The long-term metabolic and neurocognitive risks in offspring of women with type 1 diabetes mellitus

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ABSTRACT

Background and Aims: Previous studies have evaluated long-term metabolic and neurocognitive outcomes in offspring of women with diabetes. However, many studies did not differentiate between different types of diabetes. We aimed to specifically evaluate both metabolic and neurocognitive outcomes in offspring of women with type 1 diabetes mellitus (OT1D).

Methods: We conducted an extensive literature search on PubMed between February 2020 and September 2020. We performed a scoping review including 12 retrospective cohort studies, 15 prospective cohort studies, one case-control study and one cross-sectional study, comparing long-term metabolic and neurocognitive outcomes between OT1D and a control group.

Results: OT1D had a higher body mass index and an increased risk for overweight and obesity compared to offspring of mothers without diabetes. A limited number of studies showed a higher risk for (pre)diabetes, higher rates of non-alcoholic fatty liver disease and metabolic syndrome in OT1D. Index offspring had in general similar intelligence and academic achievement as control children but a higher risk for attention deficit and hyperactivity disorders. Data were conflicting concerning the increased risk for autism spectrum disorders. There is limited evidence suggesting that female offspring have more often unfavorable metabolic parameters, while male offspring are more at risk for hyperactivity/impulsivity.

Conclusion: Maternal type 1 diabetes mellitus is associated with an increased risk of several metabolic complications and neurobehavioral disorders in the offspring. Increased attention for long-term complications in this population is needed. Further research is needed to evaluate whether improved glycemic control in pregnancy can reduce these long-term complications.

KEYWORDS

Type 1 diabetes mellitus; pregnancy; offspring; long-term metabolic outcomes; long-term neurocognitive outcomes; glycemic control.

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a global public health problem. In recent decades, the incidence has been rising by as much as 5.3% annually in the U.S. and by 3% in Europe [1]. Moreover, there is an increasing incidence rate of T1DM and type 2 diabetes mellitus (T2DM) in the younger population, of 1.4% respectively 7.1% [2]. Previous research has revealed a plethora of potential harmful effects on offspring of women diagnosed with diabetes mellitus before or during pregnancy. Pregestational diabetes mellitus is associated with intrauterine hyperglycemia, which leads to fetal hyperinsulinemia and fetal overgrowth [3-5].

Past studies have researched how metabolic alterations affect the long-term outcomes of children born from diabetic pregnancies. A study showed that children of T1DM mothers had significantly higher body mass index (BMI) z-scores from prepubertal to adolescent age and higher risk of T2DM than offspring of non-diabetic mothers (ONDM) [6]. One study indicated an increase in odds of offspring from diabetic mothers of any type for non-alcoholic fatty liver disease (NAFLD) [7]. Another major concern are adverse neurological and cognitive outcomes. A recent meta-analysis showed an association between *in utero* exposure to maternal pre-existing diabetes of any type and poorer neurocognitive and behavioral outcomes [8]. The exposed group had lower pooled intelligence quotients (IQ), increased risk of autism spectrum disorders (ASD) and attention deficit and hyperactivity disorders (ADHD) [8].

However, an important limitation is that most studies did not distinguish between gestational diabetes mellitus (GDM), T1DM or T2DM in evaluating the long-term outcomes on the offspring. Despite the emergence of T2DM in young adults, T1DM remains the predominant form in children and young adults [9]. Given the differences in pathogenesis and sociodemographic profile between different types of diabetes, it is pivotal to differentiate between types of diabetes, in order to adjust for potential mediators.

The rapidly increasing amount of research in this field has created a need to cluster the existing data. We performed therefore a scoping review summarizing data from previously published studies about the metabolic and neurocognitive long-term outcomes in offspring of women with T1DM in pregnancy. We also aimed to evaluate age- and sex-specific differences in the long-term outcomes.

METHODS

From February 2020 to September 2020, we performed a literature search using PubMed. We applied the PRISMA guidelines for Scoping Reviews [10].

Study question and eligibility

This scoping review addressed the following research question: “What are the long-term metabolic and neurocognitive outcomes in offspring of women with T1DM?”. In order to be included in this review, studies needed to comply with the Population Exposure Comparison Outcome (PECO) question and the inclusion criteria. We used the following PECO:

- population: offspring born to mothers with T1DM;
- exposure: maternal T1DM in pregnancy;
- comparison: no maternal diabetes (either T1DM, T2DM or GDM) or population-based standards;
- outcome: long-term metabolic outcomes (overweight and obesity, metabolic syndrome, fatty liver disease, glucose disorders and insulin resistance) or neurocognitive outcomes (intelligence, academic performance, ASD, attention deficit disorders or ADHD), beyond the infantile age.

Study designs considered for inclusion were cross-sectional studies, case-control studies, cohort studies, randomized controlled trials and meta-analyses. We excluded animal studies, studies of low quality (case reports, case series, commentaries, expert opinions, no method section, no p-values mentioned), reviews without meta-analysis, studies that made no distinction between different types of diabetes mellitus, studies that included only GDM and/or T2DM and articles written in a language other than English, Dutch or French.

