Maternal type 1 diabetes and relative protection against offspring transmission
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Summary
Type 1 diabetes (T1D) is more common in the offspring of men with T1D than women with T1D, but the reasons for this are unclear. This review summarises the evidence for a higher rate of T1D amongst the offspring of men compared with women with T1D. We report the findings of nine major studies, and describe their relative strengths and weaknesses. Taken together, they suggest T1D is around twice as common in the offspring of men with T1D compared with women with T1D.

This review also explores possible underlying mechanisms. We consider genetic mechanisms including the selective loss of fetuses with high-risk genes in mothers with T1D, preferential transmission of susceptibility genes from fathers and parent of origin effects influencing gene expression. We also consider in utero exposures including exposure to maternal hyperglycaemia, transplacental antibody transfer, exogenous insulin exposure, and maternal microchimerism.

Understanding why T1D is more common in the offspring of men than women with T1D will help us understand how to identify individuals at high risk of the disease, and pave the way for work aimed at identifying interventions that mimic protective elements of maternal T1D to reduce T1D risk in high-risk individuals.

Keywords
Type 1 diabetes, transmission, maternal, family, offspring,

Introduction

Type 1 diabetes (T1D) is a common complex autoimmune disease, representing the result of a combination of genetic susceptibility and environmental exposures. The risk of T1D is greater amongst first-degree relatives of individuals with T1D (8-15 times higher than the background population)[1-4]. The risk is higher if the father has T1D compared with the mother. The reasons are unclear. This is a narrative review with two principal aims. First, we will provide an overview of published studies reporting different rates of T1D transmission between men and women with T1D and their offspring. We will explore the strength of the evidence for the reported higher T1D rate amongst the offspring of men with T1D compared with women with T1D, and outline the magnitude of this phenomenon. Secondly, we will consider potential underlying mechanisms and summarise the evidence for and against a role for each of these possible mechanisms.

Search strategy and selection criteria:

References were identified through searches of PubMed for articles published from January 1982 to December 2022, using the terms "type 1 diabetes" combined with 'parental transmission', 'mother AND/OR father', 'familial,' 'family', 'first-degree relative', and 'offspring'. Further relevant publications between 1982 and 2022 were identified through Google Scholar searches and review of references cited in articles reviewed. Only articles published in English were identified.

A total of 1806 publications were identified through the initial search strategy. The first author screened all abstracts and identified nine publications that reported the relationship between paternal as compared with maternal T1D and T1D in the offspring. Studies that reported the risk of T1D in the offspring of parents with T1D which did not specifically compare the risk between offspring of mothers and fathers were not included. The studies selected for inclusion fell into two categories; (i) those reporting the proportion of individuals with T1D who had an affected father compared with an affected mother, (ii) those reporting the proportion of children of men with T1D compared with women with T1D who went on to develop T1D themselves.

Following abstract screening of identified publications, the writing group identified seven main potential mechanisms that may underpin the observed higher rate of T1D amongst the offspring of men with T1D compared with women with T1D (figure 1). These include genetic mechanisms; selective loss of fetuses with high-risk genes in mothers, preferential transmission of susceptibility genes from fathers and/or parent of origin effects influencing gene expression. Possible environmental mechanisms include direct exposure to maternal hyperglycaemia in utero, transplacental transfer of maternal antibodies (including maternal islet autoantibodies, insulin antibodies and enterovirus antibodies) and exposure to exogenous insulin. Maternal microchimerism was also considered as a potential mechanism. Publications providing evidence for or against these possible mechanisms were included as references.

Evidence of different rates of T1D transmission between men and women with T1D

Over 30 years ago, Warram et al reported that amongst the offspring of a USA cohort of 289 individuals with T1D (n=419), four times as many of the offspring of men with T1D developed T1D themselves compared with the offspring of women with T1D (6·1±1.8% vs

1·3±0.9%[5]). This was the first study to report a difference in T1D risk amongst offspring of parents with T1D according to parental sex. This study was limited by low numbers of offspring developing T1D (n=17). Furthermore, the median age of offspring was 15 years, meaning offspring developing T1D later were not accounted for. Despite these limitations, the main findings have since been replicated by larger studies (figure2). These studies can be broadly divided into two groups based upon their methodology; (i) those that describe the proportion of individuals with T1D who have an affected mother and/or father (table1), (ii) those that describe the proportion of offspring of men and women with T1D who go on to develop T1D themselves (table2.)

Studies reporting the proportion of individuals with T1D with an affected father and/or mother

In a German study of 554 individuals with T1D, Tillil et al reported that twice as many individuals had an affected father than an affected mother (4·1% vs 1·7%)[6]. The study population was twice as large as Warram et al, but the number of individuals with maternal T1D was modest (n=8). In Sweden, since 1977, new diabetes diagnoses in children have been reported to a central register. In 1985, Dahlquist et al utilised the register to report that amongst 2300 children with T1D, the likelihood of having an affected father was around twice that of having an affected mother (5·7% vs 2·4%)[7]. A Danish study by Poicot et al used a similar approach to identify individuals aged 0-19 years with T1D receiving treatment in paediatric or internal medicine departments (98% of T1D cases within this age group.) They recruited 1419 individuals, and confirmed they were more likely to have an affected father than mother (6·7% vs 2·1%, p<0.0001)[8]. These findings have been replicated by the international research network, Eurodiab. Registry data from 18 European centres combined with results of a case-control study (n=1204) confirmed that amongst children with T1D, twice as many had an affected father than mother (3·4% vs 1·8%)[9,10]. Turtinen et al utilised the Finnish Paediatric Diabetes Register of children newly diagnosed with diabetes in Finland since 2002 (coverage >90%) to undertake one of the largest studies in this field (n=4993.). They reported 5·1% of children with T1D had an affected father compared with 2·8% with an affected mother (p<0.001)[11].

These studies have led to an acceptance that individuals with T1D are around twice as likely to have a father with T1D than a mother with T1D[12]. However, these studies collected family history retrospectively, largely via questionnaire and/or interview[7-9,11], and data obtained this way is often incomplete and carries a risk of diabetes misclassification. This may be particularly problematic in mothers with gestational diabetes (GDM), who may be misclassified as having T1D. In addition, family history was collected at the time of proband diagnosis, so relatives diagnosed later were missed.

