Maternal gestational diabetes and offspring type 1 diabetes: a familial or a pregnancy-specific association?

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Abstract

Background Pediatric type 1 diabetes (T1D) often remains undiagnosed until the patient present to the emergency room with potentially lethal diabetic ketoacidosis. Understanding early indicators of T1D is crucial for timely detection. Previous studies demonstrate that maternal gestational diabetes (GDM) is a risk factor for offspring T1D development. However, it remains unclear whether this association is primarily driven by pregnancy factors such as the effects of *in utero* hyperglycemia on developing β-cells or by shared familial factors (genetic and/or behavioural) promoting insulin resistance. To address these possibilities, we leveraged GDM during a first pregnancy as an indicator of familial factors and evaluated its association with T1D in a second-born offspring. We hypothesize that if familial factors play an important role, GDM during the first pregnancy would be associated with T1D in the second child. Alternatively, if *in utero* factors are predominant, we would not expect such an association, as first-pregnancy factors could not directly impact the second born.

Methods Using health administrative and vital statistics databases from the Canadian province of Quebec, we studied 485,220 second-born offspring of families with two consecutive deliveries between 1990 and 2012, with follow-up data to April 2019. We examined offspring from birth to 22 years of age. More than 85% of diabetes in children and youth is T1D in Quebec, termed diabetes hereafter. We calculated descriptive statistics and offspring diabetes incidence rates. We compared GDM in the first, second, and both pregnancies to the absence of diabetes in either pregnancy in terms of diabetes hazards for the second-born. We included preexisting maternal and paternal diabetes in these models and also examined their associations with second-born diabetes.

We created separate adjusted models for children (from birth until 12 years) and for youth (12 to 22 years).

Findings A total of 1845 subjects (960 children and 865 youth) developed T1D over an average of 11.7 years. In children, we did not identify associations between GDM at either the first, second, or both pregnancies with T1D in the second-born. Maternal (HR 2.38, 95% CI 1.60-3.53) and paternal (HR 6.60, 95% CI 4.80-9.06) pre-existing diabetes were conclusively associated with second-born diabetes in this age group. Among youth, GDM in the first pregnancy only (HR 1.54, 95% CI 1.05-2.25), GDM in the second pregnancy only (HR 1.62, 95% CI 1.17-2.26) and GDM in both pregnancies (HR 2.59, 95% CI 1.78-3.76) were associated with diabetes in the second born as were maternal pre-existing diabetes (HR 4.88, 95% CI 3.37-7.08), and paternal pre-existing diabetes (HR 4.35, 95% CI 2.71-6.97).

Interpretation In the second-born offspring of women with two consecutive singleton deliveries, GDM in the first pregnancy only and in the second pregnancy only are similarly associated with T1D in youth. This similarity suggests that familial factors are predominant in associations between GDM and diabetes in youth. The highest hazards occur with GDM in both pregnancies. Pre-existing diabetes in either parent is associated with T1D development in both childhood and youth; the association is stronger for paternal diabetes than maternal diabetes in childhood but similar in youth. Our findings underscore the importance of querying GDM, not only during pregnancy with the patient but also during other pregnancies.

Résumé

Contexte : Le diabète de type 1 pédiatrique (DT1) demeure souvent non diagnostiqué jusqu'à ce que le/la patient(e) se présente aux urgences avec une acidocétose diabétique potentiellement mortelle. Une meilleure connaissance des indicateurs du DT1 pourrait favoriser une détection plus précoce. Des études antérieures démontrent que le diabète gestationnel maternel (DGM) est un facteur de risque du DT1 chez la progéniture. Il n'est cependant pas clair si cela est principalement lié aux factuers de grossess tels que les effets de l'hyperglycémie *in utero* ou bien aux facteurs familiaux (génétiques et/ou comportementaux) favorisant la résistance à l'insuline. Pour distinguer entre ces possibilités, nous avons considéré le DGM lors d'une première grossesse comme un indicateur de facteurs familiaux et avons évalué son association avec le DT1 chez le deuxième enfant. Nous émettons l'hypothèse que si les facteurs familiaux sont importants, le DGM lors de la première grossesse serait un facteur de risque de DT1 chez le deuxième enfant. Par contre, si les facteurs *in utero* sont prédominants, on ne s'attendrait pas à une telle association car les facteurs *in utero* de la première grossesse ne pourraient pas directement impacter le deuxième enfant.

Méthodes : À travers des bases de données administratives et de statistiques vitales de la province canadienne du Québec, nous avons étudié 485 220 familles ayant eu deux accouchements consécutifs entre 1990 et 2012, avec un suivi jusqu'en avril 2019. Nous avons examiné la progéniture depuis la naissance jusqu'à l'âge de 22 ans. Plus de 85 % des cas de diabète chez les enfants et les jeunes sont dus au DT1 au Québec, appelé ci-après diabète. Nous avons évalué l'association du diabètes chez le deuxième enfant avec le DGM lors de la première, la deuxieme et lors des deux grossesse. Nous avons inclus le diabète maternel et paternel préexistant dans ces modèles et avons également examiné leurs associations avec le diabète chez le deuxième enfant.

Nous avons créé des modèles de risques proportionnels de Cox distincts pour les enfants (de la naissance jusqu'à 12 ans) et les jeunes (de 12 à 22 ans). En parallèle, nous avons examiné les associations entre le diabète préexistant chez le père et le DT1 chez l'enfant.

Résultats : Au total, 1845 sujets ont développé le diabète sur une moyenne de 11,7 ans. Chez les enfants, nous n'avons pas identifié d'associations entre le DGM lors de la première, lors de la deuxième ou lors des deux grossesses, et le diabète chez le deuxième enfant. Le diabète maternel préexistant (HR 2,38 ; IC à 95 % 1,60-3,53) et le diabète paternel préexistant (HR 6 ,60 ; 95% IC à 95 % 4,80-9,06) étaient tous deux associés au diabète chez le deuxième enfant dans ce groupe d'âge. Parmi les jeunes, le DGM lors de la première grossesse (HR 1,54 ; IC à 95 % 1,05-2,25), lors de la deuxième grossesse (HR 1,62 ; IC à 95 % 1,17-2,26) et au cours des deux grossesses (HR 2,59 ; IC à 95 % 1,78-3,76) étaient associés au développement de diabète chez le deuxième enfant, tout comme le diabète maternel préexistant (HR 4,88 ; IC à 95 % 3,37-7,08) et le diabète paternel préexistant (HR 4,35, IC à 95 % 2,71-6,97).

Interprétation : Chez le deuxième enfant de femmes ayant eu deux accouchements consécutifs, le DGM lors de la première grossesse et lors de la deuxième sont associés de manière semblable au diabète chez les jeunes. Cette similitude suggère que les facteurs familiaux sont predominant sur les associations entre le DGM et le diabète chez les jeunes. Le diabète préexistant chez les parents est associé au développement du diabète au cours de l'enfance et de la jeunesse ; l'association est plus marquée pour le diabète paternel durant l'enfance, mais est similaire au diabète maternel chez les jeunes. Nos résultats soulignent l'importance de considérer le DGM comme facteur de risque de DT1 chez l'enfant, non seulement lors de la grossesse avec le ou la patient(e) en question, mais également lors d'autres grossesses avec des frères ou sœurs.

