Associations of maternal type 1 diabetes with childhood adiposity and metabolic health in the offspring: a prospective cohort study

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Abstract

Aims/hypothesis Exposure to an intrauterine hyperglycaemic environment has been suggested to increase the offspring's later risk for being overweight or having metabolic abnormalities, but conclusive evidence for pregnancies affected by maternal type 1 diabetes is still lacking. This study aims to analyse the relationship between maternal type 1 diabetes and the offspring's metabolic health and investigate whether birthweight and/or changes in the offspring's metabolome are in the potential pathway.

Methods We analysed data from 610 and 2169 offspring having a first-degree relative with type 1 diabetes from the TEENDIAB and BABYDIAB/BABYDIET cohorts, respectively. Anthropometric and metabolic outcomes, assessed longitudinally at 0.3–18 years of age, were compared between offspring of mothers with type 1 diabetes and offspring of non-diabetic mothers but with fathers or siblings with type 1 diabetes using mixed regression models. Non-targeted metabolomic measurements were carried out in 500 individuals from TEENDIAB and analysed with maternal type 1 diabetes and offspring overweight status.

Results The offspring of mothers with type 1 diabetes had a higher BMI SD score (SDS) and an increased risk for being overweight than the offspring of non-diabetic mothers (e.g. OR for overweight status in TEENDIAB 2.40 [95% CI 1.41, 4.06]). Further, waist circumference SDS, fasting levels of glucose, insulin and C-peptide, and insulin resistance and abdominal obesity were significantly increased in the offspring of mothers with type 1 diabetes, even when adjusted for potential confounders and birthweight. Metabolite patterns related to androgenic steroids and branched-chain amino acids were found to be associated with offspring's overweight status, but no significant associations were observed between maternal type 1 diabetes and metabolite concentrations in the offspring.

Conclusions/interpretation Maternal type 1 diabetes is associated with offspring's overweight status and metabolic health in later life, but this is unlikely to be caused by alterations in the offspring's metabolome.

Keywords Birthweight · Maternal type 1 diabetes · Offspring metabolic health · Offspring metabolome · Offspring overweight

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Research in context

What is already known about this subject?

- Intrauterine exposure to hyperglycaemia is likely to influence the offspring's later risk for being overweight or having metabolic abnormalities, but conclusive evidence for pregnancies affected by maternal type 1 diabetes is still lacking
- Most previous studies on maternal type 1 diabetes were cross-sectional in design, limited in sample size and assessed children in different age groups; potential pathways were not investigated in any detail

What is the key question?

- Do offspring exposed to maternal type 1 diabetes in utero have an increased risk of being overweight or having metabolic abnormalities later in life, and by which pathways?

What are the new findings?

- Children exposed to maternal type 1 diabetes during pregnancy have a higher risk for being overweight and worse metabolic health during childhood and adolescence, independent of relevant confounders such as diet
- While increased birthweight partly explains this association, changes in the offspring's metabolomic profile are unlikely to be in the causal pathway

How might this impact on clinical practice in the foreseeable future?

- Although not yet recognised as a particular risk group, children whose mothers have type 1 diabetes might need closer attention with respect to excess weight gain and metabolic risk in later life

Abbreviations

BCAA	Branched-chain amino acid
DII	Dietary inflammatory index
SDS	Standard deviation score

Introduction

Obesity and excess weight in children and adolescents remains a major public health problem because it induces other metabolic disorders, such as diabetes and cardiovascular disease [1]. A growing body of evidence supports the concept of fuel-mediated teratogenesis, in which intrauterine exposure to hyperglycaemia leads to excess fetal glucose and insulin, and thus overgrowth of the fetus [2]. These exposures during fetal life have been reported to extend beyond the neonatal period and influence metabolic complications in later life.

Various studies have shown evidence associating gestational diabetes and type 2 diabetes with later adiposity, increased BMI, insulin resistance, impaired glucose tolerance, higher cholesterol, hypertension and type 2 diabetes in the offspring [3–6], but less evidence exists to support a similar effect of maternal type 1 diabetes on offspring health. However, it appears relevant to differentiate between type 1 diabetes, gestational diabetes and type 2 diabetes, because the last two are associated with maternal obesity, while type 1 diabetes is not. Studies which reported a positive association of maternal type 1 diabetes with

BMI or metabolic outcomes in the offspring [7–10] were cross-sectional in design and limited with respect to their sample size ($n < 600$ in each). Furthermore, two of these studies were based on children born as early as 1978–1985 [7] and 1982–1991 [10], respectively, when diabetes care in pregnant women was probably less good than nowadays [11]. Previous analyses of our own data indicated that children with non-diabetic and type 1 diabetic mothers follow different growth patterns [12, 13], and also that a potential association between maternal type 1 diabetes and risk of being overweight in the offspring is not independent of birthweight and breastfeeding duration [14].

Here, we analysed data from two prospective cohort studies containing over 2770 children of whom more than 1500 were exposed to maternal type 1 diabetes during pregnancy. A subset of 500 children were also characterised for non-targeted metabolomics; these are of particular interest as recent studies have shown significant associations between metabolic concentrations and childhood obesity [15–17], while the associations between maternal type 1 diabetes and metabolic profile in the offspring have not yet been investigated. The aims of this study were to investigate: (1) whether there are differences in anthropometric and metabolic outcomes between offspring of mothers with type 1 diabetes and non-diabetic mothers; and (2) whether birthweight and/or changes in the offspring's metabolome may be in the potential pathway from maternal type 1 diabetes to later overweight status and poor metabolic health in the offspring.

