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ORIGINAL ARTICLE

# Parental history of type 2 diabetes and cardiometabolic biomarkers in offspring

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## ABSTRACT

**Background** Parental history of type 2 diabetes (T2D) is associated with cardiometabolic risk. We aimed to investigate the associations of parental history of T2D with cardiometabolic biomarkers and to subsequently investigate to what extent these putative associations were explained by modifiable factors.

**Materials and methods** Cross-sectionally, we analysed a random sample of 2001 participants without T2D (20–70 years) from the European Prospective Investigation into Cancer and Nutrition–Netherlands (EPIC-NL). Plasma levels of 12 biomarkers – total, HDL and LDL-cholesterol, triglycerides, HbA1c, gamma-glutamyltransferase (GGT), alanine aminotransferase (ALT), asparate aminotransferase (AST), albumin, uric acid, creatinine and high-sensitivity CRP (hs-CRP) – were assessed according to categories of parental history of T2D.

**Results** In age and sex–adjusted analyses, offspring with parental history of T2D had significantly higher ALT [β = 0·074; 95% confidence interval (95%CI), 0·023–0·126] and AST levels (β = 0·033; 95%CI, 0·001 to 0·066) and a trend towards higher HbA1c (β = 0·011; 95%CI, −0·001 to 0·024) and GGT (β = 0·049; 95%CI, −0·015 to 0·112) levels. Adjustment for diet, smoking, alcohol intake, physical activity and educational level modestly attenuated the magnitude of these associations, but they remained significant for ALT and borderline significant for AST. After further adjustment for adiposity, additional attenuation was observed, but the association remained significant for ALT. Only maternal history of T2D was associated with higher ALT levels. T2D in both parents was associated with increased levels of all liver enzymes, but the association remained significant for GGT after adjustment for adiposity. Overall, the modifiable factors explained 21·2–45·4% of these associations. The contribution of adiposity was 18·2–38·9%.

**Conclusion** We conclude that parental history of T2D was associated with higher non-fasting levels of liver enzymes in a general population without T2D. Adiposity substantially contributed to these associations. The contribution of diet and lifestyle factors was modest.

**Keywords** Adiposity, biomarker, cardiometabolic, diet, lifestyle, parental history, type 2 diabetes.

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## Introduction

Type 2 diabetes (T2D) is associated with a broad range of metabolic components. There is evidence suggesting familial transmission of the metabolic components to offspring [1]. Family history of T2D contains both genetic and environmental information [2]. We and others recently demonstrated that diet, lifestyle factors and adiposity contribute to T2D risk exerted by parental history of T2D [3,4]. Diet and lifestyle intervention has been shown to modify cardiometabolic risk factors [5].

A limited number of studies evaluated the associations of parental history of T2D with levels of some diabetes-related metabolic biomarkers [6–10]. These studies found no associations of parental history of T2D with the inflammatory

marker high-sensitivity C-reactive protein (hs-CRP), glycaemia index HbA1c and blood lipid profile components, including total, and HDL-cholesterol and triglycerides [6,7,10]. They, however, found a positive association of parental history of T2D with the liver enzymes such as gamma-glutamyltranspeptidase (GGT) in non-diabetic offspring [6]. Evidence suggests that elevated liver enzymes as surrogate marker of non-alcoholic fatty liver disease (NAFLD) comprises a new component of the metabolic syndrome [11,12]. NAFLD may be linked to uric acid [13], while uric acid in turn is linked to both the metabolic syndrome and renal dysfunction [14]. Of note, the associations of parental history of T2D with uric acid and renal profile components like serum creatinine have not been examined yet. Moreover, it is still unclear whether modifiable factors including diet, lifestyle and adiposity have any effects on the associations of parental history of T2D with aforementioned cardiometabolic biomarkers.

We investigated whether parental history of T2D is associated with a broad panel of cardiometabolic biomarkers. We did this in a random sample of adults without T2D from the European Prospective Investigation into Cancer and Nutrition (EPIC) study in the Netherlands (EPIC-NL). We hypothesize that modifiable factors affect these associations; we therefore examined to what extent adiposity, diet and lifestyle factors contribute to the associations of parental history of T2D with levels of biomarkers.

## Methods

### Study population and design

This study was performed in a random sample (6·5%, $n$ = 2604) of the baseline cohort of the EPIC-NL study in the Netherlands ($n$ = 40 011). The EPIC-NL cohort comprises the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN), and Prospect cohorts set up simultaneously between 1993 and 1997. Details of the study design, recruitment and study procedures (including the random sample) were described in detail elsewhere [15].

