [33]. Generally, adherence to a healthy lifestyle could significantly attenuate the association between PRS and T2D incidence, regardless of genetic risk. One possible reason is that genome-wide arrays can only reveal less than 20% of the T2D risk [34]. Moreover, customizing pathway-specific PRS is of great significance for identifying high risk populations [35]. It should be acknowledged that adulthood lifestyle management is a crucial part of T2D prevention. To our knowledge, epidemiological evidence regarding the modification effects of later-life lifestyles on the association between early-life risk factors and T2D risk remains scarce. Our study found no significant interaction, but combined effect between healthy lifestyles, as defined by the LE8 construct, in later life and early-life risk factors on T2D risk. In our study, we additionally noted that ERS and MHS are independently associated with T2D. Therefore, we speculated that early-life exposures may be irreversible or partially reversible in terms of fetal organ development and metabolic reprogramming, and thus are not modified by adulthood lifestyles. However, a previous study reported that adopting a healthy diet or a lower inflammation diet in adulthood might reduce the T2D risk associated with maternal smoking around birth [9]. This non-significant interaction could be plausibly explained by the limited lifestyle factors selected and the different methods used to calculate MHS. In addition, considering the co-exposure of multiple risk factors may likely reflect the real-world situation (i.e., mothers who smoke during pregnancy are more likely to give birth to lower birth weight infants and are also less likely to breastfeed). From a public health perspective, identifying stage-specific risk factors is crucial to develop strategies for the prevention of T2D across the life course, such as avoiding maternal smoking during pregnancy and promoting breastfeeding. Although, intervention study of T2D from early-life was limited, the evidence that nutrition or feeding interventions in the first two years of life can have a positive impact on a child's BMI, might provide a template for T2D. However, long-term follow-up make intervention studies for T2D more difficult. Even with adequate study designs and analyses, deciding what, when, and how to intervene is also a challenge. Therefore, more rigorous, large-scale early-life interventional studies are needed to confirm these findings. In addition, we observed no significant interaction between T2D-PRS and early-life risk factors. Consistent with our results, Ye et al. reported that early-life tobacco exposure was associated with an increased risk of T2D later in life regardless of genetic background [14]. This finding highlights that individuals can benefit from the prevention of multiple early-life modifiable risk factors, regardless of their genetic predisposition to T2D.

Strengthens and limitations

Main strengths of our study included a large sample size and a population-based prospective study design with multiple early-life exposure information, which allowed us to examine the role of cumulative early-life risk factors in the development of T2D. In addition, we were able to examine the joint and the modifying influence of genetic predisposition and later-life lifestyles on the association, leveraging the cohort's genetic and comprehensive later-life lifestyle data. The present study, however, has several limitations. First, the study participants were primarily identified as White, limiting the generalizability of our findings to other populations. Second, the several characteristic differences between include and excluded participants were observed in our study, which may lead to selection biases. Third, the UK Biobank collected information on only three early-life risk factors, and hence, we were unable to examine the role of other important early-life factors, such as maternal pre-pregnancy weight status and excessive gestational weight gain, which have been previously reported to be associated with offspring metabolic dysfunction [36]. Fourth, multiple early-life factors determined the risk of T2D, which is one major challenge in deciphering early-life factor interactions in T2D. However, we observed similar trends when using the weighted ERS in the sensitivity analyses, which demonstrated the robustness of the main findings. Fifth, the early-life risk factors were collected based on self-reported questionnaire, potentially leading to recall-bias. However, we do not think that this bias would be differential between individuals who

did or did not develop T2D. Finally, we did not include molecular data, mortality or the cardiovascular diseases related to T2D in the present study, of which we believe will make the study more complex. Further studies are needed to examine the role of predictive biomarkers and constructed transition stages of T2D development and further calculated related mortality.

Conclusions

In conclusion, in this large perspective cohort study, we observed cumulative early-life risk factors were associated with a higher risk of T2D during adulthood in a dose-repose manner, regardless of genetic risk and healthy lifestyles in later life. These results underscore the importance of effective intervention strategies in early life for the prevention of T2D across life-course.

Abbreviations

T2D	Type 2 diabetes
ERS	Early-life risk scores
PRS	Polygenic risk scores
MHS	Modifiable healthy lifestyle score
HR	Hazard ratio
CI	Confidence interval
DOHaD	Developmental Origins of Health and Disease
AHA	American Heart Association
LE8	Life's Essential 8
GBP	Great Britain Pound
TDI	Townsend Deprivation Index
BMI	Body mass index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04025-x.

Additional file 1: Table S1-S18. Table S1. Healthy Diet Score using touchscreen questionnaire in the UK biobank study. Table S2. Quantitative Assessment of the 4 modifiable behavioral factors in Life's Essential 8. Table S3. Characteristics of participants of UK Biobank according to PRS for T2D. Table S4. Characteristics of participants in UK Biobank according to modifiable healthy lifestyles score. Table S5. Characteristics of participants in UK Biobank according to T2D. Table S6. Characteristics between excluded and included participants. Table S7-S9: Associations of PRS, lifestyle score, and early-life risk score with T2D. Table S10-S12: Sex-stratified associations of early-life risk score, PRS, and lifestyle with T2D. Table S13-S15: Sensitivity analyses for early-life risk score and T2D associations. Table S16. The associations of early life risk scores with the new incident T2D during the follow up. Table S17. The associations of early-life risk score with T2D in adulthood, excluding participants who died without T2D in follow-up. Table S18. The association of individual early-life risk factor combinations with T2D risk

Additional file 2: Figure S1-S5. Figure S1. Flow chart. Figure S2. Association of early-life risk score with T2D risk in adulthood, stratified by PRS for T2D. Figure S3. Association of early-life risk score with T2D, stratified by modifiable healthy lifestyle in adulthood. Figure S4. Combined association of early-life risk score and PRS with T2D risk in adulthood, stratified by sex. Figure S5. Combined association of early-life risk score and modifiable healthy lifestyle with T2D risk in adulthood, stratified by sex

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Authors' Twitter handles

Not applicable.

Authors' contributions

JH, IA and YX conceptualized this study, developed the analysis plans and defined the key study variables. JH and HY contributed to curating data, conducted all statistical analyses. JH and YL drafted an initial version of the manuscript. JH and YX secured funding for the conduct of this study, curated data, and led the statis tical analyses and administration of this study. LZ, XZ, JY, ZY, XW, BL and HC contributed to the critical reviewing and providing substantial editing. IA and HC provided substantial suggestions on the development of statistical analysis plan. IA and YX contributed to the administration of this study. All authors have provided critical reviews on the manuscript, approved the final version of the manuscript, and agreed to be responsible for all facets of this work.

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Data availability

The data that support the findings of this study are available from the UK Biobank but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the UK Biobank.

Declarations

Ethics approval and consent to participate

The protocol of the UK Biobank study was approved by the North West Multi Centre Research Ethics Committee with the reference number 16/NW/0274.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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