Methods

Our analysis was based on the prospective German cohorts TEENDIAB and BABYDIAB/BABYDIET. These cohorts include children with a familial background of type 1 diabetes and have already been combined for other research questions [18, 19]. All parents gave written informed consent for participation. The studies were approved by the ethical committees of the Technische Universität München (number 2149/08) and Hannover Medical School (number 5644); the Bavarian General Medical Council (number 95357) and Ludwig-Maximilians University (number 329/00), respectively.

TEENDIAB study

The TEENDIAB study is a prospective cohort study conducted in the cities of Munich and Hannover, Germany. During 2009–2015, this study recruited 610 children aged 6–16 years who were resident in Germany and had at least one parent or sibling with type 1 diabetes [20]. Children were followed, on average, every 6 months from 6 to 18 years of age until 2016.

Maternal characteristics and offspring measurements At the first visit, information on type 1 diabetes, smoking status and education level of the parents as well as monthly family income was obtained via self-administered questionnaire. Birthweight information was taken from health records collected during the well-baby preventive health programme, which is routinely offered to all children in Germany. During each visit, weight was measured digitally or using a beam scale with a precision of ± 100 g in light clothing. Height was measured using a stadiometer with a precision of ± 1 mm. Waist circumference was measured using a measuring tape between the pelvic crest and the lower ribs while breathing with a precision of ± 1 mm. Subscapular and triceps skinfold thickness were measured three times using a caliper at the inferior angle of the right scapula and at the posterior right upper arm, respectively, and were calculated as the average of the three measurements. Systolic and diastolic blood pressure were calculated as the average of two measurements, made using the auscultatory or oscillometric method and the upper arm, with the individual in a sitting position after 3–5 min of rest. Tanner's staging was assessed by the study doctor or local paediatrician using validated questionnaires [21]. Venous blood samples were collected to assess fasting blood glucose, insulin and C-peptide, and lipids (cholesterol and triacylglycerols). All participants were asked to fast for at least 10 h before blood collection.

Dietary intake was assessed in 330 children during their first study visit using two different methods. In 268 children, Diet Interview Software for Health Examination Studies Junior (DISHES Junior; Robert Koch Institute, Berlin, Germany), computer-assisted interview software, was used

to assess retrospectively the frequency, type and quantity of foods and beverages consumed in the last 4 weeks. In the remaining 62 children, diet was assessed using a 3 day dietary record which was entered into PRODI (Nutri-Science, Stuttgart, Germany) nutrition software. Both software packages are linked to the German Nutrient Database (Bundeslebensmittelschlüssel; Max Rubner Institut, Karlsruhe, Germany), which allows estimates to be made of the average daily intake of energy, macronutrients and micronutrients.

Metabolomic profiling Non-targeted metabolomic profiling was performed on fasting serum samples taken from 500 children at the first visit using ultra high-performance liquid chromatography and mass spectrometry on the Metabolon platform (Metabolon, Durham, NC, USA). All samples were stored at -80°C prior to analysis. Metabolites were identified following the metabolomics standardisation initiative guidelines [22]. Metabolites were quantified as outlined previously [23]. A total of 575 metabolites were quantified, of which 239 were unknown. Metabolites and samples which had more than 30% missing values were excluded, leaving a total of 441 metabolites, including 294 known and 147 unknown ones, and 485 samples. Metabolite concentrations in terms of raw ion counts were normalised to account for run-day differences and log-transformed to bring them closer to a normal distribution. Missing data were imputed using random forest imputation.

BABYDIAB/BABYDIET studies

The BABYDIAB and BABYDIET studies are two ongoing prospective studies of German birth cohorts; they include 2441 children born between 1989 and 2006 with a first-degree relative with type 1 diabetes. During 1989–2000, a total of 1650 offspring of individuals with type 1 diabetes were recruited for the BABYDIAB study. During 2000–2006, 791 additional offspring or siblings of individuals with type 1 diabetes were screened in the context of the BABYDIET study. Of those, 150 participated in the BABYDIET dietary intervention study randomising the timing of first gluten exposure; the intervention had no effect on islet autoimmunity development or on growth [24, 25]. Further details on the study design are described elsewhere [24, 26, 27]. Data from these two cohorts were combined for longitudinal analyses of maternal type 1 diabetes and anthropometric outcomes in the offspring.

Maternal characteristics and offspring measurements Information on the presence of type 1 diabetes within the family (mother, father or sibling) and smoking status of the mother during pregnancy was obtained via self-administered questionnaire. Height and weight measurements of the

offspring were obtained from health records from the well-baby preventive health programme visits, which were regularly conducted at birth and at the age of 3–10 days, 4–6 weeks and 3–4, 6–7, 10–12, 21–24, 46–48 and 60–64 months. Further height and weight measurements were assessed during study visits, which were scheduled at birth, age 9 months and at 2, 5, 8, 11, 14, 17 and 20 years of age in BABYDIAB, as well as 3-monthly from birth until the age of 3 years, and yearly until the age of 12 years in BABYDIET. These measurements were performed in the same way as described for the TEENDIAB study. From the age of 8 years, Tanner's staging was assessed by a paediatrician or trained staff using validated questionnaires at every study visit.

Exclusions We excluded from our analysis the data from BABYDIAB/BABYDIET participants who had no height and weight measurements ($n = 14$), were lost to follow-up after 0.3 years of age ($n = 44$), or who also participated in the TEENDIAB study ($n = 214$), leaving a final sample size of $n = 2169$. We further excluded all visits performed before 0.3 years of age because these measurements were likely to be highly correlated with birthweight, which we wanted to investigate separately.