From the random sample, we excluded 43 participants who had T2D (mainly defined by self-report and verified by medical records) and 560 with missing data on baseline characteristics, extreme values for energy intake (< 450 or > 6000 kcal/day) or unknown parental history of T2D, leaving 2001 participants for this cross-sectional analysis. The baseline characteristics of excluded participants were similar to those who were included in our analysis (Table S1). We asked participants whether their biological mother and/or father had been diagnosed with T2D. Parental history of T2D was categorized as none, any parent(s) (mother and/or father), maternal only, paternal only or both parental.

All participants gave written informed consent prior to study inclusion. The EPIC-NL cohort complies with the Declaration of Helsinki and was approved by the relevant local Medical Ethics Committee. Reporting of the study conforms to STROBE along with references to STROBE and the broader EQUATOR guidelines [16].

### Biomarker measurements

We collected non-fasting blood samples from participants at baseline. Blood samples were fractionated into aliquots and stored at −196 °C for future use. HbA1c was measured in erythrocytes using an immunoturbidimetric latex test. Biomarkers were assessed in EDTA (in MORGEN cohort) or citrate (in Prospect cohort) plasma. We compared EDTA and citrate measurements and validated these against serum in a sample of 50 participants, observing very good to excellent correlations [15]. Albumin and creatinine (Jaffé method) were measured using a colorimetric method. Alanine aminotransferase (ALT), asparate aminotransferase (AST), GGT, total cholesterol, triglycerides and uric acid were measured using enzymatic methods, whereas hs-CRP was measured with a turbidimetric method. We measured HDL and LDL-cholesterol using a homogeneous assay with enzymatic endpoint. These assays were all performed on an autoanalyser (LX20; Beckman Coulter, Mijdrecht, the Netherlands). Our technicians were blinded to the participants' characteristics.

### Statistical analysis

We used generalized linear models to assess the association between parental history of T2D and cardiometabolic biomarkers in model 1, adjusted for cohort, age and sex. Model 2 was further adjusted for smoking, alcohol use, physical activity level, educational level, total energy intake, and energy-adjusted intakes of fat, protein, carbohydrate, fibre, vitamin C and vitamin E [3,15], while model 3 also included body mass index (BMI) and waist circumference. The β regression coefficients (95%CI) for biomarker levels (indicating the increase or decrease in log-transformed level of biomarker) in each category of parental history of T2D were calculated. Inclusion of these factors in the model would be expected to attenuate the β coefficients [3]. We calculated the percentage attenuation of the β coefficients for each category of parental history of T2D. Percentage attenuation of β coefficient was calculated as: (β coefficient before addition − β coefficient after addition)/(β coefficient before addition) × 100. To account for the use of non-fasting blood samples, we performed sensitivity analyses after exclusion of those with high blood glucose (≥ 7·8 mM; $n$ = 34) and we adjusted the associations for time since last meal or drink (postprandial time). We considered a $P$-value of 0·05 or less from two-sided tests statistically significant. All the statistical analyses were carried out using Statistical

Package for Social Sciences version 17 (SPSS Inc, Chicago, IL, USA).

## Results

We summarized baseline characteristics of the study population according to parental history of T2D in Table 1. When compared with offspring without parental history of T2D, those who reported any parental history of T2D had higher levels of HbA1c, LDL-cholesterol, ALT and GGT. Moreover, a trend towards higher AST levels in offspring with parental history of T2D than those without parental history of T2D was found. We observed no difference for levels of other biomarkers between each category of parental history of T2D. In our data set, there were 560 individuals with missing data on baseline characteristics. We presented the comparison between included and excluded participants and found no differences (Table S1).

In regression model adjusted for cohort, age and sex, BMI was associated with levels of liver enzymes (β ranged from 0·096 to 0·316; $P < 0·001$) in both offspring with and without parental history of T2D. The $R^2$ change after adding BMI to this model showed to what extent BMI could explain the variation of levels of liver enzymes. This contribution of BMI in the variation of AST (6·9% vs. 0·9%) and GGT (9·9% vs. 3·8%) was stronger for those with parental history of T2D.