Studies reporting the incidence of T1D amongst the offspring of men compared with women with T1D

In view of the limitations of retrospective collection of family data, other groups have recruited families via the parent. This facilitates more accuracy around the parent's diagnosis. Furthermore, it detects differences in the number of children born to men and women with T1D. It has been proposed that women with T1D may have less children than male counterparts due to lower conception rates, increased pregnancy loss, and pregnancy complications impacting the likelihood of further pregnancies[13]. This could contribute to an

increased observation of paternal T1D simply because more children are born to men than women with T1D. Poicot et al refuted this, reporting the number of children was not significantly different between men and women in their cohort (1·96 vs 2·16)[8].

Bleich et al have extended the work undertaken by Warram et al at the Joslin Diabetes Centre, Boston, USA. In a study published in 1993, they reported that amongst 2156 offspring of 1244 men and women with T1D identified from a database from The Joslin Diabetes Centre, the 20 year risk of diabetes was 8.9 ± 1.0% for the offspring of men with T1D and 3.4±0.6% for the offspring of women with T1D [14]. Tumoilehto et al utilised the Finnish Hospital Discharge Register to identify individuals admitted to hospital between 1970-1984 with diabetes diagnosed prior to age 30, generating a cohort of 5225 parents and 9453 offspring. They reported the cumulative risk of diabetes was more than double in the offspring of fathers compared with mothers (7·6% vs 3·5% by age 20[15]). The main limitation was individuals diagnosed before age 30 were assumed to have T1D, which may have been inaccurate. These findings have been replicated in a large prospective population-based cohort (offspring n=5291) utilising data from the Finnish register of T1D diagnosed prior to age 18 between 1965-1979 (n=5144). This cohort was not limited to individuals diagnosed in hospital, and reportedly achieved virtually complete case ascertainment. The authors reported the risk of T1D by age 20 was 1·7 times higher in the offspring of men than women with T1D[16]. Studies with longer follow up periods are required to determine whether the higher risk of T1D in the offspring of men compared with women with T1D is still observed beyond childhood and early adult life.

Despite the limitations of published studies, taken together they provide consistent evidence for an increased risk (around double) of T1D amongst the offspring of men compared with women with T1D (figure2). However, most studies have been conducted in predominantly European populations. Studies in more ethnically diverse populations will enable an assessment of the wider generalisability of findings.

Potential mechanisms

Though maternal protection from T1D is only relative, as the offspring of mothers with T1D still have a higher T1D rate than the background population, it is nonetheless significant. A better understanding of the precise mechanisms underpinning this protection may lead to opportunities to identify interventions aimed at preventing T1D in high-risk individuals. Genetic and environmental mechanisms have been considered and the evidence for and against each of these will now be presented in turn (figure1.)

Genetic mechanisms

The genetic architecture of diabetes risk is increasingly understood[2,17,18]. The majority of heritable genetic risk for T1D is autosomal, and therefore genetic contribution to risk should be equal whether a mother or father of a child has T1D. Potential mechanisms through which genetics could explain the lower risk of T1D amongst the offspring of mothers compared with fathers with T1D include the selective loss of fetuses with high-risk genes in mothers, preferential transmission of susceptibility genes from fathers and/or parent of origin effects influencing gene expression[5,19].

Selective loss of fetuses in mothers

Perhaps one of the most simplistic explanations for the differential rate of transmission dependent on parental sex is the selective loss of foetuses with high-risk genes in mothers with T1D. The rate of spontaneous abortion is significantly higher in women with T1D[20]. One study reported the rate to be highest in mothers with earlier T1D onset[20]. This led to speculation that since high-risk HLA haplotypes are more common in early-onset T1D[21], the higher rate of spontaneous abortion in women with early-onset T1D could reflect selective loss of foetuses with high-risk HLA haplotypes. This remains highly speculative and it is more likely that the commonest cause of pregnancy loss in women with T1D is toxicity from hyperglycaemia[22]. T1D may also lead to abnormal immune adaptation during pregnancy which may predispose to pregnancy loss[23]. Further studies are required to gain a better understanding of factors associated with pregnancy loss in T1D. However, such studies are limited by pregnancy loss often occurring before the clinical detection of pregnancy. Additional insights may be gained from studies comparing T1D genetic susceptibility (utilising the T1D-genetic risk score (T1D-GRS)) of children born to men and women with T1D[24,25]. If foetuses with high-risk genes are selectively lost in mothers with T1D, such studies may demonstrate that children born to men with T1D have higher T1D genetic susceptibility than children born to women with T1D.

Preferential transmission of high-risk paternal genes

Though T1D is a polygenic disease, most of the genetic predisposition is attributable to a relatively small number of loci[2]. The highly polymorphic HLA class II genes play the most important single role[25], with heterozygotes for *DRB1*03:01-DQA1*05:01-DQB1*02:01* (commonly referred to as DR3-DQ2) and DRB1**04-DQA1*03:01-DQB1*03:02* (DR4-DQ8) at highest risk (5% by age 15)[15,26]. Children with a family history of T1D carry the DR4-DQ8 risk haplotype more commonly than children with sporadic disease[4,11]. Vadheim et al reported that in a study of 107 families, the offspring of fathers but not mothers with DR4 were more likely to inherit the parental DR4 allele than the non-DR4 allele (72% vs 56%, $p<0.001$[27]). However, the excess transmission was observed in the offspring regardless of whether they developed T1D[27]. Tuomilehto-Wolf also reported an increased transmission of high-risk HLA haplotypes to offspring of affected fathers than mothers[15]. Other studies have refuted this. Bain et al undertook a study of 172 T1D families and found no evidence of greater transmission of HLA-DR4 haplotypes from fathers[28]. Variation in HLA loci are insufficient to explain all T1D genetic susceptibility. Genome-wide associated studies (GWAS) have led to the identification of over 60 SNPs associated with T1D risk[17,18]. Large GWAS including parents and their children are required to determine whether any of these loci are preferentially transmitted depending on parental sex, and whether this significantly influences offspring T1D risk. Increased availability of whole genome and whole exome sequencing will potentially enable identification of rarer variants with high-impact. Consortia such as Early Growth Genetics (EGG) and EArly Genetics and Lifecourse Epidemiology (EAGLE) which encompass multiple population-based pregnancy and birth cohorts with genetics data, are invaluable resources for such analyses[29].