Statistical analysis

Height, weight, BMI, waist circumference, subscapular and triceps skinfold thickness and lipids were transformed into age- and sex-specific SD scores (SDSs), and blood pressure into age-, sex- and height-specific SDSs according to German reference values [28–30]. Overweight was defined as a BMI at or above an SDS of 1.31, corresponding with the 90th percentile. For waist circumference SDS, the respective reference percentiles were available for only participants aged between 11 and 18 years. Abdominal obesity was defined as a waist circumference at or above the 90th percentile or the adult threshold set by the International Diabetes Federation [31]. Birthweight was transformed into age- and sex-specific percentiles based on German reference values [32], and categorised as small for gestational age (birthweight <10th percentile), appropriate for gestational age (10th–90th percentile) or large for gestational age (>90th percentile). Participants were classified as having high overall metabolic risk at a certain visit when at least one SDS of BMI, waist, skinfold thickness, blood pressure or lipids was greater than 1.5. Insulin resistance was estimated by HOMA-IR [33].

To adjust for potential confounders, categories of socioeconomic status (high, middle and low) were calculated based on parental education and family income as described previously [34]. Energy intake was adjusted for age and sex using the residual method [35]. Further, an energy-adjusted dietary inflammatory index (DII) score was calculated based on 27 out

of a possible 45 food variables as described elsewhere [36]. A positive DII score indicates a proinflammatory diet, whereas a negative DII score indicates an anti-inflammatory diet.

Maternal type 1 diabetes and metabolic outcomes in the offspring

In all our analyses, we compared offspring of mothers with type 1 diabetes with offspring who had mothers without diabetes, but fathers or siblings with type 1 diabetes. We did this separately for TEENDIAB and BABYDIAB/BABYDIET because the studies differed in the number of outcomes assessed and the timing of the respective measurements. First, anthropometric and metabolic outcomes were visually compared at yearly time intervals between offspring of mothers with and without type 1 diabetes. Second, linear and logistic mixed-effect models accounting for repeated observations within individuals were performed. Fasting glucose, insulin and C-peptide as well as HOMA-IR were log-transformed because of non-normal residuals in the respective linear models. Associations were analysed based on stepwise adjustment. In the first model, we performed univariate analysis for all outcomes. Consistent with other studies [8], we adjusted for age and sex (except for the SDS-corrected outcomes) as well as for Tanner's staging in the second model, and additionally for socioeconomic status and maternal smoking, which are known to be potential risk factors for excess weight gain in childhood [37, 38]. In order to investigate whether birthweight was in the causal pathway from maternal type 1 diabetes to overweight status and metabolic risk in the offspring, birthweight was added as a categorical variable in the third model.

Sensitivity analyses As a first sensitivity analysis, we excluded all children who developed type 1 diabetes during follow-up (8/610 in TEENDIAB and 100/2169 in BABYDIAB/BABYDIET), and reassessed the associations between maternal type 1 diabetes and offspring metabolic outcomes. Second, we compared anthropometric outcomes from the offspring of mothers with type 1 diabetes and fathers with type 1 diabetes separately from those for offspring whose parents did not have type 1 diabetes to see whether parental genetic transmission may also be a relevant factor in addition to intrauterine hyperglycaemia. Children who had both parents with type 1 diabetes were not considered in this analysis. Third, we further investigated cross-sectional associations after adjustment for daily energy intake and DII separately in two different models in addition to Tanner's staging, socioeconomic status and maternal smoking. Fourth, we analysed BMI, weight and height outcomes (not SDS transformed) by adding interaction terms between maternal type 1 diabetes status and child's age in the combined TEENDIAB and BABYDIAB/BABYDIET cohort data to explore whether the association changed with increasing age.

Analyses of metabolomic profiles We further explored the extent to which the offspring's metabolomic profile may play a mediating role in the association between maternal type 1 diabetes and being overweight. First, we examined associations between every single metabolite concentration and being overweight in the offspring assessed at the same visit using logistic regression models. The Benjamini–Hochberg procedure was used to control the false-discovery rate based on 441 tests in order to account for multiple comparisons. Further, principal components analysis with varimax rotation was performed on the 441 log-transformed metabolites to consolidate them into 15 principal components with eigenvalues >5 , which accounted for 43% of the variance in metabolites; the associations between these 15 principal components and being overweight in the offspring were analysed. Second, we investigated whether maternal type 1 diabetes was associated with principal components or metabolites that were significant for overweight status, adjusted for age and sex. Third, associations between maternal type 1 diabetes and overweight status in the offspring were assessed after adjusting for metabolites or principal components which were significantly associated with being overweight. In addition, metabolite concentrations were categorised into 68 sub- and eight superpathways [23]. For each super- and subpathway, the mean of the metabolites belonging to that particular pathway was calculated for all samples and associated with offspring overweight status and maternal type 1 diabetes.

Results were reported as absolute change with 95% CI for SDS outcomes, per cent change with 95% CI for log-transformed outcomes and as OR with 95% CI for risk of being overweight and having metabolic abnormalities between offspring of type 1 diabetic and non-diabetic mothers. All analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC, USA) and R 3.4.1 (<http://cran.r-project.org>).

Results

The study participants in TEENDIAB and BABYDIAB/BABYDIET had a median follow-up of 3.0 and 10.7 years, respectively, which corresponds to a median of six follow-up visits (TEENDIAB range 1–13; BABYDIAB/BABYDIET range 1–18) resulting in 3583 and 13,235 observations in the TEENDIAB and BABYDIAB/BABYDIET cohorts, including 257 (42%) and 1287 (59%) children of mothers with type 1 diabetes, respectively (Table 1). The age of enrolment and follow-up duration were not significantly different between offspring of type 1 diabetic and non-diabetic mothers in either cohort ($p > 0.90$ each; Mann–Whitney U test).