### Parental history of diabetes and cardiometabolic biomarkers

The association between parental history of T2D and biomarker levels in offspring adjusted for covariates is shown in Table 2. In model 1, offspring with any parental history of T2D had significantly higher levels of ALT (β = 0·074; 95%CI, 0·023–0·126) and AST (β = 0·033; 95%CI, 0·001–0·066). Moreover, levels of HbA1c (β = 0·011; 95%CI, −0·001 to 0·024) and GGT (β = 0·049; 95%CI, −0·015 to 0·112) tended to be higher in offspring with any parental history of T2D. The association between any parental history of T2D and level of these biomarker levels was modestly attenuated in model 2. Adjustment for adiposity (model 3) further attenuated the associations, but they remained significant for ALT (β = 0·052; 95%CI, 0·002–0·101) and borderline significant for AST (β = 0·026; 95%CI, −0·006 to 0·059). The overall attenuations for HbA1c, ALT and AST were 36·4%, 29·7% and 21·2%, respectively.

To examine to what extent adiposity itself contribute to the association of parental history of T2D with HbA1c and liver enzymes, we separately added parameters of obesity and obesity (BMI ≥ 30 kg/m$^2$) to model 1. Parameters of obesity explained 18·2%, 28·4% and 21·2%, respectively, of the association of parental history of T2D with HbA1c ALT and AST, while presence of obesity explained 9·1%, 10·8% and 9·1%, respectively, of these associations.

### Maternal vs. paternal history of diabetes

In subsequent analyses, we examined whether biomarker levels differed by maternal or paternal history of T2D. In model 1, offspring with only maternal history of T2D had higher ALT levels (β = 0·084; 95%CI, 0·020–0·149). Offspring with only paternal history of T2D had higher albumin levels (β = 0·017; 95%CI, 0·002–0·032). Those with both maternal and paternal history of T2D had higher GGT levels (β = 0·423; 95%CI, 0·178–0·668), higher ALT levels (β = 0·262; 95%CI, 0·062–0·462) and higher AST levels (β = 0·129; 95%CI, (0·000–0·257). In model 3, statistically significant higher levels of GGT (β = 0·331; 95%CI, 0·095–0·566) were found for offspring with both diabetic parents, and higher levels of ALT (β = 0·065; 95%CI, 0·003–0·127) for offspring with only maternal history of T2D (Table 2). The overall attenuation of the association of maternal history of T2D with ALT was 22·6%. The overall attenuations of the association of both parental history of T2D with AST, ALT and GGT were 34·8%, 45·4% and 21·7%, respectively.

To examine to what extent adiposity itself contribute to the associations of maternal and both parental history of T2D with most-related biomarkers, we separately added parameters of adiposity and obesity to model 1 in each category. Parameters of obesity explained 23·8% of the association of maternal history of T2D with ALT, but presence of obesity explained 4·8% of this association. Parameters of obesity explained 38·9% and 26·7%, respectively, of the association of both parental history of T2D with ALT and GGT. Obesity explained 26·3% and 18·4%, respectively, of these associations.

In sensitivity analyses, we excluded those with high blood glucose (≥ 7·8 mM; $n = 34$) and further adjusted for time since last meal or drink (postprandial time) and observed similar results (data not shown).

## Discussion

In this cross-sectional analysis, we found that any parental history of T2D was associated with higher levels of liver enzymes (ALT and AST) in adults without T2D. This was particularly true for maternal history of T2D. Offspring with both diabetic parents had higher GGT levels as well, whereas those who reported only paternal diabetes had higher albumin levels. The associations between parental history of diabetes and liver enzymes were partly explained by diet and lifestyle factors (smoking status, alcohol consumption, physical activity and educational level). The parameters of adiposity contributed substantially to these associations.

Given the extensive information about modifiable factors of the participants, we were able to show the contribution of these factors in the associations between parental history of diabetes T2D and a panel of biomarkers in adults without T2D.

 