Parent of origin effects

The parent of origin effect is a phenomenon whereby the expression of the phenotypic effect of a gene depends on whether it is inherited from the mother or father. An example

is genomic imprinting, whereby an allele is epigenetically silenced if inherited from one parent, but expressed if inherited from the other.

A study published in 1991 reported possible maternal imprinting of an insulin-IGF2 region on chromosome 11p encoding a gene implicated in HLA-DR4-dependent diabetes susceptibility[30]. Several studies reported similar evidence of parent of origin effects at this region[31-33]. Bennett et al reported that variable number tandem repeat polymorphism at the insulin gene influence T1D risk whereby 26-63 repeats (class I alleles) predispose to T1D but 140-200 repeats (class III alleles) are protective, but that a particular class I allele does not predispose to T1D if paternally inherited. This is only observed if the untransmitted paternal allele is class III[34]. The authors concluded that polymorphic genetic imprinting may be important in determining T1D susceptibility.

A study of 11,023 individuals from the international Type 1 Diabetes Genetic Consortium (T1DGC) aimed to determine whether the classical HLA loci are subject to parent of origin effects. They considered the transmission of Class I genes HLA-A, Cw, B and Class II genes *HLA-DRB1, DQA1, DQB1, DPA1* and *DPB1*, and concluded there was no evidence of HLA-associated parent of origin effects in T1D[35].

GWAS have made it possible to seek evidence of genetic imprinting across the entire genome. To date, they have only yielded robust evidence of imprinting for one region associated with T1D. Wallace et al demonstrated the SNP rs941576, which lies in the *DLK-1 MEG3* gene region on chromosome 14, predisposes to T1D only when inherited paternally[36]. Whilst evidence for imprinting of this region is robust, the overall contribution of variation at this locus to T1D risk is insufficient to account for the magnitude of the difference in T1D risk observed amongst offspring of men and women with T1D. This is consistent with the findings of Blunk et al who applied complex imprinting modelling to data from 27,255 individuals with T1D identified from a Swedish population-based diabetes registry and 43,856 controls. They found no evidence of genetic imprinting in T1D susceptibility (p=0·18), but suggested maternal imprinting may impact T1D phenotype[37].

Evidence against a genetic mechanism

One argument against a genetic explanation would be if the difference in T1D risk between offspring of men and women is not apparent if maternal T1D develops after pregnancy. This would suggest fetal exposure to maternal diabetes is central to influencing T1D risk. Poicot et al reported that in their Danish cohort, a decreased T1D risk in the offspring of mothers compared with fathers was only observed if the parent was diagnosed before pregnancy. However this study included only nine children with mothers diagnosed after pregnancy[8]. In the Turtinen cohort (which included 349 children with a parent diagnosed with T1D prior to birth, and 52 after birth), the preponderance of fathers with T1D was only observed if the parent was diagnosed before birth[11]. Similarly, Lorenzen et al reported that in their study of 2380 children with parents diagnosed with T1D prior to pregnancy and 382 children with parents diagnosed after pregnancy, maternal T1D was only associated with reduced T1D risk if diagnosed pre pregnancy[38]. However, not all studies have replicated these findings. Harjutsalo et al reported, in a cohort of 9636 offspring of individuals with T1D, amongst offspring of individuals with “late onset” T1D (diagnosis 15-39 years), the T1D risk was equal between offspring of mothers and fathers. However, when they compared T1D risk for the

offspring of mothers born before (n=875) and after (n=642) maternal diabetes diagnosis, no difference was found[39]. Similarly, Bleich et al reported the risk of T1D in the offspring was similar between women who developed T1D before and after the birth of their children (2.8 vs 2.5% respectively), and amongst women diagnosed prior to pregnancy, the duration of T1D prior to childbirth was not associated with T1D risk in the child after controlling for maternal age[14]. However, in their cohort, the risk of T1D was 7.7-fold higher for the offspring of women who were diagnosed with T1D at age 8 years or younger compared with those diagnosed at an older age. These findings highlight the complex interplay between maternal age and diabetes duration. Larger studies accounting for the impact of such confounders are required.

Environmental mechanisms

In the absence of strong evidence for genetic mechanisms accounting for the higher rate of T1D amongst the offspring of men than women with T1D, environmental factors have been postulated. These include exposure to hyperglycaemia, exogenous insulin, and maternal antibodies including maternal islet autoantibodies, insulin antibodies and enterovirus antibodies (figure 3). Maternal microchimerism may also be relevant to the risk of T1D in the offspring of mothers with T1D. These mechanisms will be considered in turn.

In utero exposure to maternal hyperglycaemia

Exposure to maternal hyperglycaemia in pregnancy is associated with abnormalities of insulin secretion, increased insulin resistance and type 2 diabetes (T2D) later in life[40-42]. However, the influence of maternal hyperglycaemia on offspring T1D risk is poorly understood. BABYDIAB represents one of the largest prospective studies of children with parents with T1D. This study reported that compared with children of mothers with T1D with third trimester HbA1c<5.7%, children of mothers with T1D and moderate hyperglycaemia in the third trimester (HbA1c 5·7–7%) had a lower risk of islet autoimmunity and T1D (hazard ratio 0·35). However, the risk was significantly higher if the mother had a HbA1c>7% (HR 2.8.). This study was limited by missing maternal HbA1c data (>40% cases with incomplete data[43]). Studies with more complete data are required. These studies should consider the impact of maternal HbA1c at different timepoints during pregnancy. In humans, pancreatic development begins in the first trimester. Differentiation of endocrine cells within the pancreatic islets occurs during the second half of pregnancy, and there is evidence of ongoing pancreatic islet remodelling throughout the later stages of pregnancy and into the early childhood years[44]. It is therefore feasible that the relative impact of exposure to maternal hyperglycaemia may vary over the course of pregnancy, and studies should aim to identify whether a critical window exists during which time maternal hyperglycaemia has a greater influence on fetal pancreatic development and the offspring's long-term risk of T1D.