Maternal type 1 diabetes and metabolic outcomes in the offspring

In TEENDIAB, we observed a pattern of higher BMI SDS, weight SDS, fasting levels of glucose, insulin and C-peptide as well as insulin resistance, and of lower height SDS in offspring of mothers with type 1 diabetes in most age groups (Fig. 1 and electronic supplementary material [ESM] Fig. 1). In BABYDIAB/BABYDIET, the anthropometric associations were similar, but weaker and less consistent. However, in mixed models based on all longitudinal measurements significant associations were observed in both cohorts: offspring of mothers with type 1 diabetes had a significantly higher BMI SDS (TEENDIAB 0.35 [95% CI 0.19, 0.52]; BABYDIAB/BABYDIET 0.13 [95% CI 0.06, 0.20], Tables 2 and 3) and increased risk for being overweight (TEENDIAB OR 2.40 [95% CI 1.41, 4.06]; BABYDIAB/BABYDIET OR 1.44 [95% CI 1.20, 1.73]) compared with offspring of non-diabetic mothers. These associations did not change considerably when adjusted for Tanner's staging, socioeconomic status and maternal smoking. However, after further adjustment for birthweight, the observed associations were attenuated in TEENDIAB and were no longer significant in BABYDIAB/BABYDIET, while the negative associations for height SDS became stronger and significant in both cohorts. In TEENDIAB, weight SDS, waist circumference SDS and subscapular and triceps skinfold thickness SDSs were also significantly higher in offspring of mothers with type 1 diabetes compared with those whose mothers did not have type 1 diabetes, but only the estimates for waist circumference SDS remained significant when adjusted for potential confounders and birthweight. The offspring of type 1 diabetic mothers showed significantly increased abdominal obesity risk and metabolic risk, as well as significantly increased levels of fasting insulin and HOMA-IR, independent of potential confounders. Significant associations with fasting glucose and C-peptide were observed only after adjustment. Systolic blood pressure SDS was slightly higher in children with type 1 diabetic mothers in unadjusted analyses (+0.16 [95% CI +0.01, +0.31]), but not after adjustment, while no significant differences in lipids were observed between offspring of mothers with or without type 1 diabetes in unadjusted or adjusted models. The observed associations did not change considerably after excluding children who developed type 1 diabetes (data not shown). Also, the offspring of mothers with type 1 diabetes showed stronger anthropometric associations than offspring of fathers with type 1 diabetes when compared with offspring without parents with type 1 diabetes (ESM Table 1). Our sensitivity analyses based on 330 children indicated that the associations were independent of total energy intake or DII (ESM Table 2). Further, we observed that as children got older, BMI and weight increased at a greater rate in offspring of mothers with type 1 diabetes compared with offspring of

Table 1 Characteristics of study participants stratified by maternal type 1 diabetes in the TEENDIAB and BABYDIAB/BABYDIET cohort

Variable	TEENDIAB (<i>n</i> = 610)			BABYDIAB/BABYDIET (<i>n</i> = 2169)		
	No. obs	OT1DM (<i>n</i> = 257)	OnonDM (<i>n</i> = 353)	No. obs	OT1DM (<i>n</i> = 1287)	OnonDM (<i>n</i> = 882)
Time-constant						
Sex	610			2169		
Male		126 (49.03)	187 (52.97)		661 (51.36)	445 (50.45)
Maternal smoking ^a	581			2128		
Yes		32 (13.11)	43 (12.76)		160 (12.67)	68 (7.86)
Socioeconomic status ^b	594					
Low		7 (2.80)	5 (1.45)	–	–	–
Middle		149 (59.60)	148 (43.02)	–	–	–
High		94 (37.60)	191 (55.52)	–	–	–
Birthweight	571			2047		
SGA		12 (4.94)	37 (11.28)		89 (7.50)	90 (10.47)
AGA		155 (63.79)	252 (76.83)		745 (62.76)	689 (80.12)
LGA		76 (31.28)	39 (11.89)		353 (29.74)	81 (9.42)
Birthweight SDS	571	0.78 ± 1.39	−0.03 ± 0.99	2047	0.57 ± 1.32	−0.06 ± 1.00
Time-varying						
Age (years)	3583	11.90 ± 2.18	11.95 ± 2.15	13235	5.06 ± 4.69	4.63 ± 4.45
BMI SDS	3537	0.31 ± 1.09	−0.14 ± 1.08	13235	0.15 ± 1.08	0.01 ± 1.01
Overweight ^c	3537			13235		
Yes		282 (18.75)	194 (9.54)		1068 (13.70)	569 (10.46)
Height SDS	3537	0.27 ± 0.97	0.35 ± 0.99	13235	0.10 ± 1.01	0.15 ± 1.03
Weight SDS	3537	0.38 ± 1.06	0.09 ± 1.01	13235	0.14 ± 0.96	0.06 ± 0.91
Waist circumference SDS	2418	0.20 ± 1.10	−0.12 ± 1.05	–	–	–
Subscapular skinfold thickness SDS	765	0.18 ± 0.94	−0.04 ± 1.00	–	–	–
Triceps skinfold thickness SDS	768	−0.30 ± 1.09	−0.51 ± 1.09	–	–	–
SBP SDS	2056	−0.05 ± 1.31	−0.25 ± 1.29	–	–	–
DBP SDS	2056	0.27 ± 1.27	0.10 ± 1.31	–	–	–
HDL-cholesterol SDS	590	−0.72 ± 1.24	−0.78 ± 1.26	–	–	–
LDL-cholesterol SDS	590	−0.04 ± 1.04	−0.16 ± 1.11	–	–	–
Triacylglycerol SDS	590	0.36 ± 0.78	0.30 ± 0.83	–	–	–
Cholesterol SDS	590	−0.07 ± 0.95	−0.18 ± 1.05	–	–	–
Metabolic risk ^d (cut-off 1.5 SDS)	3545					
Yes		430 (28.51)	417 (20.47)	–	–	–
Fasting glucose (mmol/l)	3346	4.79 ± 0.62	4.74 ± 0.60	–	–	–
Fasting insulin (pmol/l)	3314	66.15 ± 59.39	60.61 ± 54.78	–	–	–
Fasting C-peptide (nmol/l)	3130	0.55 ± 0.31	0.51 ± 0.28	–	–	–
HOMA-IR	3172	2.06 ± 1.90	1.87 ± 1.72	–	–	–
Total energy intake (kJ)	330	9076.24 ± 2834.46	8634.60 ± 2489.59	–	–	–
DII score	330	0.20 ± 1.83	−0.11 ± 1.71	–	–	–