**Table 1** Baseline characteristics of the random sample according to parental history of type 2 diabetes ($n$ = 2001)

| Variables | Category of parental history of type of diabetes | | | | | | |
|---|---|---|---|---|---|---|---|
| | None ($n$ = 1611) | Any parents ($n$ = 390) | Only father ($n$ = 142) | Only mother ($n$ = 227) | Both parents ($n$ = 21) | *P*-value* | *P*-value† |
| Age, year | 49·5 (12·2) | 52·0 (9·3) | 52·3 (9·8) | 52·2 (8·8) | 47·6 (9·4) | <0·001 | 0·001 |
| Female | 1220 (75·7) | 300 (76·9) | 107 (75·7) | 175 (77·1) | 18 (85·7) | 0·62 | 0·72 |
| Body mass index, kg/m$^2$ | 25·7 (4·0) | 26·7 (3·9) | 26·4 (3·8) | 26·6 (3·8) | 29·1 (5·0) | <0·001 | <0·001 |
| Waist circumference, cm | 85·3 (11·4) | 87·2 (11·1) | 86·6 (10·9) | 87·2 (10·9) | 90·9 (14·0) | 0·003 | 0·01 |
| Alcohol consumption, g/week | 11·5 (15·0) | 9·7 (12·8) | 10·4 (13·6) | 9·3 (11·9) | 9·3 (1·7) | 0·02 | 0·13 |
| Current smoker | 489 (30·4) | 107 (27·4) | 36 (25·4) | 66 (29·1) | 5 (23·8) | 0·26 | 0·57 |
| Low educational level‡ | 916 (56·9) | 244 (62·6) | 77 (54·2) | 156 (68·7) | 11 (52·4) | 0·04 | 0·005 |
| Physically active§ | 520 (32·3) | 141 (36·2) | 46 (32·4) | 84 (37·0) | 11 (52·4) | 0·14 | 0·35 |
| Total energy intake, kcal/day | 2048·2 (599·1) | 1980·2 (582·5) | 1921·6 (551·6) | 2023·3 (601·4) | 1909·3 (563·2) | 0·04 | 0·07 |
| Nutrient intake¶, g/day | | | | | | | |
| Protein | 75·8 (10·9) | 77·7 (10·9) | 78·1 (9·7) | 77·0 (11·4) | 82·1 (11·7) | 0·003 | 0·004 |
| Fat | 77·3 (11·2) | 78·4 (10·5) | 77·1 (9·8) | 79·1 (10·7) | 78·5 (12·2) | 0·11 | 0·16 |
| Carbohydrates | 221·4 (31·2) | 220·3 (23·4) | 220·8 (27·9) | 220·3 (28·1) | 216·7 (34·2) | 0·55 | 0·87 |
| Fibre | 23·3 (4·6) | 24·0 (4·7) | 24·1 (4·6) | 23·9 (4·8) | 24·6 (3·8) | 0·008 | 0·06 |
| Vitamin C, mg/day | 110·6 (46·2) | 114·4 (44·1) | 112·1 (39·4) | 115·2 (46·6) | 121·9 (47·9) | 0·14 | 0·38 |
| Vitamin E, mg/day | 12·1 (3·2) | 12·3 (3·3) | 11·9 (2·8) | 12·5 (3·6) | 12·0 (3·0) | 0·33 | 0·23 |
| HbA1c, % | 5·36 (5·02–5·71) | 5·46 (5·14–5·82) | 5·52 (5·18–5·85) | 5·44 (5·12–5·80) | 5·45 (4·91–5·69) | <0·001 | 0·003 |
| Total cholesterol, mM | 5·2 (4·6–5·9) | 5·3 (4·6–6·0) | 5·3 (4·7–6·0) | 5·3 (4·6–6·0) | 5·1 (4·8–6·4) | 0·16 | 0·56 |
| HDL-C, mM | 1·21 (1·02–1·47) | 1·21 (1·02–1·45) | 1·22 (1·04–1·46) | 1·22 (1·00–1·45) | 1·16 (1·02–1·46) | 0·92 | 0·97 |
| LDL-C, mM | 3·07 (2·46–3·68) | 3·16 (2·61–3·75) | 3·25 (2·71–3·70) | 3·16 (2·59–3·81) | 3·00 (2·59–3·77) | 0·02 | 0·11 |
| Triglycerides, mM | 1·34 (0·92–1·95) | 1·28 (0·96–1·97) | 1·39 (0·96–1·97) | 1·23 (0·96–2·02) | 1·48 (0·80–1·48) | 0·79 | 0·85 |
| ALT, IU/L | 14·5 (11·9–18·3) | 14·9 (12·2–20·4) | 14·5 (11·97–19·52) | 15·1 (12·4–20·8) | 15·4 (12·4–27·5) | 0·008 | 0·03 |
| AST, IU/L | 19·9 (17·4–23·5) | 20·2 (17·4–24·5) | 20·4 (17·5–24·2) | 20·1 (17·3–24·6) | 21·7 (17·8–28·4) | 0·28 | 0·54 |
| GGT, IU/L | 20·3 (16·5–27·7) | 21·3 (17·1–29·5) | 20·3 (16·2–27·5) | 21·8 (17·7–29·4) | 32·2 (19·2–43·3) | 0·03 | 0·007 |
| Albumin, g/L | 38·7 (34·3–42·8) | 37·5 (34·3–42·1) | 38·1 (34·5–41·9) | 37·1 (34·0–42·0) | 39·6 (35·1–44·4) | 0·18 | 0·22 |
| Uric acid, μM | 247·6 (210·2–298·6) | 251·5 (209·3–293·4) | 252·8 (215·5–288·1) | 248·9 (208·1–299·5) | 241·1 (196·7–349·5) | 0·92 | 1·00 |
| Creatinine, μM | 61·4 (53·4–71·6) | 60·8 (54·1–70·6) | 61·3 (55·2–70·9) | 60·0 (53·2–70·6) | 60·9 (55·0–67·0) | 0·33 | 0·70 |
| hs-CRP, mg/L | 1·24 (0·56–2·69) | 1·26 (0·66–2·70) | 1·27 (0·71–2·53) | 1·24 (0·61–2·90) | 1·15 (0·69–2·49) | 0·42 | 0·88 |