If exposure to maternal hyperglycaemia protects against T1D, the risk should also be lower in children exposed to GDM or T2D during pregnancy. A Canadian study reported that GDM exposure was associated with a significant increase in childhood diabetes risk. It was assumed that since over 90% of childhood-onset diabetes in Canada is T1D, the results were evidence of GDM exposure increasing T1D risk[45]. Several studies have confirmed this, and a systematic review concluded that maternal GDM is associated with increased T1D risk in the offspring[12]. A similar trend towards increased T1D risk was observed in offspring of mothers

with T2D, though this was not statistically significant[12]. However, maternal protection against T1D is only relative, as the risk of T1D in the offspring is still higher than the background population, but lower than in offspring of fathers with T1D. Studies are therefore required which compare the risk of T1D in the offspring of mothers with GDM/T2D in pregnancy and offspring of mothers but also fathers with T1D. These studies should consider that obesity may be an important confounding factor, as maternal obesity increases the risk of maternal GDM and T2D, but also of obesity in the child (through both genetic mechanisms and a shared environment), and childhood obesity is an important independent risk factor for T1D [46,47].

There are multiple plausible mechanisms through which exposure to maternal hyperglycaemia in utero could alter offspring T1D risk (figure 3). In utero exposure to hyperglycaemia may directly stimulate beta cell growth and maturation, reducing diabetes risk. However, this may reach a threshold whereby severe hyperglycaemia exposure leads to beta cell exhaustion and increased risk of beta cell failure[19].

Another plausible link between intrauterine hyperglycaemia exposure and diabetes risk is epigenetics, whereby an exposure modifies gene expression independently of the inherited DNA sequence[19]. Mechanisms include DNA methylation, post-translational histone modification, microRNA activation. Multiple epigenetic mechanisms have been described which may influence T1D risk. A detailed description is beyond the scope of this review, and are described elsewhere[48,49]. Briefly, epigenetic effects have been described on T cell differentiation and maturation, insulin gene expression, beta cell function and beta cell surface autoantigen expression. In addition, the hyperglycaemic environment can lead to epigenetic changes which may influence T1D outcomes[48]. Exposure to maternal hyperglycaemia in utero may result in epigenetic changes that influence long-term T1D risk in the offspring. Knorr et al reported evidence of DNA methylation and altered gene expression in adolescent offspring of mothers (n=20) with T1D who were exposed to intrauterine hyperglycaemia[50]. Larger studies looking across the entire genome are required.

Studies aimed at elucidating the mechanism by which maternal hyperglycaemia influences T1D risk in the child should consider whether birth weight is a potential confounding factor in the relationship between maternal diabetes and offspring T1D risk[51]. Alternatively, birth weight may be a marker of fetal hyperinsulinaemia which may explain the relationship between maternal hyperglycaemia and offspring T1D risk. It has been widely reported that in the general population, high birth weight is associated with an increased likelihood of T1D in later life[52]. This has been postulated to be due to a higher birth weight being associated with increased beta cell secretory demand, leading to an increased risk of beta cell stress and failure and ultimately T1D development. This suggests that in the general population, an increased birth weight may play a causal role in T1D development. However, it has also been reported that high risk HLA genotypes which predispose to T1D are associated with greater intrauterine growth and higher birth weights[53]. This highlights the complexity of the relationship between birth weight and T1D. The relationship is believed to be even more complex in the offspring of mothers with T1D. Maternal T1D may lead to macrosomia due to exposure to maternal hyperglycaemia driving fetal hyperinsulinaemia and accelerated fetal growth. While this might be expected to lead to a higher risk of T1D in the offspring as

described in the general population, data from the BABYDIAB and BABYDIET studies suggest that amongst the offspring of mothers with T1D, those with birth weights in the upper tertile have a lower frequency of islet autoantibodies, and therefore T1D risk, than those in the middle tertile[54]. Those with the lowest birth weights also have a significantly lower frequency of islet autoantibodies[54]. The association between maternal T1D and intrauterine growth restriction and low birth weight is thought to be largely driven by placental dysfunction, as opposed to macrosomia which largely reflects the degree of maternal hyperglycaemia. Therefore, amongst the offspring of women with T1D, birth weight is influenced by the severity of maternal hyperglycaemia, the duration of maternal diabetes prior to pregnancy and the degree of maternal diabetes related microvascular disease[55]. It is therefore plausible that the finding of a lower T1D risk amongst offspring with both high and low birth weights may indicate greater maternal protection against T1D in the offspring when maternal disease is more severe and/or more longstanding.

Metabolomic approaches may provide useful insights into the link between hyperglycaemia exposure in utero and T1D risk. In GDM, exposure to hyperglycaemia in utero is associated with metabolomic changes characterised by elevated serum phospholipids in the offspring, which are associated with less favourable cardiovascular and metabolic profiles in later life[56]. It is increasingly recognised that abnormal metabolite patterns are measurable prior to the development of autoantibodies and T1D, and that there may be a role for metabolomics in predicting T1D[57]. Intrauterine exposure to hyperglycaemia may lead to measurable metabolomic effects which predict T1D risk and further studies are required to determine this.

Exogenous insulin exposure

Some studies have suggested exposure to exogenous insulin in pregnancy is more important than exposure to hyperglycaemia in terms of protecting offspring from T1D. Studies have shown that exposure to antigens during fetal life or early infancy can lead to tolerance[58]. Paronen et al reported that insulin-specific T cell reactivity was lower in offspring of mothers than fathers with T1D and suggested this could be due to transplacental transfer of exogenous insulin leading to immunotolerance towards insulin[59]. Studies in women with GDM and T2D treated with and without insulin, are likely to provide useful insights into the relative importance of exogenous insulin exposure in determining offspring T1D risk.

The GPPAD-POInT study is an ongoing randomized placebo-controlled trial of daily oral insulin in children from the age of four to seven months until age three as primary prevention for T1D[60]. If the results are promising, this study will pave the way for further work aimed at determining the optimal timing of such treatment, and the feasibility of in utero insulin exposure as a T1D prevention strategy for individuals at high risk of T1D.