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Author Contributions

LR contributed to the design of the study, conducted data analysis, drafted the initial manuscript, and revised it based on feedback from co-authors. ER contributed to the study's conception and design, oversaw the analysis, and critically reviewed and revised the manuscript. JM contributed to the data analyses and the derivation of variables. MD was involved in cleaning the dataset, deriving variables, and conducting statistical analyses. MN provided critical feedback on the manuscript. KD conceptualized and designed the study, supervised the analyses, interpreted the data, critically reviewed the manuscript, and supervised draft revisions. KD served as the guarantor, having full access to all study data and taking responsibility for data integrity and accuracy of the analysis. All authors approved the final version of the manuscript.

List of Abbreviations

Abbreviation	Meaning
APC	Antigen presenting cell
BIC	Bayesian information criteria
BMI	Body mass index
CCDSS	Chronic Disease Surveillance System
CCI	Canadian Classification of Health Interventions
CCP	Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures
CI	Confidence interval
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DKA	Diabetic ketoacidosis
DM	Diabetes Mellitus
ER	Endoplasmic reticulum
FIPA	*Fichier d'inscription des personnes assurées*
FPIR	First-phase insulin response
GADA	Glutamic acid decarboxylase antibodies
GDM	Gestational Diabetes Mellitus
GDM/DM_{NONE}	Absence of GDM/diabetes in either pregnancy
GDM_{BOTH}	GDM occurring in both pregnancies
$GDM_{SIBLING}$	GDM only in the first pregnancy (pregnancy with the sibling)
$GDM_{SUBJECT}$	GDM only in the second pregnancy (pregnancy with the subject)
GH	Gestational Hypertension
HIPs	Hybrid Insulin Peptides
HLA	Human Leukocyte Antigen loci
HOMA-R	Homeostasis model assessment of insulin resistance
HR	Hazards ratio
HSF	Heart and Stroke Foundation of Canada
HTN	Hypertension
IA-2A	Insulinoma Associated-2 Autoantibodies
IAA	Insulin antibodies
ICA	Islet-cell antibodies
ICD	International Classification of Disease
IGF-1	Insulin-like growth factor 1
IFN-γ	Interferon gamma
IL-1β	Interleukin 1 beta
INS	Insulin gene

INSPQ	*Institut national de santé publique du Québec*
IRS-1	insulin receptor substrate 1
ISQ	*Institut de la statistique du Québec*
MED-ECHO	*Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière*
MHC	Major histocompatibility complex
MSSS	*Ministère de la Santé et des Services Sociaux*
n	Number
NO	Nitric oxide
NPV	Negative predictive value
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor-1
PEE	Preeclampsia
PH	Proportional hazards
PPV	Positive predictive value
PTPN-22	Protein tyrosine phosphatase nonreceptor type 22
RAMQ	*Régie de l'assurance maladie du Québec*
ROS	Reactive oxygen species
RR	Risk ratio
SD	Standard deviation
SES	Socioeconomic status
SNP	Single nucleotide polymorphism
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
TNF-α	Tumour necrosis factor alpha
UPR	Unfolded protein response
VNTR	Variable number of tandem repeats
ZnT8A	Zinc transporter-8 antibodies

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1. Introduction

Type 1 diabetes (T1D) is a chronic condition that involves autoimmune-mediated pancreatic islet cell injury, resulting in insulin deficiency and consequent hyperglycemia.[1] Insulin is a hormone produced by pancreatic β-cells that facilitates the glucose uptake from the bloodstream into cells for energy or storage. Nearly 50% of T1D cases appear in childhood and youth,[2] and one-quarter of them remain undetected until diabetic ketoacidosis (DKA), a serious life-threatening complication of delayed T1D diagnosis,[3] occurs.[52-54] T1D in parents or siblings is a well-established risk factor and is, hence, commonly leveraged to ensure timely diagnosis. Nevertheless, only 10% of individuals with T1D have such a family history.[4] Recent studies indicate that not only parental T1D but more common parental type 2 diabetes (T2D) and maternal gestational diabetes (GDM) are also associated with offspring T1D. Importantly, within the young adult population comprising parents, less than 1% have T1D, approximately 6% have T2D and around 7% of pregnancies are affected by GDM.[5] T2D and GDM in parents may thus serve as risk markers for offspring T1D in a larger population of at-risk individuals, potentially expediting diagnosis. Understanding these associations is an important step in delineating how such a parental history could be leveraged to improve timely detection, prevention and/or care.

Previous studies, including a meta-analysis and a 2019 retrospective cohort study conducted by our research team, have identified links between GDM and T1D in the offspring.[6-11] However, the mechanisms driving associations between these two forms of diabetes remain largely unexplored. The elevated blood sugar levels characteristic of diabetes stem from tissue resistance to insulin action and/or from impaired insulin secretion. GDM, akin to T2D, primarily arises from insulin

resistance. In contrast, T1D predominantly involves low insulin levels due to autoimmune destruction of β-cells. Nevertheless, some degree of insulin production impairment is also present in many cases of GDM.[12] Similarly, while typically linked to GDM and T2D, insulin resistance can also trigger or exacerbate the autoimmune processes that drive T1D.[13] Given these shared characteristics between GDM and T1D, we conceptualize two overarching possibilities to explain the association between maternal GDM and offspring T1D in our rationale.

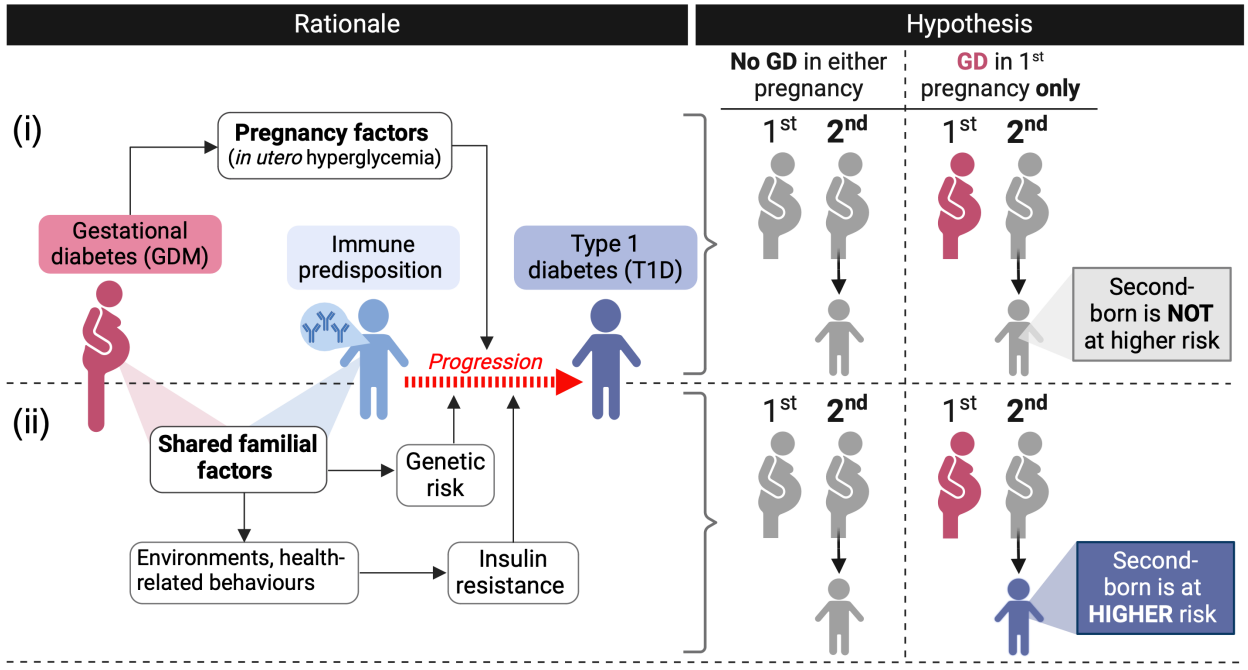
(i) *In utero* factors, such as those related to maternal hyperglycemia, can increase the demand for insulin in developing fetal β-cell, leading to stress, exhaustion, and ultimately cell failure later in life. In addition, *in utero* hyperglycemia can induce fetal epigenetic changes in genes involved in T1D pathogenesis (**Figure 1; i**).