HbA1c, glycosylated haemoglobin; HDL-C, high-density cholesterol; LDL-C, low-density cholesterol; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase; hs-CRP, high-sensitivity C-reactive protein.
Data were given as mean (SD) or median (IQR) for continuous variables and numbers (percentage) for categorical variables.
*For the comparison between participants with any parental history of type 2 diabetes and none using chi-squared test (categorical data), and $t$-test or Mann–Whitney $U$-test (continuous data).
†For the comparison between participants with paternal, maternal or both history of type 2 diabetes and none (as referent) using chi-squared test (categorical data), and ANOVA or Kruskal–Wallis (continuous data).
‡Low education level was assigned for participants who had primary education up to completing intermediate vocational education.
§Physical activity level was defined based on Cambridge Physical Activity Index.
¶Intakes of nutrients were adjusted for total energy intake and given as g/day unless otherwise indicated.

**Table 2** Association between parental history of type 2 diabetes and offspring biomarker levels ($n$ = 2001)

| | β regression coefficients (95%CI) by category of parental history of type 2 diabetes* | | | |
|---|---|---|---|---|
| **Log-transformed biomarker** | **Any parents ($n$ = 390)** | **Only father ($n$ = 142)** | **Only mother ($n$ = 227)** | **Both parents ($n$ = 21)** |
| HbA1c, % | | | | |
| Model 1 | 0·011 (−0·001 to 0·024) | 0·015 (−0·004 to 0·035) | 0·008 (−0·008 to 0·024) | 0·019 (−0·030 to 0·067) |
| *P*-value | 0·08 | 0·12 | 0·32 | 0·45 |
| Model 2 | 0·009 (−0·003 to 0·022) | 0·016 (−0·004 to 0·035) | 0·004 (−0·011 to 0·020) | 0·019 (−0·029 to 0·068) |
| *P*-value | 0·15 | 0·11 | 0·59 | 0·43 |
| Model 3 | 0·007 (−0·005 to 0·020) | 0·015 (−0·005 to 0·034) | 0·003 (−0·012 to 0·019) | 0·009 (−0·039 to 0·057) |
| *P*-value | 0·24 | 0·14 | 0·73 | 0·71 |
| Total cholesterol, mM | | | | |
| Model 1 | 0·015 (−0·011 to 0·041) | 0·014 (−0·026 to 0·053) | 0·018 (−0·014 to 0·051) | −0·010 (−0·110 to 0·090) |
| *P*-value | 0·25 | 0·50 | 0·26 | 0·84 |
| Model 2 | 0·015 (−0·011 to 0·040) | 0·014 (−0·026 to 0·054) | 0·018 (−0·015 to 0·050) | −0·012 (−0·112 to 0·088) |
| *P*-value | 0·26 | 0·48 | 0·29 | 0·81 |
| Model 3 | 0·013 (−0·012 to 0·039) | 0·014 (−0·026 to 0·054) | 0·016 (−0·016 to 0·048) | −0·020 (−0·120 to 0·080) |
| *P*-value | 0·31 | 0·49 | 0·33 | 0·70 |
| HDL-C, mM | | | | |
| Model 1 | 0·020 (−0·016 to 0·056) | 0·027 (−0·029 to 0·083) | 0·022 (−0·023 to 0·067) | −0·051 (−0·191 to 0·089) |
| *P*-value | 0·27 | 0·34 | 0·33 | 0·47 |
| Model 2 | 0·027 (−0·007 to 0·061) | 0·025 (−0·028 to 0·078) | 0·036 (−0·007 to 0·079) | −0·063 (−0·196 to 0·070) |
| *P*-value | 0·12 | 0·36 | 0·10 | 0·35 |
| Model 3 | 0·028 (−0·005 to 0·062) | 0·031 (−0·020 to 0·081) | 0·037 (−0·006 to 0·080) | 0·002 (−0·125 to 0·128) |
| *P*-value | 0·10 | 0·23 | 0·10 | 0·97 |
| LDL-C, mM | | | | |
| Model 1 | 0·034 (−0·008 to 0·075) | 0·036 (−0·028 to 0·101) | 0·036 (−0·016 to 0·089) | −0·012 (−0·175 to 0·150) |
| *P*-value | 0·12 | 0·27 | 0·18 | 0·88 |
| Model 2 | 0·030 (−0·012 to 0·072) | 0·035 (−0·030 to 0·100) | 0·032 (−0·021 to 0·084) | −0·018 (−0·180 to 0·144) |
| *P*-value | 0·15 | 0·29 | 0·24 | 0·83 |
| Model 3 | 0·025 (−0·016 to 0·067) | 0·033 (−0·031 to 0·097) | 0·027 (−0·025 to 0·079) | −0·045 (−0·207 to 0·117) |
| *P*-value | 0·23 | 0·31 | 0·31 | 0·59 |
| Triglycerides, mM | | | | |
| Model 1 | −0·0002 (−0·074 to 0·075) | 0·032 (−0·083 to 0·147) | −0·017 (−0·111 to 0·076) | −0·026 (−0·315 to 0·263) |
| *P*-value | 1·00 | 0·58 | 0·72 | 0·86 |
| Model 2 | −0·0001 (−0·074 to 0·074) | 0·046 (−0·069 to 0·160) | −0·029 (−0·122 to 0·064) | 0·003 (−0·283 to 0·289) |
| *P*-value | 1·00 | 0·43 | 0·56 | 0·98 |
| Model 3 | −0·022 (−0·092 to 0·049) | 0·037 (−0·072 to 0·146) | −0·050 (−0·139 to 0·038) | −0·115 (−0·389 to 0·159) |
| *P*-value | 0·54 | 0·51 | 0·26 | 0·41 |
| ALT, IU/L | | | | |
| Model 1 | 0·074 (0·023 to 0·126) | 0·030 (−0·050 to 0·110) | 0·084 (0·020 to 0·149) | 0·262 (0·062 to 0·462) |
| *P*-value | **0·005** | 0·46 | **0·01** | **0·01** |