Transplacental transfer of maternal autoantibodies

T1D is an autoimmune disease characterized by islet autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA), islet antigen 2 (IA-2A) and zinc transporter 8 (ZnT8A)[19]. Since these antibodies cross the placenta, the transfer of maternal antibodies could influence offspring T1D risk (figure 3).

Islet autoantibodies have been detected in cord blood. Most studies suggest these reflect transplacental transfer, as they are strongly correlated with maternal titres[61-63]. In most cases, they are lost within nine months[61,64-66]. They are not associated with increased T1D risk, and may even be associated with reduced T1D risk[65]. Maternal transmission of beta cell-reactive autoantibodies followed by their elimination prevents diabetes in prediabetic nonobese diabetic mice[67]. The BABYDIAB group reported that in a cohort of 720 offspring of mothers with T1D, 66% had antibodies to GADA and/or IA-2A at birth (vs 0% of babies of fathers with T1D). They had a significantly lower T1D risk (1·1% by age 8 vs 3·0%) than babies of mothers with T1D who were autoantibody negative at birth[63]. This was independent of maternal diabetes duration, birth weight and gestational age.

The mechanisms by which transplacental autoantibody transfer influence T1D risk are unknown but may include early exposure to maternal autoantibodies leading to immune tolerance against autoantigens, and/or more efficient elimination of autoreactive T cell clones[63]. Reports that the offspring of fathers with T1D are more likely to be positive for multiple autoantibodies later in life compared with offspring of mothers with T1D support this theory[62,68-71].

Transplacental transfer of maternal antibodies to exogenous insulin

Measurement of IAA is complicated by the fact that individuals treated with insulin are known to develop antibodies to exogenous insulin (IA), and they are indistinguishable from IAA. However, the frequency of IAA decreases with increasing age at diagnosis and therefore most IAA detected in pregnancy is likely to be IA[72]. IA titres remain stable throughout pregnancy[73], and around delivery 74-90% of mothers with T1D have IA[61,74]. Their titre positively correlate with insulin requirements, and inversely correlate with markers of glycaemic control[75]. These antibodies cross the placenta, and are detectable in cord blood, but typically disappear by 9 months[73,76]. In BABYDIAB there was no difference in T1D risk between individuals with and without IA in cord blood[63].

Though IAs may not directly impact the offspring's T1D risk, they may be important mediators of the impact of exposure to exogenous insulin during fetal life on T1D risk. It is recognized that insulin does not freely cross the placenta. However, insulin can cross the placenta when coupled to insulin antibodies. Thereafter, dissociation of these insulin-insulin antibody complexes leads to elevated fetal free insulin concentrations. Knip et al reported that infants of women with insulin treated diabetes had ten times higher concentrations of free insulin compared with infants of mothers without diabetes, and this was correlated with fetal macrosomia and neonatal hypoglycaemia [77]. Notably, the elevation in free insulin concentrations was disproportionate to the degree of elevation noted in c-peptide concentrations, which was only three times higher in the infants of insulin treated mothers compared with controls. They suggested that the grossly elevated fetal insulin concentrations were due to transplacental passage of maternal insulin coupled to IAs but also reduced metabolic clearance of insulin in the fetal circulation due to IA binding leading to prolongation of insulin half-life. IAs may therefore be important in determining the degree of exposure to exogenous insulin and fetal hyperinsulinaemia, which in turn may have consequences for beta cell maturation and/or the development of immunotolerance towards insulin. Further studies, including not only women with T1D treated with exogenous insulin during pregnancy, but also women with insulin treated GDM

and/or T2D, are required to determine the implications of IA exposure in utero for future T1D risk in the offspring.

Previous maternal enterovirus infection

It has been postulated that viral infections may represent a key trigger for T1D development. Many studies report a correlation between T1D and enterovirus infection prevalence, particularly coxsackie B serotypes, at a population level. Studies have also shown that enteroviruses are more frequent in pancreatic and gut tissue of individuals with T1D, compared with healthy controls[78,79]. In animal studies, enteroviruses have been shown to result in beta cell damage[80,81]. It has therefore been suggested that enterovirus infections may be an important precipitant for islet autoimmunity and T1D in genetically susceptible individuals.

If enterovirus infection is a key precipitant of T1D, it would be expected that many women with T1D will have had previous enterovirus infection and therefore have enterovirus antibodies. Consequently, they may provide their offspring with passive immunity against enterovirus through transplacental antibody transfer. High levels of enterovirus antibodies in the maternal circulation and breast milk are associated with reduced enterovirus infections in the offspring[82]. In mice, this is associated with reduced virus-induced diabetes in the offspring [83]. Studies are required to determine whether this type of passive immunity to enterovirus translates to a lower T1D risk in humans. Any protection afforded this way is likely to be greatest earlier in life, and when maternal enterovirus infection has occurred in close proximity to pregnancy. Designing prospective cohort studies to examine this will be challenging due to the need for large cohorts and prolonged follow up. It is likely more practical to utilize registry data to identify women with T1D and data linkage approaches to obtain data regarding pregnancy (including timing relative to T1D diagnosis and maternal enterovirus infections) and offspring outcomes (enterovirus infections and T1D.)

Maternal microchimerism

Maternal microchimerism is a phenomenon whereby some maternal cells enter the fetal circulation and are recognized by the fetus as its own. These can persist for years and induce the development of regulatory T cells that suppress fetal antimaternal immunity[84]. In T1D, the transmission of maternal cells could promote regulatory T cell mediated tolerance against maternal beta cell antigens. Some studies have reported a higher frequency of maternal microchimerism in the periphery and pancreata of individuals with T1D compared with healthy controls[85,86], whilst others report a similar prevalence of maternal microchimerism between children with T1D and unaffected siblings[87]. The largest study of maternal microchimerism in T1D was undertaken in the Norwegian Mother and Child Cohort. Cord blood was obtained from 197 children of mothers with T1D, of whom 71 developed T1D. Detectable maternal microchimerism was detected in 48% compared with 42% of children who did not develop T1D. Evidence of maternal microchimerism did not predict future T1D risk [88]. Larger studies are required.