(ii) Familial factors related to genetics or insulin resistance may contribute to the onset of GDM and trigger or accelerate the development of T1D in the offspring. The familial factors associated with insulin resistance can stem from environmental influences (e.g., food insecurity, low neighbourhood walkability, structural racism) and/or behavioural patterns (unhealthy dietary habits, reduced physical activity). Such factors are often shared between mothers and their offspring (**Figure 1; ii**).

To understand the relative importance of *in utero* hyperglycemia compared to shared familial factors, we examined associations between GDM across two consecutive pregnancies and diabetes development in the second born. Over 85% of child and youth diabetes in Quebec is T1D.[14] We leveraged GDM during the first pregnancy with the first offspring (sibling) as an

indicator of familial factors rather than *in utero* ones when considered in relationship to second-born diabetes. Siblings and parents share similar home environments, health behaviours and genetic traits. We reasoned that an association between GD during a first pregnancy and diabetes in a second born would reflect the importance of shared familial factors, as first-pregnancy factors could not directly impact the second-born offspring. On the other hand, if pregnancy-specific factors such as *in utero* hyperglycemia are predominant, we would not expect GDM during the first pregnancy to be associated with diabetes in the second born. We hypothesize that familial factors are important and therefore there is an association between first-pregnancy GDM and second-born diabetes.

Figure 1. Rationale and hypothesis



In the following sections, I provide background information, elaborate on the study's rationale, and offer a comprehensive overview of our investigation's methods, results, and interpretation.

2. Background

2.1 Type 1 Diabetes

2.1.1 Type 1 Diabetes: Epidemiology

T1D represents 5-10% of all diabetes cases worldwide.[15] Large international registries (DIAMOND and EURODIAB) highlight the rise of T1D global incidence over recent decades.[16,17] In 2021, there were about 8.4 million cases globally, and that number was estimated to double to 13.5-17.4 million by 2024.[18,19] Incidence varies across populations, with China and Venezuela exhibiting the lowest rates (0.1 per 100,000 per year) and Europid populations, notably Finland and Sardinia, the highest ones (37 per 100,000 per year).[20] Canada is amongst the ten countries with the highest prevalence of T1D,[18] with between 200,000 and 400,000 cases in 2022, representing 0.5-1% of the national population.[21]

T1D is the predominant form of pediatric diabetes and constitutes over 85% of diabetes instances among children and youth under 20 years old.[14] In pediatric populations, the lowest risk is for those under 5 years of age, while children aged 5-9 and 10-14 years face the highest risks (risk ratios [RR] 1.62, 95% confidence interval [CI] 1.57-1.66 and RR 1.94, 95% CI 1.89-1.98, respectively).[22] In the province of Quebec, T1D incidence per 100,000 among children

and youth rose from 15.5 (95% CI 11.7-20.2) to 25.5 (95% CI 20.4-31.5) between 2002 and 2010.[23]

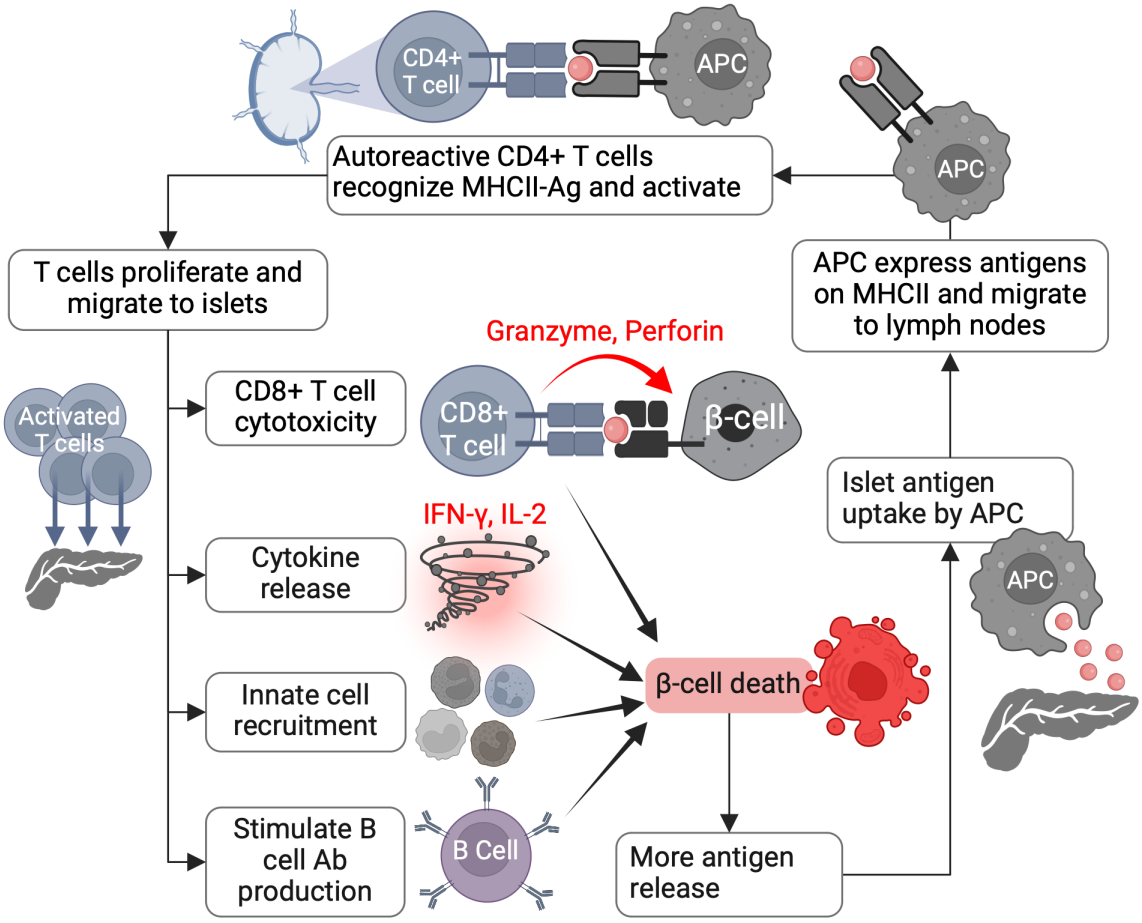
Alarmingly, one in four cases of pediatric T1D in Quebec remains undetected until the onset of DKA, a potentially fatal complication of untreated diabetes.[3] This may be partly attributed to the unspecific nature of early symptoms such as polydipsia, polyuria, weight loss, blurry vision, and fatigue, which healthcare providers and patients often overlook.[24] DKA is characterized by markedly elevated glucose levels, causing osmotic diuresis with dehydration and acidemia, potentially impairing organ function.[25] DKA prevalence at diagnosis increased by an annual average of 2% between 2001 and 2014, among Quebec children.[26] Long-term complications of T1D due to inadequate glycemic management include stroke, heart disease, kidney failure, foot ulcers, and retinopathy. To study the risk factors that can be leveraged to ensure timely detection and better management of T1D, it is essential to first understand its pathophysiology.