Data are number (%) or mean ± SD. Percentages were calculated based on the observations available for each variable

^a Smoking during pregnancy in BABYDIAB/BABYDIET and general smoking status in TEENDIAB

^b Based on the education level of parents and monthly net income of the family

^c BMI at or above an SDS of 1.31, corresponding with the 90th percentile

^d High risk when SDS >1.5 for at least one of BMI, waist circumference, subscapular and triceps skinfold thickness, BP and lipids

AGA, appropriate for gestational age; DBP, diastolic BP; LGA, large for gestational age; No. obs, total number of observations available for the variable; OnonDM, offspring of non-diabetic mothers; OT1DM, offspring of mothers with type 1 diabetes; SBP, systolic BP; SGA, small for gestational age; DII, dietary inflammatory index

Fig. 1 Mean and 95% CI for BMI (a, d), weight (b, e) and height (c, f) SDSs stratified by age and maternal type 1 diabetes in the TEENDIAB (a–c) and BABYDIAB/BABYDIET (d–f) cohorts. Black circles, offspring of mothers with type 1 diabetes; white circles, offspring of non-diabetic mothers

non-diabetic mothers, whereas height increased at a greater rate in offspring of non-diabetic mothers (ESM Fig. 2 and 3).

Analyses of metabolomic profiles

The metabolomics blood samples were taken at a median age of 10 years (range 6–16 years), and 48 individuals (10%) were overweight at that time. Of the children included in the metabolomics analyses ($n = 485$), 247 (51%) were male and 197 (41%) had mothers with type 1 diabetes. Of the 441 metabolites analysed, 28 showed significant associations with being overweight after multiple testing correction, and 19 of these were of known identity (Table 4). All these metabolites were upregulated in overweight individuals, including four metabolites from the amino acid class (valine, kynurenate, tyrosine and alanine), 11 from the lipid class (androgenic steroids such as androsterone sulphate, epiandrosterone sulphate, carnitine and the short-chain acyl-carnitine [butyryl carnitine (C4)],

glycerol, thromboxane B_2 , stearidonate and 2-aminoheptanoate), and four metabolites from other classes (N1-methyl-4-pyridone-3-carboxamide, urate, γ -glutamyltyrosine and piperine). At the pathway level, several subpathways such as androgenic steroids and branched-chain amino acid (BCAA) metabolism were upregulated in overweight individuals, as was the superpathway nucleotide (Fig. 2). Similarly, three principal components, characterised by androgenic steroids, BCAAs and related metabolites or composed of amino acid, lipid and acetylated peptides, were associated with being overweight (ESM Fig. 4 and ESM Table 3). The principal components related to androgenic steroids and BCAAs were also positively associated with HOMA-IR ($p < 0.0001$ and $p = 0.002$ respectively), fasting insulin ($p < 0.0001$ and $p = 0.005$) and fasting C-peptide ($p = 0.002$ and $p < 0.0001$).

In contrast, there was no significant association of any metabolite with maternal type 1 diabetes when corrected for

Table 2 Effect estimates for anthropometric and metabolic outcomes in offspring born to a mother with vs without type 1 diabetes in the TEENDIAB cohort