Duration of maternal protection

If maternal protection relates to a specific intrauterine exposure, for example transplacental transfer of maternal antibodies, which are typically lost within nine months, maternal protection may be strongest early in life, and wane with advancing age. Bonifacio et al

reported that the lower rates of islet autoimmunity observed in the offspring of women compared with men with T1D was most marked at nine months of age. The difference became less significant at subsequent visits, and by age eight there was a higher incidence of new islet autoantibodies in the offspring of mothers with T1D[43]. Further studies are required, and if they confirm these findings, it will be important to determine at what age maternal protection is maximal, and when it begins to wane.

Impact of parental T1D on disease presentation in the offspring

Studies have reported that diabetic ketoacidosis at diagnosis is less common in children with a family history of T1D [11,89-92]. This is thought to be because these families are more likely to recognise early symptoms, have the ability to check blood sugars, and potentially have a lower threshold for seeking medical advice, increasing the likelihood of early diagnosis [11,92]. Metabolic control one year after diagnosis is comparable between those with and without a family history of T1D[93]. This supports the notion that the difference at presentation relates to parental awareness rather than differences in disease pathogenesis.

Turtinen et al reported a higher frequency of diabetic ketoacidosis at diagnosis in offspring of men than women with T1D, which remained significant after adjusting for age and sex (9.7% vs 3.6%, p=0.033). They also reported more significant weight loss prior to diagnosis amongst children with an affected father[11]. It is possible that mothers with T1D may be more likely to notice emerging signs of T1D in their children. It is also possible that the natural history of the disease is different, with paternal T1D being associated with a more severe phenotype. If this is the case, it may be expected that the age at diagnosis is younger for children of fathers with T1D. Turtinen et al did not observe this in their cohort (median age at diagnosis 7.59 years for offspring of fathers vs 6.74 years for offspring of mothers)[11]. However, this was a cross-sectional study of offspring diagnosed prior to age 15 years. Prospective studies which follow offspring for several decades are required to accurately determine whether age at diagnosis differs between the offspring of men and women with T1D, but are difficult as they are long and costly. The use of population-based diabetes registries and linkage to routinely collected data may overcome some of these challenges. If there is convincing evidence that T1D presents differently in offspring of fathers and mothers with T1D, it will be important to determine whether this translates into differences in longterm outcomes.

Conclusion

There is consistent evidence for a lower T1D risk amongst the offspring of mothers compared with fathers with T1D. Though published studies in this field are not without limitation, taken together they suggest that the risk of T1D is around twice as high in the offspring of men with T1D compared with women with T1D. This supports the hypothesis that maternal T1D offers relative protection against the development of T1D in the offspring. Though maternal protection from T1D is only relative, as the offspring of mothers with T1D still have a higher T1D rate than the background population, it is clinically significant.

Several possible underlying mechanisms have been proposed. To date, though genetic mechanisms have been explored, there is no strong evidence to suggest a genetic basis for maternal protection against T1D in the offspring. Furthermore, studies reporting that the

duration of maternal diabetes prior to pregnancy and/or the age of the mother at T1D diagnosis influence the risk of T1D in the offspring suggest an important role for in utero exposure to maternal diabetes and/or its consequences. Specifically, exposure to maternal hyperglycaemia, exogenous insulin and maternal antibodies (islet autoantibodies and insulin antibodies) via transplacental transfer may be important. It is also plausible that the transplacental transfer of maternal enterovirus antibodies may protect the offspring from developing enterovirus, thought to be an important trigger for islet autoimmunity and T1D, thus contributing to relative protection against T1D in the offspring of mothers with T1D. Maternal microchimerism is an additional potential mechanism that warrants further assessment.

Further research is required to accurately determine the relative contribution of the proposed genetic and environmental factors discussed in this review. Studies should address whether: 1) maternal protection is dependent on maternal T1D being diagnosed prior to pregnancy, 2) maternal protection relies on exposure specifically to maternal islet autoimmunity rather than hyperglycaemia from any type of diabetes, 3) maternal protection is most significant during early life (Panel1). A better understanding of mechanisms contributing to maternal protection against T1D may offer opportunities to identify interventions that could prevent T1D in high-risk individuals.

Statements:

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We confirm that this paper has not been submitted to another journal, and has not been published in whole or in part elsewhere previously.

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Figures & Tables

Table 1: Summary of studies comparing the proportion of the **offspring** of men and women with T1D who developed T1D themselves