2.1.2 Type 1 Diabetes: Pathophysiology

T1D results from the selective autoimmune destruction of insulin-producing pancreatic β-cells.[1] Autoreactive CD4+ T cells with specificities against β-cell antigens are the primary drivers of the autoimmune response.[27] T cells are a type of lymphocyte that plays a central role in the adaptive immune response against infected cells, cancerous cells, and other pathogens.[28]

In healthy individuals, self-reactive T cells are typically eliminated through thymic negative selection during fetal development and early childhood. However, in T1D, autoreactive T cells manage to evade thymic selection and migrate to the lymph nodes as naïve T cells. Antigen-presenting cells (APCs), such as macrophages and dendritic cells, uptake and express pancreatic islet antigens through the major histocompatibility complex class II (MHC II). These cells then travel to the lymph nodes, where they present the antigen-MHC II complex to naïve CD4+ T cells. Autoreactive T cells with specificities for these complexes get activated, proliferate, and infiltrate pancreatic islets, where they mount an immune response. In the pancreas, CD4+ T cells release cytokines such as interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), which promote inflammation and induce β-cell apoptosis. They also stimulate antibody production by B lymphocytes and recruit macrophages, which contribute to β-cell destruction through phagocytosis and the release of cytotoxic molecules. CD8+ T cells recognize islet antigens bound to MHC class I on β-cells and induce their apoptosis through cytotoxicity and the release of perforin and granzymes. (**Figure 2**).[29] The chronic inflammation so triggered perpetuates a self-sustained cycle of immune-driven damage, causing the progressive loss of β-cells. This loss leads to insulin deficiency, which results in hyperglycemia, eventually reaching the diagnostic criteria for T1D. To address insulin deficiency, patients with T1D require lifelong exogenous insulin injections or continuous insulin infusion.

Figure 2. T1D autoimmune response against pancreatic β-cells



Although T1D is typically diagnosed upon the manifestation of symptoms of hyperglycemia and/or DKA, its initial phase involves an asymptomatic immunological predisposition characterized by the presence of islet autoantibodies. This predisposition is often linked to genetic risk. Importantly, not all individuals with such susceptibility develop T1D. It is estimated that 70% of children get diagnosed within ten years following the appearance of at least two islet antibodies.[13] This progression may be triggered by various environmental factors operating at different life stages.[13] The following sections will delve into the genetic factors

underlying the immunological predisposition and discuss the environmental triggers that drive the progression toward T1D.

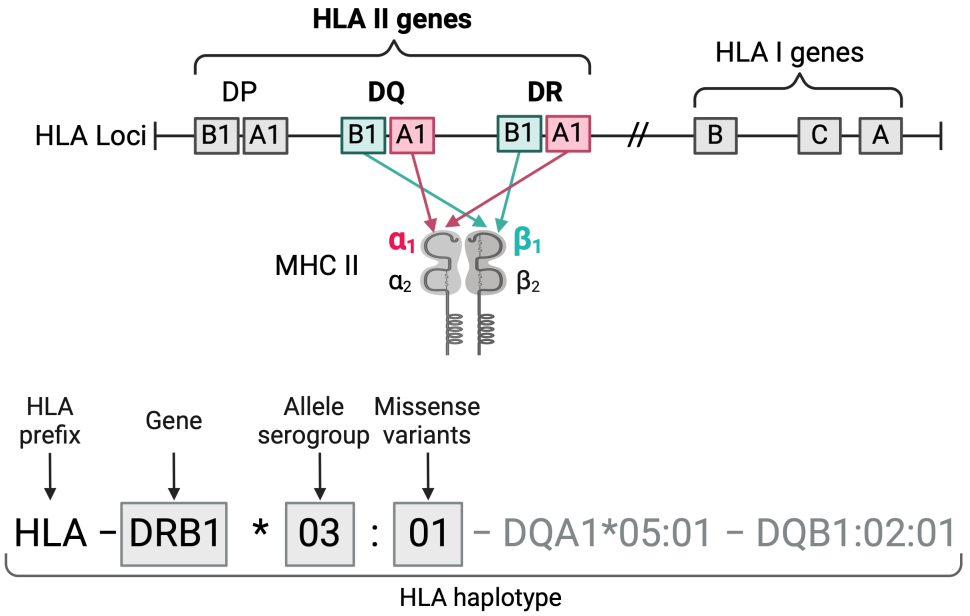
2.1.3 Type 1 Diabetes: Genetic Susceptibility

T1D diabetes is a multifaceted polygenic disease with a strong genetic component. The primary genetic contribution to T1D genetic risk comes from the Human Leukocyte Antigen (*HLA*) gene loci, which account for 30-50% of T1D heritability.[30,31] The different *HLA* haplotypes are inherited in Mendelian fashion, and allele expression is co-dominant, meaning paternal and maternal alleles are equally expressed. The *HLA* genes encode the MHC found on the surface of APCs. The MHC plays a crucial role in adaptative immunity by presenting T cells with a diverse array of antigens and peptides found in pathogens and cells. This interaction is highly specific, with each T cell recognizing a unique antigen-MHC complex. It follows that the *HLA* region is amongst the most polymorphic in humans, providing the MHC with a wide range of peptide-binding specificities.[32]

The *HLA* loci contain the genes encoding MHC class I antigens (A, B, C) and MHC class II antigens (*DR, DQ, DP*). The latter is a heterodimer of two polypeptide chains (α and β) and is thus formed by the products of 2 genes (i.e. *DRA1* for the α and *DRB1* for the β chain of the *DR* antigen). Each of these genes contains many allelic variants.[33] Different alleles are designated using a nomenclature system depicted in **Figure 3**. In addition, due to their

proximity in the genome, *HLA* genes, particularly those encoding *DR* and *DQ*, exhibit linkage disequilibrium, meaning specific alleles of these genes are frequently inherited conjunctively. These allelic combinations are referred to as haplotypes.

Figure 3. *HLA* loci structure and nomenclature



In the context of T1D, the highest risk is attributable to class II *DR*-and *DQ*-encoding genes. Most of the genetic variation in *DR* comes from the *B1* gene, whereas in *DQ*, both *A1* and *B1* genes are highly polymorphic. The *HLA-DRB1-DQA1-DQB1* haplotypes that confer the strongest risk for T1D in Caucasians are *HLA-DR3* (*DRB1*03:01-DQA1*05:01-DQB1*02:01)* and three forms of *HLA-DR4* (*DRB1*04:05-DQA1*03:01-DQB1*03:02, DRB1*04:01-DQA1*03:01-DQB1*03:02* and *DRB1*04:02-DQA1*03:01-DQB1*03:02*) (**Table 1**).[34,35] A study found the *HLA-DR17-DQ2* haplotype was also associated with T1D development (OR 0.03,