Search strategy and study selection

We developed the search strategy in collaboration with a medical librarian of the university hospital UZ Leuven, using key words and Medical Subject Heading (MeSH) terms. The following search was conducted in PubMed:

((("Pregnancy in Diabetics"[Mesh] OR ("Diabetes Mellitus, Type 1"[Mesh] OR diabetes[tiab] OR diabetic[tiab]) AND ("Pregnancy" [Mesh] OR pregnan*[tiab] OR maternal[tiab] OR pregestational[tiab]))) AND ("Child"[Mesh] OR child*[tiab] OR minor*[tiab] OR preschool-child*[tiab] OR "Adolescent"[Mesh] OR "Adult Children"[Mesh] OR offspring[tiab] OR pediatric*[tiab] OR paediatric*[tiab] OR toddler*[tiab] OR baby[tiab] OR babies[tiab] OR adolescen*[tiab] OR adulthood[tiab] OR adults[tiab] OR juvenile[tiab] OR puber*[tiab] OR teen[tiab] OR teens[tiab] OR teenager*[tiab])) AND ("Insulin Resistance"[Mesh] OR "Obesity"[Mesh] OR "Overweight"[Mesh] OR "Adiposity"[Mesh] OR "Body Mass Index"[Mesh] OR "Metabolic Syndrome"[Mesh] OR "Fatty Liver"[Mesh] OR "Cognitive Dysfunction"[Mesh] OR "Intelligence"[Mesh] OR "Intellectual Disability"[Mesh] OR "Learning Disabilities"[Mesh] OR "Academic Success"[Mesh] OR "Academic Performance"[Mesh] OR "Attention Deficit Disorder with Hyperactivity"[Mesh] OR "Attention Deficit and Disruptive Behavior Disorders"[Mesh] OR "Autism Spectrum Disorder"[Mesh])).

First, we scanned title and abstract of all citations resulting from our literature search to assess eligibility for our review. Next, we performed a full-text review of all articles eligible after title and abstract evaluation. In addition, we hand-searched references of included studies and other related articles in order to detect additional articles for inclusion. We used EndNote for citation management and Rayyan QCRI to facilitate article screening.

Data extraction, synthesis and analysis

For every study included, we extracted the following data: author, year of publication, country, study design, number of exposed subjects, offspring age, metabolic or neurocognitive outcome relevant to our study question and potential confounding factors adjusted for. If data for a particular outcome were reported using multiple models with increasing amounts of adjustments, only data from the model with the highest number of confounding factors adjusted for, were mentioned, unless otherwise stated. P-values were considered significant according to the criteria described in the original article. We reported our findings in a descriptive fashion.

RESULTS

Search results

Our search strategy identified 2890 citations, of which 2884 remained after removal of duplicates. After selection based on title and abstract, we executed a complete-text review of 119 articles, of which twenty-four were included. In addition, we included five hand-searched articles, leading to a total of 29 articles included in this review (Figure 1).

Study characteristics

Table 1 shows an overview of the study characteristics. Of all 29 studies included, there were 12 retrospective cohort studies (42%), 15 prospective cohort studies (52%), one case-control study (3%) and one cross-sectional study (3%). Twenty-four studies were performed in Europe (83%), three in the United States (11%), one in Oceania (3%) and one study was multinational (3%). Included articles were published between 1998 and 2019, with 18 studies (62%) carried out from 2010 onwards. The number of study participants, exposed to maternal T1DM, ranged from 16 to 15615 subjects. Age of offspring at follow-up varied from 0.3 year to 45 years. Four articles did not report the age ranges of the offspring.

Metabolic outcomes

1. Overweight and obesity

Nine included studies reported on overweight or BMI as a main outcome in offspring of women with T1DM (OT1D) (Table 1). Overall, the prevalence of overweight and obesity tended to be higher in OT1D than in controls, although results were not consistent and differences were not always significant [5,11-15].

Three studies only presented BMI or BMI standard deviation scores (SDS), without data on overweight or obesity using specific cut-offs (Table 2) [16-18]. Mughal *et al.* and Vlachová *et al.* showed significantly higher BMI-SDS in OT1D, with mean differences of 0.32 (0.44 vs. 0.12; $p=0.018$) and 0.44 ($p<0.001$) respectively [16,18]. Vlachová *et al.* adjusted their data on BMI-SDS for pubertal development and maternal pre-pregnancy BMI [18]. In another study, OT1D had significantly higher BMI and percent body fat based on the sum of skinfold measures [17]. Weight-for-height z-scores and percent body fat based on impedance analysis were also higher in OT1D, but these associations were not significant [17].

Four articles reported odds ratios (OR) for overweight and/or obesity (Table 2). ORs for overweight ranged from 0.80-2.27 in OT1D and for obesity from 1.48-1.97 [5,11,13,15]. One study showed a significant OR for both overweight and abdominal obesity, which remained significant after adjustment for age, pubertal development, maternal smoking, socioeconomic status and birthweight ($p<0.05$) [13]. In another study, there was a higher prevalence of overweight (OR 1.60) and obesity (OR 1.84) in OT1D, but these associations did not remain significant after adjustment for birthweight [5]. Hummel *et al.* assessed overweight in children at 2, 5 and 8 years of age, but did not find a significantly higher rate of overweight in OT1D at any age [11].

Three studies detailed proportions of overweight and obesity. The prevalence of overweight in these articles ranged from 15.2-41.0% in OT1D compared to 0-24.0% in ONDM (Table 2) [12,14,15]. For obesity, the prevalence varied from 3.8-12.0% in OT1D and from 2.0-6.7% in ONDM. One study found a significantly higher proportion of children with overweight in OT1D, corresponding to an OR of 2.27 ($p<0.05$) after adjustment for multiple confounders [15]. No significant association could be demonstrated for obesity [15]. Another study reported a significant increase in BMI and a higher prevalence of overweight, obesity and central obesity in OT1D [12]. The association for BMI remained significant after adjustment for maternal BMI ($p=0.03$), but not for BMI-SDS ($p=0.08$). Maternal and offspring BMI were not related in OT1D ($p=0.34$) [12]. One study did not find a significant difference in overweight nor obesity proportions between index and control groups [14].