 

**Table 2** *Continued*

| Log-transformed biomarker | β regression coefficients (95%CI) by category of parental history of type 2 diabetes* | | | |
|---|---|---|---|---|
| | Any parents (*n* = 390) | Only father (*n* = 142) | Only mother (*n* = 227) | Both parents (*n* = 21) |
| Model 2 | 0·068 (0·017 to 0·120) | 0·026 (−0·054 to 0·106) | 0·080 (0·016 to 0·145) | 0·232 (0·032 to 0·431) |
| *P*-value | **0·01** | 0·52 | **0·01** | **0·02** |
| Model 3 | 0·052 (0·002 to 0·101) | 0·017 (−0·059 to 0·094) | 0·065 (0·003 to 0·127) | 0·143 (−0·049 to 0·335) |
| *P*-value | **0·04** | 0·66 | **0·04** | 0·14 |
| AST, IU/L | | | | |
| Model 1 | 0·033 (0·001 to 0·066) | 0·028 (−0·023 to 0·080) | 0·027 (−0·015 to 0·068) | 0·129 (0·000 to 0·257) |
| *P*-value | **0·05** | 0·28 | 0·21 | **0·05** |
| Model 2 | 0·032 (−0·001 to 0·065) | 0·026 (−0·025 to 0·077) | 0·028 (−0·014 to 0·069) | 0·112 (−0·016 to 0·240) |
| *P*-value | 0·06 | 0·30 | 0·19 | 0·08 |
| Model 3 | 0·026 (−0·006 to 0·059) | 0·024 (−0·026 to 0·075) | 0·022 (−0·019 to 0·063) | 0·084 (−0·042 to 0·211) |
| *P*-value | 0·11 | 0·34 | 0·28 | 0·19 |
| GGT, IU/L | | | | |
| Model 1 | 0·049 (−0·015 to 0·112) | −0·027 (−0·125 to 0·071) | 0·061 (−0·019 to 0·140) | 0·423 (0·178 to 0·668) |
| *P*-value | 0·13 | 0·59 | 0·13 | **0·001** |
| Model 2 | 0·058 (−0·005 to 0·121) | −0·015 (−0·111 to 0·082) | 0·069 (−0·009 to 0·148) | 0·433 (0·191 to 0·675) |
| *P*-value | 0·07 | 0·76 | 0·08 | **<0·001** |
| Model 3 | 0·039 (−0·022 to 0·100) | −0·026 (−0·119 to 0·068) | 0·053 (−0·023 to 0·129) | 0·331 (0·095 to 0·566) |
| *P*-value | 0·21 | 0·59 | 0·17 | **0·006** |
| Albumin, g/L | | | | |
| Model 1 | 0·006 (−0·003 to 0·016) | 0·017 (0·002 to 0·032) | −0·002 (−0·014 to 0·011) | 0·021 (−0·017 to 0·059) |
| *P*-value | 0·20 | **0·03** | 0·80 | 0·27 |
| Model 2 | 0·006 (−0·004 to 0·016) | 0·015 (0·000 to 0·030) | −0·001 (−0·013 to 0·011) | 0·015 (−0·023 to 0·052) |
| *P*-value | 0·23 | **0·04** | 0·90 | 0·44 |
| Model 3 | 0·006 (−0·003 to 0·016) | 0·016 (0·001 to 0·031) | −0·0005 (−0·013 to 0·012) | 0·018 (−0·020 to 0·055) |
| *P*-value | 0·19 | **0·04** | 0·94 | 0·35 |
| Uric acid, μM | | | | |
| Model 1 | 0·006 (−0·024 to 0·036) | −0·002 (−0·050 to 0·044) | 0·006 (−0·032 to 0·044) | 0·060 (−0·058 to 0·177) |