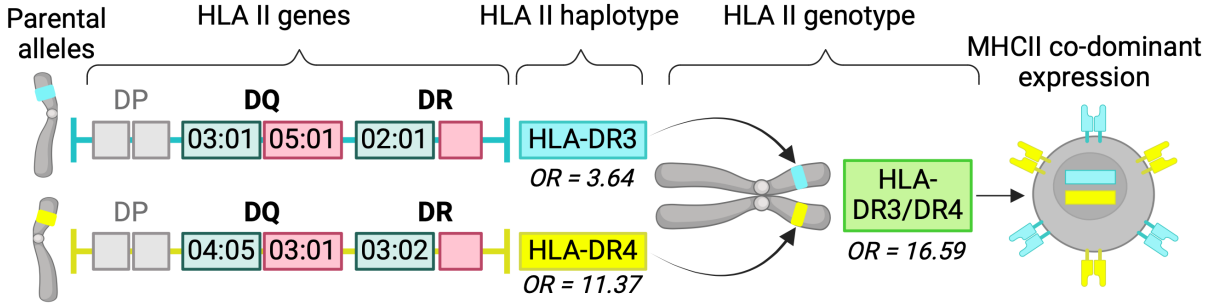
95% CI 0.01-0.07).[36] On the other hand, the *HLA-DR2* (*DRB1*15:01-DQA1*01:02-DQB1*06:02*) haplotype was found to be strongly protective against T1D (OR 0.03, 95% CI, 0.01-0.07).[37]

T1D *HLA*-related risk is not only attributed to haplotypes of individual alleles but also to maternal/paternal genotype combinations, as these are expressed co-dominantly. The highest genotypic risk was found in heterozygotes of the two haplotypes: *HLA-DR3/DR4* (OR 16.59, 95% CI 13.7-20.1) followed by *HLA-DR3/DR3* and *HLA-DR4/DR4* homozygotes (OR 6.32, 95% CI 5.12-7.80 and OR 5.68, 95% CI 3.91 - 8.23, respectively; **Figure 4**).[37]

Table 1. Risk of T1D associated with *HLA* haplotypes

Haplotype	DRB1	DQA1	DQB1	OR (95% CI)
HLA-DR3	*DRB1*03:01*	*DQA1*05:01*	*DQB1*02:01*	3.64 (2.89-4.58)
HLA-DR4	*DRB1*04:05*	*DQA1*03:01*	*DQB1*03:02*	11.37 (2.71-47.68)
HLA-DR4	*DRB1*04:01*	*DQA1*03:01*	*DQB1*03:02*	8.39 (5.97-11.80)
HLA-DR4	*DRB1*04:02*	*DQA1*03:01*	*DQB1*03:02*	3.63 (1.76-7.49)
HLA-DR17-DQ2	*DRB1*03:01*	*DQA1*05:01*	*DQB1*02:01*	3.00 (2.30-3.80)
HLA-DR2	*DRB1*15:01*	*DQA1*01:02*	*DQB1*06:02*	0.03 (0.01-0.07)

Figure 4. *HLA-DR3* and *DR4* risk alleles at different levels of gene expression



The insulin (*INS)* gene contributes to 10% of the genetic risk of T1D.[30] Interestingly, the genetic regions implicated are non-coding regulatory elements called variable number of tandem repeats (VNTR). A study found that T1D susceptibility comes from the genetic transcription modulation of *INS* during thymic T cell development.[38] Specifically, short class I VNTR alleles were associated with increased risk, while class III VNTRs, which correlate with *INS* upregulation, exhibited a dominant protective effect. A possible mechanistic explanation is that higher levels of pro-insulin during thymic development may enhance the negative selection of autoreactive insulin-specific T cells. Other genes that contribute to a lesser extent to T1D risk include the cytotoxic T-lymphocyte-associated antigen-4 (*CTLA-4*) gene[39] and the protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*),[40] both of which play essential roles in downregulating T cell activation. *CTLA-4* encodes for an inhibitory receptor expressed primarily by CD4+ T cells, and *PTPN22* encodes for lymphoid tyrosine phosphatase found in T regulatory cells. T regulatory cells help modulate the immune response by suppressing autoreactive T cell activity. In most cases, genetic risk drives the development of T1D immune predisposition. The next section will discuss such predisposition and its link to genetic markers.

2.1.4 Type 1 Diabetes: Immunological Predisposition

Immunological predisposition to T1D is characterized by the presence of autoantibodies against islet cells (ICA), insulin (IAA), glutamic acid decarboxylase (GADA), insulinoma-associated antigen 2 (IA-2A), and/or zinc transporter-8 (ZnT8A).[13] Pancreatic islet

autoimmunity in children tends to appear early in life. According to the Finnish Diabetes Prediction and Prevention Study, 4-6% of children with a parental history of T1D develop islet autoantibodies before two years of age.[41] Another study found that the incidence rate of autoantibodies peaked between 9 months and two years of age. Children who became antibody-positive before the age of 2 years were the most susceptible to developing multiple autoantibodies rapidly.[42] The predictability of disease progression in immune-predisposed individuals varies between different autoantibodies. For instance, one study found that IA-2A was the strongest predictor of diabetes development, with over 85.9% of newly diagnosed children testing positive for it. Among patients with newly diagnosed T1D, 71.3% had three antibodies, with the IA-2A$^+$GADA$^+$ICA$^+$ combination being the most prevalent. [43]

Autoantibody prevalence is strongly associated with genetic risk, particularly from the *HLA*, *PTPN22, INS* and *CTLA-4* genes, as well as with patient age. IA-2A is frequently present before age 20 and often found in combination with the *HLA-DR4*/not-*HLA-DR3* genotype.[43] The *HLA-DR4-DQ8* allele and the *HLA-DR3-DQ2/DR4-DQ8* genotype are associated with the presence of GADA or IA-2A at five years of age.[44] Moreover, the *HLA-DR* genotype is related not only to variations in frequencies of different autoantibodies but also to their sequence of appearance during childhood. For instance, one study found that the incidence of IAA peaks during the first year of life and then declines. In contrast, GADA levels rise for the first two years until reaching a relatively constant plateau.[45]

The *PTPN22* 1858C→T single nucleotide polymorphism (SNP) associated with T1D was found to be a risk factor for IAA (HR 1.71 95% CI 1.36-2.16) and GADA (HR 1.51, 95% CI 1.16-1.99) positivity. The *INS* risk allele (SNP-A) was associated with the presence of IAA alone (HR 1.85, 95% CI 1.44-2.38) and the *CTLA-4* risk allele (SNP-G) with GADA alone (HR 1.28, 95% CI 1.05-1.55). Both alleles were associated with the GADA/IAA combination (*INS:* OR 0.55, 95% CI 0.39-0.82; *CTLA-4:* OR 1.40, 95% CI 1.02-1.92).[46] Importantly, autoantibody positivity alone does not predict T1D development. Environmental triggers and behavioural risk factors strongly influence disease progression in individuals with immune markers.

2.1.5 Type 1 Diabetes: Environmental Risk Factors

Environmental factors are crucial in triggering T1D progression among immune-predisposed individuals. Such factors operate at different stages of human development. During perinatal and postnatal life, enteroviral infections (Coxsackie B, mumps or rubella) have been implicated in T1D as both triggering islet autoimmunity (pooled OR 3.7, 95% CI 2.1-6.8) and contributing to the progression into clinical manifestation (pooled OR 9.8, 95% CI 5.5-17.4) in a 2011 meta-analysis.[47] Additional cohort studies have also demonstrated that these infections are more frequently present before the appearance of islet autoantibodies.[48,49] This could be due to the fact that β-cells express enteroviral receptor isoforms and allow the establishment of a persistent infection.[50] Maternal food consumption during pregnancy and lactation, mainly processed meat and gluten-rich foods, are risk factors for β-cell autoimmunity and T1D development in the offspring.[51] In addition, shorter breastfeeding times (<3-4 months) and early introduction to gluten

and cereals were found to increase risk in a number of studies.[13,52-54] Later in life, promoters of progression include overweight, high glycemic intake, puberty, and psychological stress, all associated with autoimmunity and insulin resistance (discussed in **section 2.2.5**).[13] Additional risk factors included as covariates in this study (i.e. birth through cesarean section, high birth weight, older maternal age) will be described in more detail in **section 3.6**.