Outcome	Model 1		Model 2		Model 3	
	No. participants (No. obs)	Estimates (95% CI)	No. participants (No. obs)	Estimates (95% CI)	No. participants (No. obs)	Estimates (95% CI)
Absolute change in SDS						
Height SDS	610 (3537)	−0.12 (−0.28, 0.03)	562 (3122)	−0.07 (−0.23, 0.08)	527 (2955)	−0.27 (−0.43, −0.10)**
Weight SDS	610 (3537)	0.20 (0.04, 0.36)*	562 (3122)	0.22 (0.06, 0.39)*	527 (2955)	0.07 (−0.10, 0.25)
BMI SDS	610 (3537)	0.35 (0.19, 0.52)**	562 (3122)	0.36 (0.19, 0.53)**	527 (2955)	0.28 (0.09, 0.46)**
Waist circumference SDS ^a	489 (2418)	0.29 (0.12, 0.46)**	452 (2152)	0.24 (0.06, 0.42)**	426 (2057)	0.19 (0.00, 0.39)*
Subscapular skinfold SDS	570 (765)	0.19 (0.03, 0.35)*	499 (662)	0.17 (0.01, 0.33)*	471 (626)	0.12 (−0.05, 0.30)
Triceps skinfold SDS	572 (768)	0.19 (0.02, 0.37)*	500 (663)	0.15 (−0.04, 0.33)	472 (627)	0.09 (−0.10, 0.29)
SBP SDS	597 (2056)	0.16 (0.01, 0.31)*	543 (1825)	0.13 (−0.03, 0.30)	510 (1727)	0.10 (−0.07, 0.28)
DBP SDS	597 (2056)	0.12 (−0.03, 0.26)	543 (1825)	0.14 (−0.01, 0.30)	510 (1727)	0.17 (0.00, 0.34)*
HDL-cholesterol SDS	590	0.06 (−0.14, 0.27)	502	0.04 (−0.18, 0.27)	471	0.06 (−0.19, 0.30)
LDL-cholesterol SDS	590	0.10 (−0.07, 0.28)	502	0.08 (−0.11, 0.28)	471	0.10 (−0.11, 0.31)
Triacylglycerol SDS	590	0.06 (−0.07, 0.19)	502	0.10 (−0.05, 0.24)	471	0.12 (−0.04, 0.27)
Cholesterol SDS	590	0.10 (−0.06, 0.27)	502	0.09 (−0.09, 0.27)	471	0.13 (−0.07, 0.32)
% change in metabolic outcome						
Fasting glucose	606 (3346)	1.00 (−0.32, 2.34)	558 (2937)	1.71 (0.29, 3.16)*	523 (2785)	2.05 (0.51, 3.62)*
Fasting insulin	608 (3314)	8.32 (0.68, 16.55)*	560 (2902)	8.45 (1.06, 16.38)*	525 (2749)	9.70 (1.71, 18.31)*
Fasting C-peptide	601 (3130)	6.01 (−0.23, 12.64)	553 (2744)	5.18 (−0.59, 11.28)	519 (2602)	6.61 (0.33, 13.27)*
HOMA-IR	606 (3172)	8.36 (0.38, 16.99)*	558 (2781)	9.49 (1.69, 17.88)*	523 (2641)	11.55 (3.02, 20.79)*
OR						
Overweight	610 (3537)	2.40 (1.41, 4.06)**	562 (3122)	2.28 (1.29, 4.01)**	527 (2955)	2.06 (1.12, 3.78)*
Abdominal obesity ^{a,b}	498 (2564)	1.92 (1.15, 3.20)*	460 (2273)	1.91 (1.11, 3.30)*	433 (2168)	1.97 (1.10, 3.55)*
Metabolic risk ^c (cut-off 1.5 SDS)	610 (3545)	1.45 (1.10, 1.92)*	562 (3128)	1.46 (1.07, 1.97)*	527 (2961)	1.37 (0.98, 1.90)

Model 1, crude model; model 2, adjusted for age, sex (except for overweight, abdominal obesity, metabolic risk and SDS outcomes), Tanner's staging, maternal smoking and socioeconomic status; model 3, model 2 + birthweight

^a Calculated only in children ≥ 11 years of age

^b Waist circumference ≥ 90 th percentile or the adult threshold (International Diabetes Federation)

^c High risk when SDS > 1.5 for at least one of BMI, waist, subscapular and triceps skinfold thickness, blood pressure and lipids; otherwise defined as low risk

* $p < 0.05$ and ** $p < 0.01$

No., number of; Obs, observations (if different from number of participants)

Table 3 Effect estimates for anthropometric outcomes in offspring born to a mother with vs without type 1 diabetes in the BABYDIAB/BABYDIET cohort

Outcome	Model 1		Model 2		Model 3	
	No. participants (No. obs)	Estimates (95% CI)	No. participants (No. obs)	Estimates (95% CI)	No. participants (No. obs)	Estimates (95% CI)
Absolute change in SDS						
Height	2169 (13235)	−0.06 (−0.13, 0.02)	2128 (11757)	−0.06 (−0.14, 0.02)	2010 (11374)	−0.13 (−0.21, −0.06)**
Weight	2169 (13235)	0.06 (−0.01, 0.13)	2128 (11757)	0.06 (−0.01, 0.13)	2010 (11374)	−0.05 (−0.12, 0.02)
BMI	2169 (13235)	0.13 (0.06, 0.20)**	2128 (11757)	0.14 (0.07, 0.21)**	2010 (11374)	0.04 (−0.04, 0.11)
OR						
Overweight	2169 (13235)	1.44 (1.20, 1.73)**	2128 (11757)	1.45 (1.20, 1.74)**	2010 (11374)	1.15 (0.95, 1.40)

Model 1, crude model; model 2, adjusted for Tanner's staging and maternal smoking during pregnancy; model 3, model 2 + birthweight

* $p < 0.05$ and ** $p < 0.01$

No., number of; Obs, observations

multiple testing, and there was not even a significant association at the 5% level for any of the metabolites found to be associated with being overweight (ESM Table 4). No significant associations were observed between maternal type 1 diabetes and any of the principal components (ESM Fig. 5) or super- and subpathways (ESM Fig. 6) after correcting for multiple testing.

Further, the associations between maternal type 1 diabetes and offspring overweight status remained significant and were not markedly attenuated after adjustment for any potentially relevant single metabolite concentration or principal components (Table 5), indicating that none is in the causal pathway.

Discussion

Our findings suggest that the offspring of mothers with type 1 diabetes have a higher BMI and increased risk for being overweight as well as increased insulin resistance compared with offspring of non-diabetic mothers. The association between maternal type 1 diabetes and excess weight later in life could be substantially explained by birthweight in our birth cohort data, but only partially in our TEENDIAB data, perhaps because these did not include measurements before school age. Metabolic alterations, however, do not seem to be involved in the pathway. Although some metabolic patterns were found to be associated with being overweight, no such associations were observed with respect to maternal type 1 diabetes.