Six included articles reported that there was no significant association between maternal glycemic control during pregnancy – measured by HbA_{1c} or mean glucose – and overweight, obesity or BMI-SDS in OT1D [12,14-18].

2. Glucose disorders and insulin resistance

Nine articles assessed insulin resistance and glucose intolerance in OT1D. Four of these studies did not adjust for any potential mediators. Various assays and criteria were used to define the outcomes (Supplementary Table 1).

Three studies reported on prediabetes (impaired glucose tolerance [IGT] and impaired fasting glucose [IFG]) or diabetes as outcomes (Table 2). One study found a significantly higher risk for T2DM or prediabetes in OT1D, after correction for family history of diabetes, maternal overweight, offspring age and overweight (OR 3.19) [19]. They did not observe significant differences for T2DM, IGT and IFG separately [19]. In another study, there was a significantly higher prevalence of IGT in OT1D, but not of IFG and diabetes [20]. IGT was found more often in offspring with macrosomia at birth or overweight/obesity at 2-5 years ($p<0.05$) [20]. Vlachová *et al.* reported significantly more prediabetes cases in OT1D than in ONDM (15.4% vs. 8.1%, $p=0.011$) [18].

Seven studies used parameters from glucose tolerance testing as substitute outcomes. Homeostatic model assessment of insulin resistance (HOMA-IR) results were described in four articles. In two of these, HOMA-IR was significantly increased in OT1D, correcting for multiple factors [13,18]. Two other studies showed no statistic differences between groups [21,22]. One study used HOMA-B to quantify β -cell function, but there was no significant association, nor for fasting serum insulin concentration or first-phase insulin response [23]. Another study reported higher insulin resistance in OT1D, as measured by insulin/glucose quotients ($p<0.05$) [24]. In one cohort, insulin sensitivity was lower in OT1D, based on β -cell function insulin sensitivity glucose tolerance testing, but the Matsuda index showed no statistic differences [22].

One study found that elevated maternal blood glucose in late pregnancy was significantly associated with a higher risk of T2DM and prediabetes in OT1D [19]. In contrast, two articles reported a lack of association between maternal glycemic control in pregnancy and insulin sensitivity in OT1D [18,22].

3. Fatty liver disease

Only one study reported on fatty liver disease in OT1D [25]. OT1D showed a significantly higher fatty liver index (FLI) than ONDM, with median values of 5.3 versus 3.6 respectively ($p=0.001$) (Table 2). Similarly, there was a significant difference in waist-to-height ratio (WHtR) between both groups ($p<0.001$). More children of T1DM mothers had NAFLD based on $FLI\geq 60$ ($p=0.02$) or $WHtR>0.496$ ($p<0.001$) than controls. There was no association between maternal HbA_{1c} during pregnancy and offspring FLI group. In OT1D, a $WHtR>0.496$ was associated with a significantly higher maternal HbA_{1c} in the third trimester of pregnancy ($p=0.04$), but not in the pregestational period, the first or second trimester [25].

4. Metabolic syndrome

Two articles evaluated the risk of metabolic syndrome (MetS) in OT1D, using the International Diabetes Federation criteria (Supplementary Table 1) [15,18]. In one study, the risk of MetS was significantly higher in adult OT1D than in the offspring of the background population group (OR 2.73; $p<0.05$) (Table 2) [15]. After adjustment for confounding factors, this association remained significant (OR 2.59). Subgroup analyses showed no significant association between maternal mean glucose in first or third trimester and the risk of MetS in OT1D [15]. The other study reported a higher prevalence of MetS in OT1D (children 13-19.8 years old) than in controls, though the association was not significant ($p=0.054$). There were no

significant associations between maternal HbA_{1c} levels in pregnancy and the components of MetS [18].

Neurocognitive outcomes

1. Intelligence

One study assessed cognitive function in adolescents using four intelligence and memory indices from the Reynolds Intellectual Assessment Scales [26]. OT1D had lower scores on all cognitive measures, compared to ONDM. The associations remained only significant for composite intelligence and composite memory after adjustment for several potential mediators (Table 3). Furthermore, learning difficulties in Danish and mathematics classes were significantly more frequent in OT1D. After adjusting for potential mediators, the difference remained significant for mathematics, but not for Danish learning difficulties. No differences were found regarding reading and writing problems. Glycemic control in pregnancy, measured by HbA_{1c}, was not directly associated with offspring cognitive function [26]. Another study calculated a global cognitive score from four subtests (Supplementary Table 1) [27]. OT1D obtained significantly lower scores (94.8 vs. 100.0 in controls, $p=0.004$). When adjusted for potential mediators, the difference was no longer significant [27]. A third study found no significant difference between groups in the full-scale IQ, based on subtests from the Wechsler Intelligence Scale for Children [28]. One subtest – digit span – showed significantly lower results in OT1D than the UK normative data ($p<0.01$) [28].