Having described the different genetic risk factors that lead to the development of autoimmunity and the environmental triggers driving T1D, we will address GDM and parental T2D and their link to offspring T1D in the following sections.

2.2 Gestational Diabetes and Offspring Type 1 Diabetes Associations

2.2.1 Pediatric Type 2 Diabetes Overview

T2D is the most common form of diabetes, constituting over 90% of all diabetes cases worldwide.[55] It is primarily characterized by tissue resistance to insulin resistance and deficient compensatory insulin secretion in response. Driving factors include sedentary lifestyles, energy-dense intakes, and consequent overweight and obesity, which have markedly increased over the past decades, notably in North America.[56] Even though most individuals with T2D are diagnosed during adulthood, T2D incidence in childhood and youth has risen significantly.[57]

In most Canadian provinces, including Quebec, new-onset diabetes before 22 years remains predominantly T1D. However, some jurisdictions with larger numbers of Indigenous people, such as Manitoba and Northwestern Ontario, experience an increasingly high incidence of early-onset T2D. Between 2006 and 2008, the overall incidence of T2D in Canadian children aged 1 to 18 was 1.54 per 100,000, with Manitoba recording the highest rates at 12.5 per 100,000 children.[58] In more recent years, Manitoba's rates surpassed 20/100,000.[59]

T2D is disproportionally prevalent among young Indigenous populations. Specifically, in Manitoba, children under 18 exhibit the highest rates, surpassing T1D in some instances.[60,61] A Manitoban epidemiological study reported a yearly incidence rate increase of 73.4 to 121.2/100,000 Indigenous children between the periods of 2009-2010 and 2017-2018.[60] Moreover, obesity, a significant determinant of T2D, was twice as frequent amongst Indigenous children compared to the general pediatric population in Canada (28.2 % versus 13.4 %).[60,62] A study on an aboriginal (Anisininew) community in northern Manitoba reported a 5-fold increased risk for T2D in obese children.[63]

These discrepancies between Indigenous and non-Indigenous populations may be attributed to a combination of genetic as well as historical and political factors related to colonialism, persistent structural racism and inequities. Behavioural shifts towards energy-dense diets and sedentary lifestyles driving the global rise of T2D are particularly pronounced within Canadian First Nations. Social determinants of health, including low socioeconomic status, food insecurity, limited access to healthcare and poor neighbourhood walkability, exacerbate such behaviours among these communities.[64] About 40-50% of available food in Indigenous reserves consists of sweetened

beverages, fast foods, and baked goods.[65] Additionally, genetic studies identified an *HNF-1α G319S* private polymorphism associated with decreased insulin secretion and early-onset T2D in the Anisininew Indigenous people in Northwestern Ontario and Northeastern Manitoda.[61,66]

2.2.2 Gestational Diabetes Overview

GDM is a form of diabetes that is first identified during pregnancy, typically during the second and third trimesters. The prevalence of GDM varies globally, but it is estimated to affect 7-10% of pregnancies.[67] In Canada, it is one of the most common endocrinopathies.[68] A meta-analysis reported a prevalence of 11.8% in Canada and the US, which was higher than European and global estimates.[69] Like T2D, GDM has been on the rise as a result of increasing rates of pre-pregnancy obesity, sedentary lifestyles, and older maternal age at birth,[70] and is also disproportionally prevalent amongst Indigenous women. A study on Anisininew communities in Quebec found that 25% of pregnancies are affected by GDM.[65] A history of GDM confers a significantly higher risk of developing T2D post-pregnancy,[71,72] particularly for Indigenous women.[65]

Unlike T1D, GDM is not driven by a robust autoimmune response against β-cells. Instead, its pathophysiology is more similar to that of T2D. It primarily involves a combination of insulin resistance and chronic β-cell defects that exist before pregnancy yet are not advanced enough to cause T2D. During the later stages of pregnancy, the normal rise in insulin resistance, prompted by placental hormones,[73] is a metabolic adaptation that facilitates transplacental glucose delivery to nourish the developing fetus.[74] However, it also poses additional stress on maternal β-cells to

maintain normoglycemia.[75] In women with pre-existing β-cells defects, the added burden of pregnancy-induced insulin resistance may render β-cells incapable of compensating for the increase in insulin demand, resulting in hyperglycemia and GDM.[76]

GDM and maternal T2D during pregnancy can lead to adverse obstetrical outcomes for both the fetus and the mother. These include a higher likelihood of perinatal mortality, cesarean delivery, preterm birth, as well as fetal hyperinsulinism and overgrowth resulting in macrosomia.[77] Moreover, as for the mother, GDM increases the risk of diabetes development for the offspring. While existing literature predominantly focuses on the risk of offspring T2D, emerging evidence suggests that GDM is also associated with offspring T1D, as discussed in the next section.

2.2.3 Associations of GDM with Offspring T1D: my Meta-analysis and Systematic Review

A parental history of T1D is a well-established risk factor for offspring diabetes, with first-degree relatives facing an 8 to 15-fold higher risk of developing the condition.[78-80] On the other hand, GDM and T2D have traditionally been considered pathologically distinct from T1D. However, a growing body of evidence indicates that GDM and parental T2D may also contribute to the risk of offspring T1D and share significant similarities with this autoimmune condition.

As part of my master's research, I am conducting a systematic review and meta-analysis with Dr. Isabella Albanese, another of my supervisors' trainees, on the association of GDM, maternal and paternal T2D with offspring T1D. We identified 14 studies on GDM associations (of which 10 met the quality criteria for inclusion in the meta-analysis), 8 on maternal T2D and 7 on paternal T2D

associations. Seven GDM studies focused exclusively on children under 15 years of age, and the other 7 studies, on children and youth under 22 (**Figure 2**).