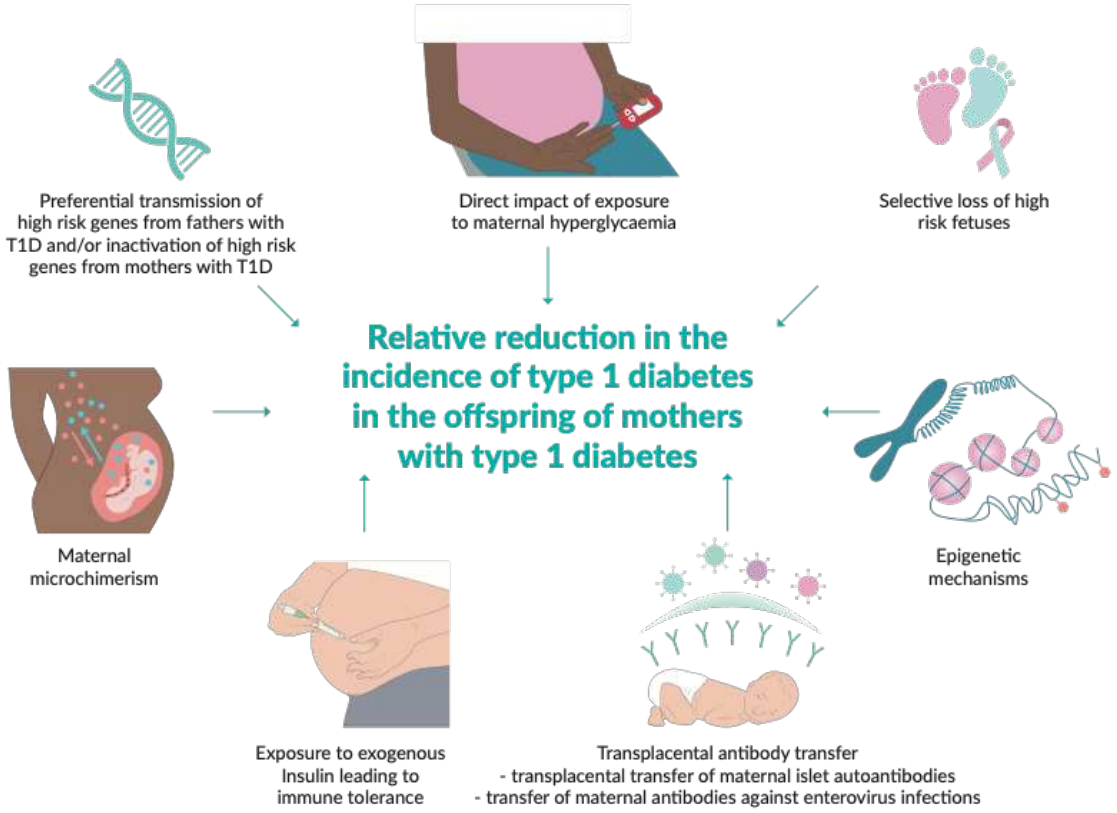
Study	Study setting	Sample size	Key Result(s)
Warram et al [5]	Identification of "parents" through medical records of patients with insulin dependent diabetes mellitus diagnosed before age 20 and attending the Joslin Diabetes Centre within two years of diagnosis and during the period 1928-1939. These individuals and their offspring were contacted in 1968 to determine the occurrence of T1D in the offspring.	187 parents 419 offspring	By age 20, 6.1±1.8% of offspring of the fathers developed T1D compared with 1.3±0.9% of the offspring of the mothers.
Bleich et al [14]	The Joslin Diabetes Centre in Boston database of patients with T1D was used to identify "parents". Offspring were contacted by letter and asked regarding diabetes status.	1244 parents 2156 offspring	8.9±1.0% of the offspring of fathers developed T1D by age 20 compared with 3.4±0.6% of the offspring of mothers.
Tumoilehto et al [15]	Finnish Hospital Discharge Register used to identify individuals with T1D diagnosed prior to age 30, admitted to hospital between 1970-1984. These individuals represent the "parents." Data linkage was used to link to the records of the children of these individuals. The diabetes status of the children was determined using the Hospital Discharge Register.	5225 parents 9453 offspring	3.8% of offspring of fathers developed T1D by age 30 compared with 1.7% of the offspring of mothers.
Harjutsalo et al [16]	Finnish national register of cases of T1D diagnosed before the age of 18 years used. Cases registered between 1965-1979 included. These individuals represent the "parents". Data linkage techniques were used to identify the offspring, and diabetes status was	5144 parents 5921 offspring	5.9% of offspring of fathers developed T1D by age 20 compared with 3.7% of the offspring of mothers. This translated to a relative risk of 1.7 (95% confidence intervals 1.3-2.2)

	determined using the nationwide Hospital discharge register, Finnish Diabetes Register and Central Drug Register.		

Table 2: Summary of studies comparing the proportion of **individuals with T1D** who had an affected father with those with an affected mother

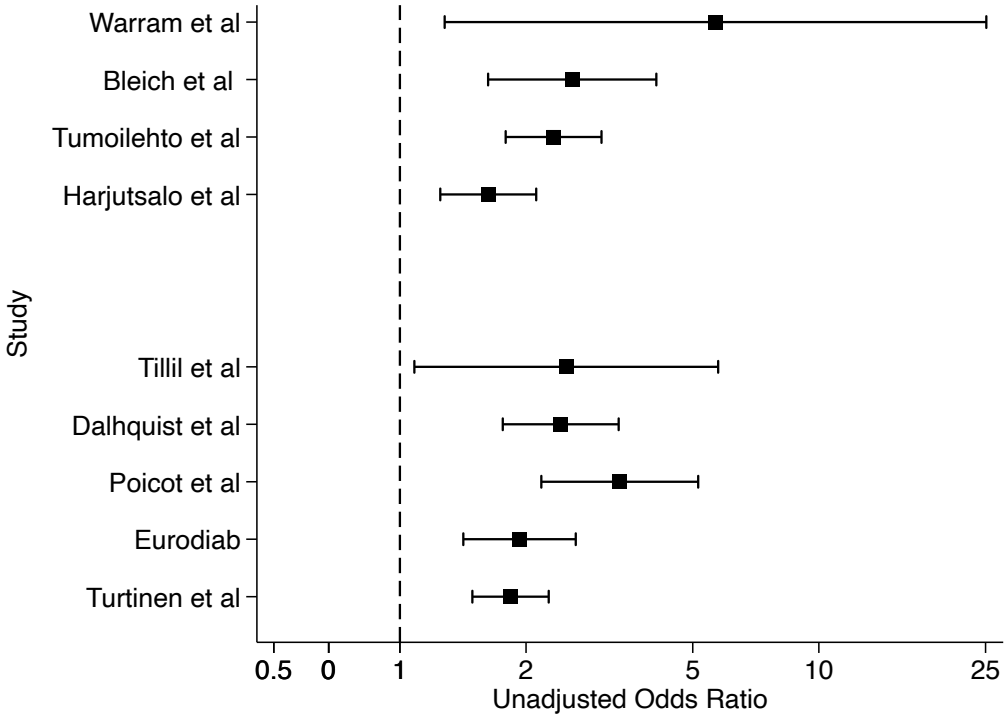
Study	**Study setting**	**Sample size**	**Key result(s)**
Tillil et al [6]	Individuals with T1D diagnosed at any age, recruited from diabetes departments at two hospitals in Germany between 1978-1982. Parental diabetes status was ascertained through interviews and questionnaires sent to the offspring.	554 offspring	4.1% had a father with T1D, 1.7% had a mother with T1D.
Dalhquist et al [7]	Children (age 0-14 years) with newly diagnosed diabetes registered on a central diabetes register in Sweden between 1977-1983. These children and their families were asked to complete a form recording family history of T1D at the time of diagnosis.	2300 offspring	5.7% had a father with T1D, 2.4% had a mother with T1D.
Poicot et al [8]	1419 individuals with T1D aged 0-19 years and receiving treatment in either paediatric or internal medicine departments. Parental diabetes status was ascertained by questionnaire.	1419 offspring	6.7% had a father with T1D, 2.1% had a mother with T1D.
Eurodiab [9]	1204 individuals with T1D recruited as part of a multicentre research network (18 centres). Family history data was collected either by interview or extraction from the hospital notes.	1204 offspring	3.4% had a father with T1D, 1.8% had a mother with T1D.
Turtinen et al [11]	4993 children identified from the Finnish Paediatric Diabetes register of newly diagnosed diabetes since 2002. Information regarding parental diabetes was collected via questionnaire.	4993 offspring	5.1% had a father with T1D, 2.8% had a mother with T1D.