2. Academic achievement

Knorr *et al.* collected data from grades obtained by OT1D and a control group, at 15-16 years of age [29]. The average school grade was 6.37 for OT1D and 6.52 for controls (Table 3). After adjustment for sex, maternal age and parental educational status, there was no significant difference. Gestational age was not found to be a significant confounder, as offspring born prematurely or at a gestational age of ≥ 37 weeks had similar average grades as the controls. Nevertheless, they observed a significant association between average school grades in offspring and glycemic control in the mothers with T1DM, measured by HbA_{1c}. The association appeared significant in the pregestational stage ($p=0.04$), as well as in the first ($p<0.001$), second ($p=0.03$) and third ($p<0.001$) trimester [29].

3. Autism spectrum disorders

Results from two studies investigating ASD in OT1D were inconsistent (Table 3). One study found in general no increased prevalence of ASD in OT1D [30]. However, one specific disorder within the autism spectrum, infantile autism, was significantly more prevalent in OT1D with an incidence rate ratio (IRR) of 2.14 ($p<0.05$) [30]. In contrast, another study found a significantly higher risk of ASD in OT1D, with a hazard ratio (HR) of 2.36 ($p=0.003$), after correction for multiple confounders. This association remained significant after additional adjustment for maternal smoking during pregnancy and pre-pregnancy BMI (HR 2.33, $p=0.005$) [31].

4. Attention deficit (and hyperactivity) disorders

Four studies showed a significantly higher risk of ADHD in OT1D than in controls, correcting for potential mediators like birth year, parental education and parental history of

ADHD (Table 3) [1,4,32,33]. One study created a regression model with data from women with T1DM, T2DM and GDM, resulting in a HR of 1.56 for OT1D ($p=0.02$) [4]. Numbers for OT1D remained consistent when the GDM mothers were separated by medication use in the model (HR 1.57, $p=0.01$) [4]. Nielsen *et al.* showed an IRR of 1.36 ($p<0.05$) for ADHD in OT1D [33]. One study evaluated attention using Conners Continuous Performance Test version II, a high signal-to-noise test [34]. Based on individual test measures, there was no increase in attention deficits in adolescent OT1D. However, a higher proportion of children in the OT1D group reported ADHD medication use (2.2% vs. 0% in ONDM, $p=0.01$) [34].

Age and sex-specific differences in long-term offspring outcomes

1. Age

Among studies with metabolic outcomes, seven corrected for offspring age (Table 2). One study described an increasing difference with higher age for insulin sensitivity between index and control groups, the difference becoming significant at 17 years of age [35]. For HOMA-IR, there were no significant age-specific differences [35]. Similarly, in the study by Hunter *et al.*, glucose regulation parameters were not influenced by offspring age [36]. In one cohort, total body fat percentage was in general increasingly higher in OT1D than in control offspring with increasing age [35]. A similar tendency was demonstrated for BMI [35]. Another study found a higher average BMI-SDS increase per year increase in age in OT1D compared to controls, as well as a 13% relative increase in overweight risk per year increase in age [5]. Knorr *et al.* found that age was significantly higher in the group with WHtR >0.469 (a cut-off to rule in NAFLD), but did not find such statistical difference in FLI groups [25]. In studies evaluating neurocognitive outcomes, eight adjusted for age or birth year (Table 3). Bytoft *et al.* found no significant correlation between age at follow-up and attention deficit parameters [34].

2. Sex differences

Three studies with metabolic outcomes corrected for offspring sex (Table 2). One study reported a higher total body fat percentage and BMI in female OT1D than in control children throughout puberty, but not in male offspring [35]. Three studies reported no influence of sex on overweight risk or anthropometric measurements in OT1D [11,14,17]. Four studies showed no significant influence of offspring sex on glucose metabolism [14,19,22,36]. In contrast, Weiss *et al.* showed that metabolic differences were more distinct in male than in female offspring [24]. In Knorr *et al.*, there was a higher female proportion in the groups with FLI 30-60 and FLI ≥ 60 , although the difference between FLI groups was not significant [25]. In addition, the group with WHtR >0.469 included significantly more females ($p=0.01$) [25]. Among studies with neurocognitive outcomes, nine made adjustments for sex (Table 3). One study reported that male sex was an independent negative predictor of composite memory score [26]. However, another study found that male sex was an independent positive predictor of cognitive function [27]. In Knorr *et al.*, female OT1D had higher average school grades than males [29]. Two studies found no significant differences between male and female OT1D regarding attention deficits [32,34]. Bytoft *et al.* only described a higher male score for hyperactivity/impulsivity ($p<0.001$) [34]. Instanes *et al.* found a non-significantly higher OR for ADHD in female OT1D [32].

DISCUSSION

In this scoping review, we report a growing body of evidence suggesting negative long-term outcomes in offspring exposed to maternal T1DM during pregnancy. We showed that OT1D had less favorable metabolic outcomes. In addition, studies showed in general a higher risk of neurobehavioral disorders in OT1D.

In our review, we found that OT1D tended to have higher BMI and higher prevalence of overweight and obesity. This is in line with a previous meta-analysis, which found overall higher BMI z-scores and a higher frequency of overweight and obesity in 5- to 10-year-old offspring, but not in 11-year-olds [6]. However, we found that differences were often less distinct when adjusted for confounding factors such as maternal BMI.