| *P*-value | 0·69 | 0·92 | 0·74 | 0·32 |
| Model 2 | 0·006 (−0·024 to 0·037) | −0·0004 (−0·047 to 0·047) | 0·005 (−0·032 to 0·044) | 0·052 (−0·066 to 0·169) |
| *P*-value | 0·71 | 0·99 | 0·75 | 0·39 |
| Model 3 | 0·006 (−0·035 to 0·023) | −0·009 (−0·053 to 0·036) | −0·004 (0·040 to 0·032) | −0·016 (−0·128 to 0·096) |
| *P*-value | 0·68 | 0·71 | 0·84 | 0·77 |
| Creatinine, mg/L | | | | |
| Model 1 | −0·013 (−0·039 to 0·012) | −0·007 (−0·046 to 0·033) | −0·020 (−0·052 to 0·012) | 0·013 (−0·086 to 0·112) |
| *P*-value | 0·30 | 0·74 | 0·22 | 0·79 |
| Model 2 | −0·011 (−0·036 to 0·015) | −0·006 (−0·046 to 0·033) | −0·016(0·048 to 0·016) | 0·014 (−0·084 to 0·113) |
| *P*-value | 0·40 | 0·76 | 0·32 | 0·77 |
| Model 3 | −0·013 (−0·038 to 0·013) | −0·007 (−0·047 to 0·037) | −0·017 (0·049 to 0·015) | 0·006 (−0·093 to 0·105) |

**Table 2** *Continued*

| Log-transformed biomarker | β regression coefficients (95%CI) by category of parental history of type 2 diabetes* | | | |
|---|---|---|---|---|
| | Any parents (*n* = 390) | Only father (*n* = 142) | Only mother (*n* = 227) | Both parents (*n* = 21) |
| *P*-value | 0·34 | 0·72 | 0·28 | 0·91 |
| hs-CRP, mg/L | | | | |
| Model 1 | 0·028 (−0·127 to 0·182) | −0·011 (−0·250 to 0·229) | 0·050(−0·144 to 0·244) | 0·046 (−0·554 to 0·647) |
| *P*-value | 0·73 | 0·93 | 0·61 | 0·88 |
| Model 2 | 0·035 (−0·118 to 0·188) | 0·019 (−0·211 to 0·264) | 0·039 (−0·154 to 0·231) | 0·103 (−0·491 to 0·696) |
| *P*-value | 0·65 | 0·83 | 0·69 | 0·73 |
| Model 3 | −0·018 (−0·165 to 0·130) | −0·015 (−0·243 to 0·214) | −0·004 (−0·190 to 0·181) | −0·187 (−0·761 to 0·386) |
| *P*-value | 0·81 | 0·90 | 0·96 | 0·52 |

HbA1c, glycosylated haemoglobin; HDL-C, high-density cholesterol; LDL-C, low-density cholesterol; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase; hs-CRP, high-sensitivity C-reactive protein.
*Model 1 was adjusted for cohort, age and sex. Model 2 was adjusted for model 1 plus smoking, alcohol use, physical activity level, educational level, total energy intake and energy-adjusted dietary factors, including the amount of intake of fat, protein, carbohydrate, fibre, vitamin C and vitamin E. Model 3 was adjusted for model 2 plus body mass index and waist circumference. Significant *P* values were indicated in bold type.