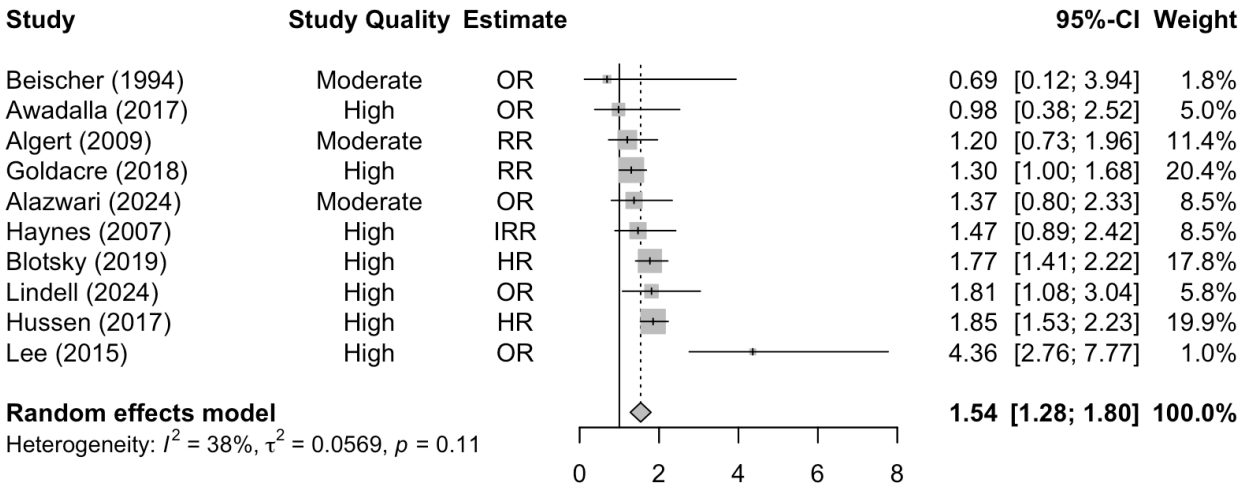
Among GDM studies included in the meta-analysis, a large 2015 Swedish retrospective study found that exposure to GDM or maternal T2D during pregnancy was associated with an 85% increase in risk (HR 1.85, 95% CI 1.53-2.23) before age 18, compared to the absence of any maternal diabetes.[8] The categories of maternal T2D and GDM were combined, so specific associations could not be distinguished. Similarly, a Swedish 2018 case-control study reported an OR of 1.81 (95% CI 1.08-3.04) for children under 19 years, exposed to GDM.[9] In a subsequent 2019 Canadian retrospective cohort study, my supervisors and their team identified associations between GDM and offspring T1D in children under 12 years of age (HR 1.43, 95% CI 1.09-1.89) and in youth between 12 and 22 years (HR 2.53, 95% CI 1.67-3.85),[7] with a stronger association in youth. Other smaller studies in the meta-analysis showcasing conclusive associations included a Taiwanese case-control study (OR 4.36, 95% CI 2.76-7.77)[11] and a British retrospective study (HR 1.3, 95% CI 1-1.68).[10] We calculated a pooled estimate of 1.54 (95% CI 1.28-1.80, I^2 = 38% heterogeneity) for T1D risk in the offspring of mothers with GDM (**Figure 5**). This was similar to the pooled 66% risk increase reported by a previous 2019 meta-analysis encompassing five studies on GDM-specific associations.[6]

Table 2. Characteristics for studies assessing associations of GDM with offspring T1D

Author, year	Country	Study type	Age (yrs)	N	Covariates	Effect measure (95% CI)
Children (0-15 years old)						
Algert, 2009	Australia	RC	0-6	502,312	Not adjusted	RR_{crude} 1.20 (0.73-1.96)
Lee, 2015	Taiwan	CC	0-10	6952	BW, GA, perinatal conditions/ infections, population density of living areas, maternal age, delivery mode, PET, maternal infection	OR_{adj} 4.36 (2.76-7.77) *
Goldacre, 2018	England	RC	1-13	3,831,495	Not adjusted	HR_{crude} 1.30 (1.00-1.68) *
Haynes, 2007	Australia	RC	0-15	558,633	Age, maternal age	IRR_{adj} 1.47 (0.89-2.42)
Alazwari, 2024	Saudi Arabia	CC	0-15	1142	City, residency, cow's milk, nutrition, family history T1D, macrosomia, maternal age	OR_{adj} 1.37 (0.80-2.33)
Ayati, 2020	Iran	CC	0-15	200	Adjusted but covariates unreported	OR_{adj} 3.7819 (p = 0.05) *
Al-Haddad, 2015	Bahrain	CC	6-12	112	Not adjusted	OR_{crude} 3.22 (0.93-11.13)
Children and youth (0-22 years old)						
Hussen, 2015	Sweden	RC	0-18	1,071,196	Sex, age, maternal BMI, maternal age, size for GA, smoking, parental education, delivery mode, sex,	IRR_{adj} 1.85 (1.53-2.23) *
Abdelmoez, 2017	Egypt	CC	2-16	220	Adjusted but covariates unreported	OR_{adj} 3.97 (1.19-13.24) *
Lindell, 2024	Sweden	CC	0-19	16,179	Maternal BMI, gestational weight gain, maternal age, parity, smoking habits, pregnancy length and maternal diabetes	OR_{adj} 1.81 (1.08-3.04) *
Beischer, 1994	Australia	CC	0-19	68,897	Adjusted but covariates unreported	OR_{adj} 0.69 (0.12-3.94)
Awadalla, 2017	Egypt	CC	6-16	Unreported	Adjusted but covariates unreported	OR_{adj} 0.98 (0.38-2.52)
Alenezy, 2013	Saudi Arabia	CC	12-18	294	Sex, neonatal illness, mumps, measles, varicella, breastfeeding, family history of T1D, PET, maternal age.	OR_{adj} 5.1 (3.4-6.3) *
Blotsky, 2019	Canada	RC	0-22	73,180	Sex, age, GA, BW, ethnicity, material deprivation, previous pregnancy, maternal autoimmune diseases	HR_{adj} 1.77 (1.41-2.22) *

N: Study size; RC: Retrospective cohort; CC: Case-control; RR: risk ratio; OR: odds ratio; HR: hazards ratio; crude: unadjusted estimate; adj: adjusted estimate; *: conclusive associations; BW: birthweight; GA: gestational age; BMI: body mass index; PET: Positron emission tomography; **Bold**: moderate to high-quality studies included in the meta-analysis

Figure 5. Meta-analysis on associations of GDM and offspring T1D



The primary focus of my thesis project was the associations between GDM and offspring T1D. While a link between these conditions has been established, the mechanisms driving these associations remain unclear. Different possibilities include shared genetic susceptibility between GDM and T1D (**section 2.2.3**), the effects of GDM-induced *in utero* hyperglycemia on the developing fetus (**section 2.2.4**), and insulin-resistance-promoting factors shared within the family/household (**section 2.2.5**). We will discuss each in more detail and address how my epidemiological study design can provide mechanistic insights.

2.2.4 Shared Genetic Susceptibility

Several studies have identified T1D-related autoantibody markers, such as ICA and GADA, in the serum of pregnant women with GDM.[81-84] As explained previously, autoantibody presence strongly correlates with T1D genetic risk. Early studies found that the frequencies of *HLA-DR3* and *HLA-DR4* T1D risk alleles are twice as frequent in women with GDM compared to healthy controls.[81] More recently, a 2016 meta-analysis identified associations between GDM and the T1D

HLA risk alleles: *HLA-DQB1*02* (OR 1.36, 95% CI 1.13-1.63) and *HLA-DRB1*03* (OR 1.37, 95% CI 1.03-1.83).[85] Both alleles were found to be in linkage disequilibrium, and the *HLA-DQB1*02/ DRB1*03* haplotype is among the greatest genetic risk factors for T1D. [34,35] In terms of haplotypes, the strongest association with GDM was reported for the *HLA-DR17* (OR 3.16, 95% CI 1.31-7.64) and *HLA-DQ2* (OR 1.36, 95% CI 1.10-1.67) alleles. When found in genotypic combination (HLA-DR17-DQ2), these alleles yield a high risk of T1D (see **section 2.1.3**).[36] Additionally, multiple studies have demonstrated a higher prevalence of T1D-related autoantibodies such as ICA, IA-2A and GADA in women with GDM.[86,87] Similar to T1D patients, autoantibody positivity in women with GDM was strongly correlated with T1D genetic markers.[82] Further highlighting the commonalities between these two conditions, evidence indicates that women with GDM are at a higher risk of developing T1D post-partum, particularly those who are positive for autoantibodies. [88-90] These findings underscore the shared pathophysiological and genetic mechanisms between GDM and T1D and emphasize the importance of further investigating their connection.