The findings for glucose disorders and insulin resistance were inconsistent, with few studies demonstrating significant differences in terms of (pre)diabetes or substitute outcomes. This may be partially due to the young age of participants in most studies. Only two studies investigated OT1D in adulthood and showed lower insulin sensitivity and increased risk of T2DM and prediabetes [19,22]. Previously, the association between maternal diabetes and offspring glucose intolerance has often been explored without distinction between diabetes types. Studies have shown that offspring of women with T2DM and GDM have higher degrees of hyperglycemia and insulin resistance than OT1D [35,37]. Besides the effect of intrauterine exposure to hyperglycemia, this may indicate a genetic effect, as children of mothers with T2DM and GDM are genetically more prone to T2DM than OT1D [35].

The data on the long-term risk for NAFLD are very limited. One study suggested an elevated risk of NAFLD in OT1D. This is in accordance with a previous study, which showed a six-fold increase in odds of NAFLD in offspring of mothers with diabetes in pregnancy, although they did not differentiate according to diabetes types [7]. Data on the risk for MetS are also very limited, as only one study reported higher rates of MetS in OT1D. Similarly, research in Mexican children and adolescents demonstrated a higher proportion of MetS in those with a family history of diabetes [38]. It is reasonable to hypothesize that OT1D could be at risk of MetS, assuming they are more prone to the components of MetS and poorer cardiovascular health in general.

The underlying mechanisms for the increased metabolic risk in OT1D remain largely unknown. Epigenetic alterations in (pre)adipocytes of OT1D, mainly DNA methylation, were previously linked to elevated leptin secretion [39,40]. High leptin levels have in turn been associated with obesity, insulin resistance and MetS [40]. These changes were likely induced by the hyperglycemic fetal environment rather than genetics, as similar results were found in offspring of mothers with GDM, who have a higher genetic disposition to T2DM [39,40]. In addition, animal studies suggested a different programming of hypothalamic neurons, leading to postnatal overeating and adiposity [16].

Globally, we did not find substantial evidence for lower intelligence nor less academic achievement in OT1D. Some studies showed significantly lower scores only in subsets of cognitive function measurements. Other studies showed that differences did not remain significant after adjustment for potential mediators. Maternal glycemic control during pregnancy, as judged by HbA_{1c}, seemed to be related to offspring academic achievement, but not to cognition. A recent meta-analysis demonstrated a significantly lower pooled IQ in offspring of women with diabetes, as well as in OT1D, but they used crude unadjusted data [8]. They found variable results regarding the role of maternal glycemic control [8].

Data on ASD in OT1D were inconclusive, with one study showing an increased risk, while another study found no association. Data from studies in children of mothers with pre-existing diabetes (combining T1DM, T2DM and GDM) also showed conflicting results, with some studies demonstrating a higher risk of ASD [8,41], while other studies showed no difference

[42]. Our review suggests that the odds of ADHD are higher in OT1D than in ONDM. This is in accordance with findings from a previous meta-analysis [8]. However, another study in children of mothers with pregestational diabetes (T1DM and T2DM) or GDM showed no significant difference [41]. Exposure to hyperglycemia *in utero* may interfere with fetal brain development and neurobehavioral disorders later in life through chronic inflammation and hypoxia [4]. Moreover, animal studies suggested epigenetic pathways, including increased activation of the receptor for advanced glycation end products, causing increased hippocampal excitement and altered behavior in offspring [4].

Data on the influence of age and sex of the offspring on metabolic and neurocognitive long-term outcomes were limited. Increasing age was associated with insulin sensitivity and weight outcomes, but not with HOMA-IR or other glucose regulation parameters. There was a correlation between age and composite intelligence outcomes, but not with attention deficit. Several studies reported an association between female sex and unfavorable NAFLD parameters, total body fat, BMI and higher school grades. Male OT1D showed to be more at risk for hyperactivity/impulsivity and lower composite memory scores but had better cognitive function.

Our review has important clinical implications. Increased attention for primary prevention and early screening for metabolic and neurobehavioral disorders in OT1D is needed. Timely detection of long-term metabolic complications and cognitive problems might allow for a more timely prevention of the medical and social consequences of these complications. However, further research with larger cohorts is necessary to provide higher quality evidence and to elucidate inconsistencies in the currently available literature. Moreover, more research is needed on the impact of glycemic control before and during pregnancy on these outcomes.

Strengths and limitations

We performed an extensive review on the long-term metabolic and neurocognitive risks in OT1D. We also specifically assessed age and sex differences in these outcomes. However, our review had also some limitations. We did not perform a systematic review or meta-analysis due to the heterogeneity of studies. Most studies had only a small sample size. In addition, some studies assessed outcomes within a wide range of offspring ages but did not list results per age category. Studies used a variety of outcomes, often including substitute outcomes instead of hard outcomes. Moreover, some studies did not correct for confounding factors. Specifically, there is an important lack of information about a potential link between the presence and degree of neurocognitive deficits in the mothers and neurocognitive outcomes in OT1D. The majority of studies did not correct for lifestyle and socioeconomic factors. Due to lack of data from randomized controlled trials, no causal relationship between maternal T1DM and long-term outcomes in the offspring could be established.

Conclusion

In conclusion, our review indicates that OT1D are at increased risk of overweight, obesity, (pre)diabetes, NAFLD, MetS, ASD and ADHD. These findings suggest that increased attention for metabolic and neurobehavioral disorders in OT1D is needed.