Figure 1: Potential mechanisms of maternal protection against T1D in the offspring



Potential mechanisms for the lower rate of T1D in the offspring of mothers compared with fathers with T1D may include genetic mechanisms such as the selective loss of fetuses with high-risk genes in mothers with T1D, the preferential transmission of high-risk susceptibility genes from fathers with T1D and/or parent of origin effects leading to differences in gene expression between the offspring of men and women with T1D. Possible environmental mechanisms include exposure to maternal hyperglycaemia in utero leading to either direct stimulation of fetal beta cell maturation or modified gene expression as a result of epigenetic mechanisms. Additional environmental exposures of interest include exposure to exogenous insulin leading to immunotolerance towards insulin in the offspring of mothers with T1D, transplacental transfer of maternal islet autoantibodies influencing the development of the immune system in the child, transplacental transfer of maternal insulin antibodies indirectly leading to fetal hyperinsulinaemia which may in turn influence fetal pancreatic development and/or promote immune tolerance towards insulin, and previous maternal enterovirus infection and transplacental transfer of enterovirus antibodies leading to protection against enterovirus (thought to be a key trigger for T1D development) in the child. Maternal microchimerism may also impact immune system development to reduce T1D in the offspring of mothers with T1D.

Figure 2: Comparison of results of studies describing increased transmission of T1D between men with T1D and their offspring

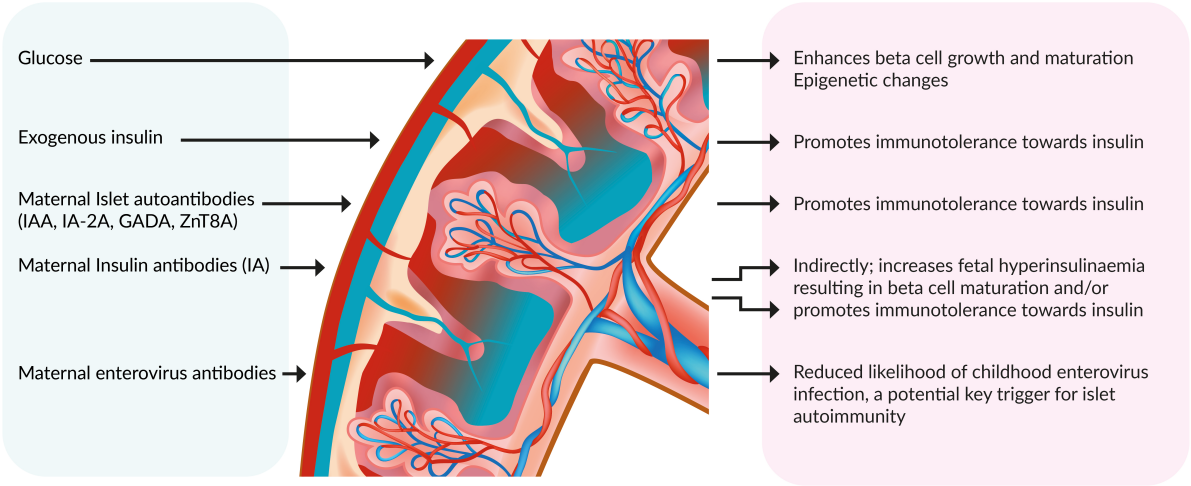


Unadjusted odds ratios calculated using raw data provided within the manuscript of each individual published study. (Reference numbers for the relevant papers in tables 1 & 2.)

For the four studies in the upper section of the chart (outlined in table1), odds ratios have been calculated as the odds of offspring of fathers with T1D developing T1D divided by the odds of the offspring of mothers with T1D developing T1D.

For the five studies in the lower section of the chart (outlined in table 2), odds ratios have been calculated as the odds of a child having an affected father divided by the odds of a child having an affected mother.

Figure 3: Potential mechansims through which transplacental transfer of molecules and/or antibodies may impact T1D risk in the offspring



Studies have suggested that the duration of maternal diabetes prior to pregnancy and/or the age of the mother may be important in determining the risk of T1D in the offspring of mothers with T1D. It is therefore believed that in utero exposure to maternal T1D and/or its consequences is critical to any relative protection maternal T1D confers on the offspring's T1D risk. Exposure to maternal hyperglycaemia, maternal antibodies (via transplacental transfer) and/or exogenous insulin may be important.

Panel 1: Key unanswered questions

1. Does the lower risk of T1D in offspring of mothers relative to the offspring of fathers with T1D become less significant with advancing age in the offspring?
2. Is genetic susceptibility to T1D different between offspring of men and women with T1D? Is maternal protection against T1D in the offspring dependent on diabetes being diagnosed prior to pregnancy?
3. Is T1D risk in offspring of mothers with gestational diabetes and/or type 2 diabetes diagnosed prior to pregnancy different to that seen in offspring of mothers and fathers with T1D diagnosed prior to pregnancy?
4. Does maternal T1D influence the rate of progression from autoimmunity to clinical T1D in affected offspring?
5. Is T1D phenotype different in the offspring of mothers and fathers with T1D?

These questions represent questions that are pertinent for future research studies to address (not necessarily in a particular order) to advance our understanding of the differential rates of T1D in the offspring of men and women with T1D. A better understanding of how genetic and environmental factors influence T1D risk will pave the way for ongoing research aimed at identifying therapeutic strategies that can be used to reduce T1D risk in those most vulnerable to developing the disease.

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