Nevertheless, our study has some limitations. The study is a cross-sectional investigation, and causal relationships cannot be inferred. Another limitation is that parental history of T2D was obtained by self-report. Furthermore, we excluded the individuals with missing data or unknown parental history of T2D. However, most of the baseline characteristics of excluded participants were similar to those who were included in our analysis. Therefore, it is unlikely that this may have led to selection bias in some categories of parental history of T2D. We used data on non-fasting blood samples as fasting samples were not available, but further adjustment for postprandial time did not change the results. Although non-fasting conditions could be argued as a severe limitation of our study, there is evidence suggesting that overnight fasting status might have minimal effects on concentrations of most biomarkers which we studied [17,18], also in our cohort [19]. Of note, data on non-fasting lipids such as triglycerides and inflammation-related biomarkers such as CRP and adiponectin have been shown to improve the risk prediction of T2D and cardiovascular events independent of traditional cardiometabolic risk profile [18–20]. Finally, we had no data on more specific factors to T2D, such as HOMA/insulin and adiponectin to examine their associations with parental history of T2D, but the metabolic syndrome was not a primary focus of this study.

Among different cardiometabolic biomarkers, only liver enzymes were associated with parental history of T2D. Our findings are in line with the limited prior information, suggesting that female workers with family history of T2D had elevated levels of ALT, AST and GGT [6]. However, this study also observed an association with triglycerides, which we could not confirm [6]. Similar to our results, the recent studies also showed no association of family history of T2D with lipid profile components and proinflammatory markers in adults without T2D [7,8,10]. Our results were similar by excluding those with high non-fasting glucose concentrations and were therefore more likely to be a direct consequence of parental history of T2D rather than secondary to pre-diabetes state.

Adjusting for diet and lifestyle attenuated the association between parental history of T2D and liver function profile. This supports the suggestion of lifestyle modification has positive effect on cardiometabolic risk [5]. Further adjustment for adiposity led to a more attenuation in the associations. In fact, this indicated that adiposity contributed to parental transmission of liver function profile independent from diet and lifestyle factors. Furthermore, increased adiposity, in itself, could substantially explain the associations of parental history of T2D with HbA1c and liver enzymes. These findings are generally in line with those of other epidemiologic studies, showing that adiposity plays an important role in transmission of cardiometabolic risk [10,21]. Mild elevated levels of liver enzymes may have occurred in early or subclinical metabolic abnormality underlying NAFLD. Of note, the lack of association of parental history of T2D with markers of glycaemia, lipids and low-grade inflammation may show that these subclinical changes in liver function are important for further progression to pre-diabetes state and T2D [22,23]. This extends the available information for a possible link between NAFLD, adiposity and T2D. Of note, these traits partly share common genetic and environmental components [24]. Further prospective investigations are warranted, showing whether the link between liver function and adiposity contributes to transmission of risk of T2D and its complications to the next generation [2–4].

In our study, there was a stronger association of maternal history of T2D with liver enzymes. This difference might be partly explained by genetic and environmental conditions such as X-linked traits, gene imprinting intra-uterine programming and

 

a more prominent maternal role in raising children. A recent study among Japanese men showed that maternal but not paternal adiposity was associated with a higher level of ALT [25]. Similar to our data, another study on offspring of diabetic parents has shown that defects in insulin sensitivity and β-cell glucose sensitivity were accentuated along the maternal line of inheritance [10]. The specific relation of maternal history of T2D and liver enzymes observed in our study could also be explained by the fact that the mother might have a more prominent role in raising her children from early life, that is, during pregnancy, to later life. For example, it has been shown that maternal pre-pregnancy overweight increased the risk of offspring overweight and abdominal obesity [26]. Adiposity in turn associates with elevated liver enzymes and NAFLD [27–29].

In conclusion, we found that parental history of T2D was associated with higher non-fasting levels of ALT, AST and GGT in a general population without T2D. Adiposity, substantially, contributed to the associations between parental history of T2D and liver function profile. The contribution of diet and lifestyle factors was modest.

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**Conflict of interest**

None of the study sponsors had a role in study design, in data collection, analysis or interpretation, in writing the report or in the decision to submit for publication. No financial disclosures relevant to this manuscript were declared.

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## Supporting Information

Additional Supporting information can be found in the online version of this article:

**Table S1.** Baseline characteristics of the random sample according to missing data.

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