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Fig. 1 Literature search and selection process

Table 1 Characteristics of included studies

Author, year	Country	Study design	Subjects exposed (n)	Offspring age	Outcome
Atladóttir, 2009 [30]	Denmark	Retrospective cohort study	46	>1y	ASD or infantile autism
Bytoft, 2016 [26]	Denmark	Prospective cohort study	277	13-19y	Intelligence and learning difficulties
Bytoft, 2017 [34]	Denmark	Prospective cohort study	269	13-19y	Attention deficits
Clausen, 2008 [19]	Denmark	Retrospective cohort study	160	18-27y	Type 2 diabetes and pre-diabetes
Clausen, 2009 [15]	Denmark	Retrospective cohort study	160	18-27y	Overweight and metabolic syndrome
Clausen, 2011 [27]	Denmark	Retrospective cohort study	158	18-27y	Cognitive function
Hummel, 2009 [11]	Germany	Prospective cohort study	783	2, 5, 8y	Overweight
Hunter, 2004 [36]	New Zealand	Prospective cohort study	17	5-10y	Insulin sensitivity
Instanes, 2017 [32]	Norway	Case-control study	2 913	4-45y	ADHD
Ji, 2018 [1]	Sweden	Retrospective cohort study	15 615	Median follow-up 25y	ADHD
Buinauskiene, 2004 [20]	Lithuania	Prospective cohort study	51	2-5y	Glucose tolerance
Kelstrup, 2013 [22]	Denmark	Retrospective cohort study	153	18-27y	Insulin sensitivity
Knorr, 2019 [25]	Denmark	Prospective cohort study	278	13-20y	Fatty liver disease
Knorr, 2015 [29]	Denmark	Prospective cohort study	707	15-16y	Academic achievement
Lindsay, 2010 [12]	United Kingdom	Prospective cohort study	100	7y	Overweight and obesity
Lohse, 2018 [35]	Denmark	Prospective cohort study	278	13-24y	Differential effects of age and sex on insulin sensitivity and body composition (based on data from Vlachová, 2015)
Manderson, 2002 [21]	United Kingdom	Retrospective cohort study	61	5-11y	Insulin resistance
Mughal, 2010 [16]	United Kingdom	Cross-sectional study	67	5-18y	Body composition (including overweight)
Nielsen, 2017 [33]	Denmark	Retrospective cohort study	190	5-22y	ADHD
Pirkola, 2008 [23]	Finland	Prospective cohort study	16	3-6y	Insulin resistance
Pitchika, 2018 [13]	Germany	Prospective cohort study	2 426	0.3-18y	Overweight and insulin resistance
Pitchika, 2018 [5]	Multinational	Prospective cohort study	225	5.5y	Overweight and obesity
Rijpert, 2009 [14]	Netherlands	Retrospective cohort study	213	6-8y	Overweight and obesity
Rodrigues, 1998 [17]	United States	Prospective cohort study	17	5.9-9y	Overweight and obesity
Temple, 2011 [28]	United Kingdom	Retrospective cohort study	40	6-12y	Intelligence
Vlachová, 2015 [18]	Denmark	Prospective cohort study	278	13-19.8y	Overweight, insulin resistance, MetS
Weiss, 2000 [24]	Austria	Prospective cohort study	75	5-15y	Insulin resistance
Xiang, 2018 [4]	United States	Retrospective cohort study	522	>4y	ADHD
Xiang, 2018 [31]	United States	Retrospective cohort study	621	>1y	Autism spectrum disorder

647 ASD: autism spectrum disorder; ADHD: attention deficit and hyperactivity disorder; MetS:
648 metabolic syndrome

Table 2 The association between T1DM and long-term metabolic outcomes in offspring

Article	Offspring age	Outcome	OR/Percentage/Mean		P-value	Adjusted for
Hummel, 2009	2, 5, 8y	Overweight at 2y Overweight at 5y Overweight at 8y	1.1 (0.7-1.6) 1.1 (0.7-1.8) 0.8 (0.5-1.4)		0.7 0.7 0.4	Maternal diabetes, breast-feeding duration, birth size, and maternal age
Pitchika, 2018 (TEENDIAB and BABYDIAB/BABYDIET cohort)	0.3-18y	BMI absolute change in SDS Overweight Abdominal obesity HOMA-IR	0.28 (0.09, 0.46) 2.06 (1.12, 3.78) 1.97 (1.10, 3.55) 11.55 (3.02, 20.79)		<0.01 <0.05 <0.05 <0.05	Age, Tanner's staging, maternal smoking, socioeconomic status, birth weight HOMA-IR additionally adjusted for sex.
Pitchika, 2018 (TEDDY cohort)	5.5y	BMI absolute change in SDS Overweight Obesity ^a	-0.007 (-0.14-0.13) 1.15 (0.81-1.62) 1.48 (0.85-2.59)		0.91 0.44 0.17	Sex, country, maternal pre-pregnancy BMI, breastfeeding, maternal smoking and drinking during pregnancy, gestational weight gain, maternal age and education, birth weight
			OT1D	ONDM		
Clausen, 2008	18-27y	Type 2 diabetes and pre-diabetes	11% 3.19 (1.03-9.90)	4%	<0.05	Family history of diabetes, maternal overweight, offspring age, offspring overweight
Clausen, 2009	18-27y	Overweight (including obesity) Obesity Metabolic syndrome	41% 2.27 (1.30-3.98) 10% 14% 2.59 (1.04-6.45)	24% 5% 6%	<0.05 NS <0.05	For overweight and obesity: maternal age at delivery, maternal pregestational BMI, offspring age, family occupational social class, maternal hypertension at first visit For metabolic syndrome: maternal age at delivery, maternal pregestational BMI, ethnic origin, family occupational social class
Hunter, 2004	5-10y	S _i AIR S _g K _g Fasting glucose Fasting insulin	11 (7.8-1.4) 386 (320-524) 1.92 +/- 0.28 2.8 +/- 0.3 4.9 +/- 0.1 4.1 (3.4-8.3)	11.8 (9.1-18.3) 366 (216-459) 2.07 +/- 0.16 2.9 +/- 0.3 4.9 +/- 0.1 4.2 (2.7-7.1)	0.2 ^b 0.3 ^b 0.8 ^b 0.8 ^b 0.8 ^b 0.4 ^b	No adjustments made