Previous studies that examined the offspring of mothers with type 1 diabetes reported similar findings with respect to excess weight gain, the metabolic syndrome and related outcomes at different ages [7–10]. However, one study [39] found that the prevalence of being overweight in 6–8-year-old offspring of mothers with type 1 diabetes under adequate glycaemic control was similar to that in a reference

population, potentially pointing to a possible approach for the early prevention of excess weight gain in these children.

Our analysis indeed suggests that offspring of mothers with type 1 diabetes are more prone to worsening of metabolic profile than offspring of fathers with type 1 diabetes when compared with offspring whose parents did not have type 1 diabetes, thus providing evidence to support a potential role for intrauterine hyperglycaemia rather than for parental genetic transmission. Previous analyses of the BABYDIAB data (without BABYDIET and with much shorter follow-up than here) suggested that maternal type 1 diabetes may not be an independent predictor of overweight status during childhood but associated factors such as birthweight may predispose individuals to risk of being overweight [14]. Indeed, the associations between maternal type 1 diabetes and offspring overweight status were attenuated by 62% after adjustment for birthweight in the BABYDIAB/BABYDIET study, but only by 10% in the TEENDIAB study. Moreover, the effect estimates were generally weaker in BABYDIAB/BABYDIET compared with TEENDIAB. We assume that these differences come from the different age structures in the studies. The BABYDIAB/BABYDIET cohort followed children from birth, with most anthropometric measurements taken during the preschool period, whereas recruitment started at a minimum age of 6 years in TEENDIAB. Although both studies followed children until 18 years, anthropometric data were not available after 6 years of age for 30% of the BABYDIAB/BABYDIET participants. Birthweight is more strongly associated with a child's BMI in early childhood than later, which may explain the observed differences between the two studies. It has also been suggested that maternal diabetes may have a delayed influence on the offspring's adiposity that increases with age [40, 41]. We consider it less likely that the differences observed between our two cohorts are caused by different environmental conditions around the time of birth, as the median birth year in TEENDIAB was 2001 compared with 1997

Table 4 Cross-sectional associations between metabolite concentrations and overweight status in the offspring

Exposure	Cross-sectional models (<i>n</i> = 485)	
	OR ^a (95% CI)	<i>p</i> value
Amino acid		
Alanine ^b	9.23 (2.42, 35.23)*	0.0011
Valine ^b	88.27 (7.79, 999.85)*	0.0003
Kynurenate ^b	9.32 (3.14, 27.64)*	5.7×10 ^{−5}
Tyrosine ^b	37.21 (5.66, 244.55)*	0.0002
Lipid		
Androsterone sulphate ^b	2.02 (1.37, 2.98)*	0.0004
Androstenediol (3β,17β) disulphate (1) ^b	1.92 (1.33, 2.77)*	0.0005
Epiandrosterone sulphate ^b	1.96 (1.34, 2.88)*	0.0005
5α-Androstan-3β,17β-diol disulphate ^b	1.92 (1.31, 2.81)*	0.0007
Dehydroisoandrosterone sulphate (DHEA-S) ^b	1.94 (1.26, 2.98)*	0.0028
Carnitine ^b	139.11 (11.03, 1754)*	0.0001
Thromboxane B ₂	2.32 (1.44, 3.73)*	0.0005
Butyrylcarnitine (C4) ^b	2.90 (1.63, 5.17)*	0.0003
2-Aminoheptanoate ^b	4.32 (1.68, 11.11)*	0.0024
Glycerol	5.90 (2.11, 16.50)*	0.0007
Stearidonate (18:4 <i>n</i> -3)	3.40 (1.53, 7.54)*	0.0026
Cofactor/vitamin		
N ¹ -methyl-4-pyridone-3-carboxamide ^b	4.37 (1.85, 10.31)*	0.0008
Nucleotide		
Urate ^b	35.05 (4.58, 268.08)*	0.0006
Peptide		
γ-Glutamyltyrosine ^b	8.24 (2.29, 29.62)*	0.0012
Xenobiotic		
Piperine	1.81 (1.32, 2.47)*	0.0002

Cross-sectional models: crude associations between overweight status and metabolite concentrations at the same visit. Only the metabolites significantly associated with being overweight in the cross-sectional models after multiple testing correction are reported in the table

^a OR for overweight status

^b Reported in the literature [15, 16] to be associated with overweight status in children

*Significant after correction for multiple testing

for BABYDIAB/BABYDIET, and a significant association between maternal type 1 diabetes and offspring being overweight has been consistently observed in previous studies irrespective of when the children were born [7–10].

Our findings are similar to previous studies on metabolomics and overweight status in children and adolescents without a type 1 diabetes background. Of the 19 metabolite concentrations associated with being overweight in our data, 16 have previously been reported in the literature [15, 16]. For example, our finding that elevated androgenic steroids and BCAA-related metabolite pattern are associated with being overweight and increased insulin resistance is consistent with other studies based on data from children without family history of type 1 diabetes [15, 16]. Studies on the association of exposure to maternal diabetes and changes in the offspring's metabolome are rare. We are aware of only one study which

found no significant associations of gestational diabetes and offspring metabolites [16]. Similarly, we found no associations of maternal type 1 diabetes with metabolite concentrations in the offspring. Nevertheless, we were able to identify differences between the metabolomes of overweight and normal-weight children. It may be possible that these differences were observed as an effect, rather than a cause, of being overweight, and hence are not in the causal pathway between maternal type 1 diabetes and excess weight gain in offspring.