Table 2 (continued)

Buinauskiene, 2004	2-5y	Normal glucose tolerance Impaired fasting glycemia Impaired glucose tolerance Diabetes	68.6% 11.8% 17.6% 2%	86.2% 8.3% 4.6% 0.9%	<0.001 NS <0.05 NS	No adjustments made
Kelstrup, 2013	18-27y	BIGTT-S _{I0-30-120} Matsuda index HOMA-IR	8.27 (3.36) 23.28 (21.37–25.36) 9.28 (8.49–10.15)	9.79 (3.39) 27.00 (24.77–29.45) 8.47 (7.71–9.31)	<0.0001^c NS NS	No adjustments made
Knorr, 2019	13-20y	FLI WHtR	5.3 (2.3-13.7) 0.44 (0.05)	3.6 (2.1-6.8) 0.42 (0.04)	0.001 <0.001	No adjustments made
Lindsay, 2010	7y	BMI Overweight Obesity Central obesity ^d	17.3 +/- 0.24 22% 12% 36%	16.4 +/- 0.35 0% 6.7% 9%	0.03 0.001 0.001 <0.001	No adjustments made BMI was adjusted for maternal BMI.
Manderson, 2002	5-11y	HOMA-IR	0.95 (0.62–1.48)	1.06 (0.67–1.49)	0.36	No adjustments made
Mughal, 2010	5-18y	BMI-SDS	0.44 (-0.33-1.29)	0.12 (-0.43-0.79)	0.018	No adjustments made
Pirkola, 2008	3-6y	Fasting serum insulin concentration First-phase insulin response HOMA-B	38.4 373.2 83.6	No value No value No value	NS NS NS	Maternal pre-pregnancy BMI, maternal weight gain during pregnancy, birth weight, age and relative weight at examination
Rijpert, 2009	6-8y	Overweight Obesity	15.2% 3.8%	13.5% 2%	0.8 0.2	No adjustments made
Rodrigues, 1998	5.9-9y	BMI Weight-for-height Z-score Percent body fat (skinfold measures) Percent body fat (bioelectrical impedance analyzer)	19.47 (0.82) 2.12 (2.73) 24.62 (1.72) 23.95 (2.42)	16.91 (0.79) 1.27 (2.25) 18.11 (1.67) 21.13 (2.34)	0.04 0.79 0.02 0.43	No adjustments made BMI and percent body fat based on skinfold measures were adjusted for age.

Table 2 (continued)

Vlachová, 2015	13-19.8y	BMI-SDS	0.44 (0.21, 0.66)		<0.001	Sex, age, Tanner stage and maternal pre-pregnancy BMI HOMA-IR additionally adjusted for offspring BMI.
		HOMA-IR	10.4% (0.8, 21.0)			
		Metabolic syndrome	2.8%	0.7%	0.054	
		Prediabetes	15.4%	8.1%		
Weiss, 2000	5-15y	I/G _{sum}	1.475 (0.815)	1.183 (0.625)	<0.05	No adjustments made

Data are expressed as percentages (%), odds ratios or mean (SD). Significant values are marked in bold. Only the most adjusted data were mentioned, except when stated differently.

T1DM: type 1 diabetes mellitus; OT1D: offspring of mothers with pregestational type 1 diabetes mellitus; ONDM: offspring of mothers without diabetes mellitus; NS: not significant; BMI: body-mass index; SDS: standard deviation score; HOMA-IR: homeostatic model assessment of insulin resistance; S_i: insulin sensitivity; AIR: acute insulin response; S_g: glucose effectiveness; K_g: glucose disposal coefficient; BIGTT-S_{1/0-30-120}: β -cell function insulin sensitivity glucose tolerance test based on measurements at 0, 30 and 120 minutes into the oral glucose tolerance test; FLI: fatty liver index; WHtR: waist-to-height ratio; HOMA-B: homeostatic model assessment of β -cell function; I/G_{sum}: sum of insulin/glucose quotients.

a: Longitudinal data between 0.25-6y of age not mentioned here.

b: In calculating p-value, T1DM/type 2 diabetes mellitus were compared to ONDM as one group.

c: Still significant (p=0.001) when adjusted for maternal age at delivery, pregestational overweight, parity, family history of diabetes, Nordic Caucasian ethnicity, offspring age at follow-up, physical activity in the adult offspring, healthy diet and social-economic position.

d: Waist circumference $\geq$ 90th percentile.

Table 3 The association between T1DM and long-term neurocognitive outcomes in offspring

Article	Offspring age	Outcome	OR/HR/Mean/IRR	P-value	Adjusted for
Atladóttir, 2009	>1y	ASD Infantile autism	0.93 (0.52-1.51) 2.14 (1.07-3.77)	NS <0.05	Age, gender, calendar year, place of birth, ages of the mother and father at the time of the child's birth
Instanes, 2017	4-45y	ADHD	1.6 (1.3-2.0)	<0.0001	Year of birth, parity, mother's age at birth, mother's educational level, mother's marital status
Ji, 2018	Median follow-up 25y	ADHD	1.35 (1.18-1.55)	<0.0001	Year at birth, sex, parental history of ADHD and other psychiatric disorders, parental education and income, small for gestational age, maternal smoking and urinary tract infection during pregnancy, low Apgar score, and hypoglycemia.
Nielsen, 2017	5-22y	ADHD	1.36 (1.17-1.56)	<0.05	Calendar year, sex, the interaction of sex with age, and parental history of psychiatric admission
Xiang, 2018	>4y	ADHD ^a ADHD ^b	1.56 (1.09–2.25) 1.57 (1.09–2.25)	0.02 0.01	Random sibling effect, birth year, maternal age at delivery, parity, education, household income, maternal race/ethnicity, history of comorbidity, history of maternal ADHD, and sex of the child
Xiang, 2018	>1y	ASD	2.36 (1.36-4.12) 2.33 (1.29-4.21)	0.003 0.005^c	Birth year, maternal age, parity, education, median household income based on census tract of residence, self-reported race/ethnicity, history of comorbidity (≥1 diagnosis of heart, lung, kidney, or liver disease; cancer), sex of the child

Table 3 (continued)

			OT1D	ONDM		
Bytoft, 2016	13-19y	<u>Intelligence indices:</u>				Offspring sex, age at follow-up, parity, parental educational length, maternal age at delivery, neonatal complications, pregnancy complications, gestational age, birth weight SDS
		Composite Intelligence Index	95.7 (17.3)	100 (15)	0.001^d	
		Verbal Intelligence Index	96.2 (16.8)	100 (15)	0.004	
		Nonverbal Intelligence Index	96.4 (17.0)	100 (15)	0.008	
		Composite Memory Index	95.7 (15.3)	100 (15)	0.001^d	
		<u>Learning difficulties:</u>				
		Reading problems	22.4% (62)	18.7% (56)	0.269	
		Writing problems	19.3% (52)	16.3% (48)	0.353	
Bytoft, 2017	13-19y	Learning difficulties, Danish	23.3% (64)	13.8% (41)	0.003	Offspring gender, age at follow-up, parity, parental educational length, maternal age at delivery, gestational age, birth weight SDS, pregnancy complications and neonatal complications
		Learning difficulties, mathematics	16.4% (45)	7.7% (23)	0.001^d	
		<u>CCPT version II:</u>				
		Omissions	51.1 (13.3)	49.6 (9.6)	0.12	
		Comissions	54.5 (10.4)	55.2 (11.2)	0.47	
		Hit RT	44.2 (8.7)	43.5 (9.2)	0.36	
		Hit RT standard error	45.0 (10.4)	44.6 (10.2)	0.64	
		Hit RT block change	48.5 (9.5)	48.6 (7.7)	0.88	
		Hit SE block change	51.9 (10.2)	52.8 (10.0)	0.30	
		Hit RT ISI change	47.0 (9.1)	46.9 (8.2)	0.90	
		Hit SE ISI change	47.5 (10.0)	48.1 (10.7)	0.46	
		Variability	45.9 (11.3)	45.9 (11.3)	0.99	
		Detectability	54.7 (8.8)	54.6 (8.5)	0.94	
Clausen, 2011	18-27y	Response style	48.2 (7.8)	47.2 (6.4)	0.10 ^e	No longer significant when adjusted for maternal age at delivery, parity, smoking during pregnancy, gender and offspring age at follow-up, birthweight and gestational age, family occupational social class, parental educational level
		Perseverations	50.3 (10.1)	51.2 (13.1)	0.34	
		Global cognitive score	94.8 (14.8)	100 (15)	0.004	

Still significant when adjusted for perinatal complications alone.

Table 3 (continued)

Knorr, 2015	15-16y	School grades at the end of final year at primary school	6.37 (2.34)	6.52 (2.36)	0.37	Sex, maternal age, original grading scale, parental educational status
Temple, 2011	6-12y	Full-scale IQ Digit span	97.54 8.4 (2.2)	100.22 ^f 10.1 (3.2) ^f	NS <0.01	No adjustments made

Data are expressed as odds ratios, hazard ratios, mean (SD) or incidence rate ratios. Significant values are marked in bold. Only the most adjusted data were mentioned, except when stated differently.

T1DM: type 1 diabetes mellitus; OT1D: offspring of mothers with pregestational type 1 diabetes mellitus; ONDM: offspring of mothers without diabetes mellitus; NS: not significant; ASD: autism spectrum disorder; ADHD: attention deficit and hyperactivity disorder; BMI: body-mass index; SDS: standard deviation score; CCPT: Conners Continuous Performance Test; RT: reaction time; SE: standard error; ISI: inter stimulus intervals; IQ: intelligence quotient.

a: Mothers with gestational diabetes considered overall as one group in the model.

b: Mothers with gestational diabetes separated by whether anti-diabetes medication was used during pregnancy or not.

c: Additionally adjusted for maternal smoking during pregnancy and pre-pregnancy BMI.

d: Still significant after adjustment for confounders and potential mediators mentioned.

e: Significant (p=0.02) after adjustment for offspring gender, age at follow-up, parity, parental educational length, maternal age at delivery.

f: UK normative data.

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