The main strength of our study is the prospective design with multiple follow-ups and the availability of a wide range of anthropometric and metabolic outcomes in addition to metabolomics data. As we had data available from two large study populations, we could validate the results for overweight status and BMI. Both cohorts were based on children with a first-degree relative with type 1 diabetes, who were at

Fig. 2 Association between super- and subpathways of metabolites and overweight status in the offspring. Pathways located to the right of the zero line indicate upregulation, and left of the zero line indicate downregulation, in overweight individuals. Pathways lying beyond the dashed grey line on both sides indicate associations with $p < 0.05$ without adjustment for multiple testing. After multiple testing correction, the subpathways of androgenic steroids, fatty acid metabolism (also BCAA

metabolism), glycerolipid metabolism, lysine metabolism, polypeptide and food component/plant were upregulated in overweight individuals. Similarly, the superpathway nucleotide was also found to be upregulated in overweight individuals. *Significant after correction for multiple testing. The numbers in brackets represent the number of metabolites in each super- or subpathway. Black squares, superpathway; grey squares, subpathway. SAM, *S*-adenosyl methionine; TCA, tricarboxylic acid

increased risk of developing type 1 diabetes themselves, but otherwise healthy. Despite adjustment for some important covariates in our analyses, we cannot rule out the possibility of unmeasured confounding in our study. In particular, we had no data on maternal pre-pregnancy BMI, which is known to play a major confounding role with respect to childhood excess weight gain. However, it should not be as relevant when comparing mothers with and without type 1 diabetes as it

would be in the context of other diabetes forms. While the mothers of all BABYDIAB/BABYDIET children had been diagnosed with type 1 diabetes before the index pregnancy, we did not have this information available for the TEENDIAB children. Although we therefore cannot rule out that a small number of the TEENDIAB children had not been exposed to type 1 diabetes in utero, we believe that this is not a major concern as the onset of type 1 diabetes occurs most frequently

Table 5 Association between maternal type 1 diabetes and being overweight in the offspring adjusting for different covariates in the metabolomics subset ($n = 485$)

Model and adjustment	OR for overweight status (95% CI)	<i>p</i> value
Model 1	2.44 (1.33, 4.50)	0.004
Model 2	2.51 (1.23, 5.12)	0.004
Model 2 ^a		
Birthweight	2.20 (1.04, 4.66)	0.040
Model 2 ^b		
Amino acid		
Kynurenate	2.81 (1.34, 5.89)	0.006
Tyrosine	2.55 (1.23, 5.31)	0.012
Valine	2.76 (1.33, 5.70)	0.006
Alanine	2.51 (1.21, 5.21)	0.013
Lipid		
Androsterone sulphate	2.54 (1.23, 5.24)	0.012
Androstenediol (3 β ,17 β) disulphate (1)	2.47 (1.20, 5.09)	0.014
Epiandrosterone sulphate	2.57 (1.24, 5.32)	0.011
5 α -Androstan-3 β ,17 β -diol disulphate	2.37 (1.15, 4.89)	0.020
Dehydroisoandrosterone sulphate (DHEA-S)	2.50 (1.22, 5.14)	0.013
Carnitine	2.52 (1.22, 5.20)	0.013
Thromboxane B ₂	2.66 (1.29, 5.49)	0.008
Butyrylcarnitine (C4)	2.72 (1.32, 5.63)	0.007
2-Aminoheptanoate	2.47 (1.20, 5.07)	0.014
Glycerol	2.47 (1.19, 5.12)	0.015
Stearidonate (18:4 <i>n</i> -3)	2.58 (1.25, 5.34)	0.011
Cofactor/vitamin		
N ¹ -Methyl-4-pyridone-3-carboxamide	2.64 (1.27, 5.47)	0.009
Nucleotide		
Urate	2.45 (1.18, 5.08)	0.016
Peptide		
γ -Glutamyltyrosine	2.54 (1.23, 5.25)	0.011
Xenobiotic		
Piperine	2.66 (1.28, 5.51)	0.009
Model 2 ^c		
PC3	2.50 (1.21, 5.18)	0.014
PC5	2.87 (1.37, 6.04)	0.005
PC13	2.59 (1.25, 5.37)	0.010

Model 1: crude model; Model 2: adjusted for Tanner's staging, maternal smoking and socioeconomic status

^a Further adjusted for birthweight

^b Further adjusted for metabolites significant for being overweight

^c Further adjusted for principal components significant for being overweight

PC, principal components

at a young age and hence before women get pregnant for the first time. To our knowledge, this is the first study examining the influence of the metabolomics profile on the association between maternal type 1 diabetes and offspring overweight status. With 441 metabolites analysed in 485 children, and a number of metabolites confirming previously reported associations with being overweight, we believe that the missing associations between maternal type 1 diabetes and metabolites in our data are not likely to be false-negative findings.

In summary, offspring of mothers with type 1 diabetes showed increased adiposity, insulin resistance, fasting insulin and C-peptide compared with offspring of non-diabetic mothers. Certain metabolite concentrations were positively associated with being overweight in the offspring. However, metabolic changes seem unlikely to be in the causal pathway between maternal type 1 diabetes and excess weight in offspring, as this association could not be explained by any of the potentially relevant metabolites.

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Data availability The datasets analysed during the current study are available from the corresponding author on reasonable request.

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Contribution statement AP reviewed data, undertook statistical analysis, interpreted results and wrote the first and final draft of the manuscript together with AB. MJ contributed to data management and statistical analysis and reviewed the manuscript. CW, SH, NH, JR and OK acquired data and reviewed the manuscript. JK and GK interpreted results and reviewed the manuscript. A-GZ is the principal investigator of the BABYDIAB/BABYDIET and TEENDIAB studies, designed the studies and concept, interpreted the results and critically reviewed the manuscript for intellectual content. All authors approved the final version of the manuscript. A-GZ is the guarantor of this work.

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