2.2.5 In utero Hyperglycemia

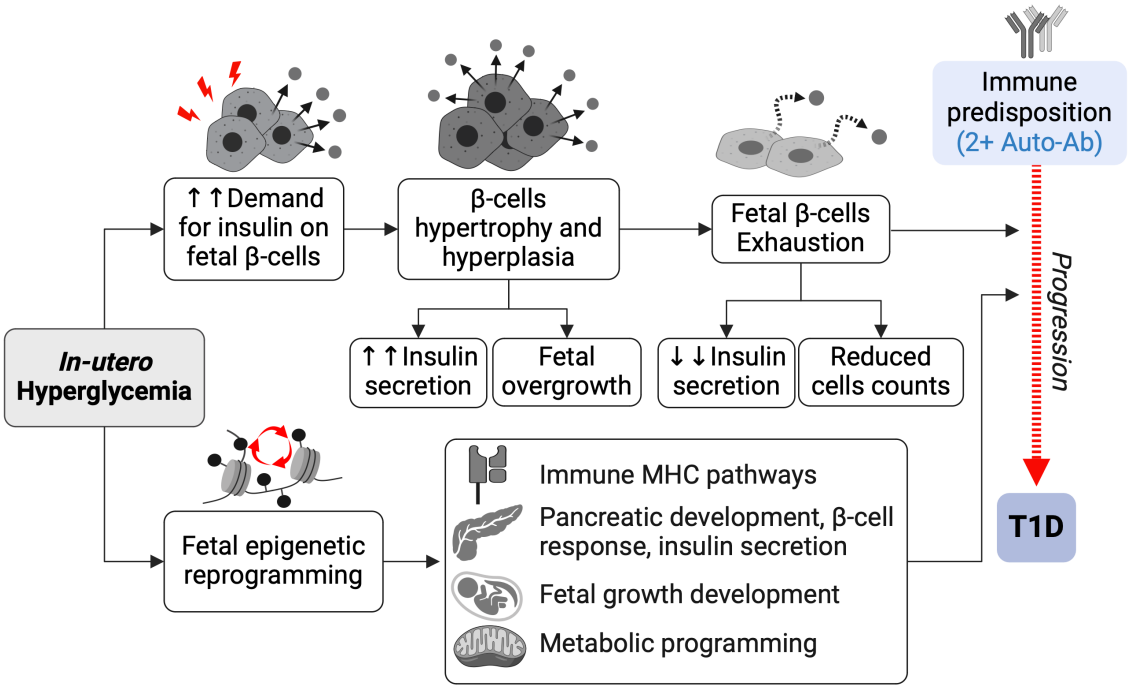
(i) Fetal β-cell development and direct injury through hyperglycemia. In pregnancies affected by GDM, *in utero* hyperglycemia can have significant implications for developing β-cells in the fetus. An excess of maternal glucose crosses the placenta through facilitated diffusion and exposes the fetus to consistently elevated glucose levels. Initially, in response to acute hyperglycemia, fetal β-cell undergo hyperplasia and neogenesis to produce more insulin. The resulting fetal hyperinsulinemia promotes fetal overgrowth, leading to macrosomia at birth. Prolonged exposure to high glucose levels from the maternal circulation eventually results in β-cell exhaustion,

dysfunction, and impaired insulin secretion.[91] Supporting this, rat models have found evidence of fetal islet hypertrophy, β-cell hyperplasia, and lower pancreatic and plasma insulin levels in fetuses of mothers with mild hyperglycemia. In cases of severe hyperglycemia, fetal β-cells were degranulated.[92,93] Human studies have also reported evidence of fetal β-cells hyperplasia and islet hypertrophy leading to β-cell dysfunction during perinatal life in pregnancies complicated by maternal diabetes.[94,95] The consequences of exposure to maternal hyperglycemia, such as reduced insulin secretion, may persist into adulthood.[96,97] If concurrently confronted with an autoimmune predisposition, this could render offspring more susceptible to T1D development (**Figure 6**).

(ii) Epigenetic effects of maternal hyperglycemia. *In utero* hyperglycemia can also induce epigenetic modifications that alter gene expression patterns and cellular function in the offspring.[98] Interestingly, growing evidence supports that past metabolic experiences, such as exposure to hyperglycemia during gestation, can be "memorized" at the level of the epigenome and have implications in later life stages.[77,99] Therefore, such epigenetic changes occurring in fetal life can have long-lasting effects on the offspring's β-cell development, immunogenicity, and metabolic health. In murine models, embryos exposed to GDM exhibited impaired transcriptional profiles.[100-102] Similarly, human studies demonstrated differential DNA methylation in infants exposed to GDM, particularly in genomic regions involved in T1D, immune MHC-related pathways, and pathways related to fetal growth, development, and metabolic programming.[103,104] One study found that CpG methylation of the retinoid X receptor-α in offspring of mothers with GDM was associated with childhood adiposity.[105] Another study reported that maternal glucose levels correlated with offspring leptin methylation and consequent downregulation. Low leptin levels increase the risk of obesity and diabetes.[106] Finally, a study found that the most differentially

methylated pathways in offspring exposed to GDM involved pancreatic development, β-cell response to glucose and insulin secretion (**Figure 6**).[107]

Figure 6. Mechanisms whereby maternal hyperglycemia in pregnancy could increase offspring type 1 diabetes risk



2.2.6 Insulin Resistance and Related Factors

Insulin resistance manifests as diminished sensitivity and responsiveness of tissues to insulin, prompting elevation of insulin levels in an attempt to regulate glucose levels in the bloodstream. As the insulin demand surpasses capacity, glucose levels rise to diabetic thresholds, which are slightly lower for GDM compared to T1D and T2D. Excessive consumption of refined sugars and overall caloric intake not only overwhelms the insulin

production machinery in β-cell but also the insulin signaling pathways in target cells. Prolonged exposure to high insulin levels creates a detrimental cycle leading to the development of insulin resistance through mechanisms such as insulin receptor downregulation and reduced receptor signalling.[108]

Additionally, unhealthy dietary patterns, including high consumption of red meat, processed foods, refined sugars and low levels of physical activity, contribute to adipose tissue accumulation, reflected by elevated BMI and waist circumference. Adipose tissue, particularly the visceral type, produces pro-inflammatory cytokines such as TNF-α, IL-1 β, and IL-6, as well as plasminogen activator inhibitor-1 (PAI-1), leading to chronic low-grade inflammation. This inflammatory state disrupts insulin signalling pathways by inhibiting insulin receptor substrate 1 (IRS-1) through serine phosphorylation, ultimately exacerbating insulin resistance.[109]

Although high BMI and insulin resistance have traditionally been linked to GDM and T2D, a growing body of evidence supports their involvement in β-cell destruction and disease progression in T1D.[110,111] The 'Accelerator Hypothesis' posits that high BMI and insulin resistance potentiate the autoimmune response against β-cells, expediting the progression to T1D in immune-predisposed individuals. A Finish population-based retrospective study investigating the relation between infant weight gain and T1D risk found that a 10% increase in relative weight was associated with a 50-60% risk increase in T1D before age 3 and a 20-

40% risk increase from 3 to 10 years of age.[111] Another retrospective study reported that in individuals aged 1 to 16 years, the age at T1D onset was associated with BMI and weight changes.[112]

The homeostasis model assessment of insulin resistance (HOMA-IR) and the first-phase insulin response (FPIR) are commonly used to measure insulin resistance and secretion.[113,114] The Melbourne Pre-Diabetes Family Study found that insulin resistance predicted T1D progression (HOMA-R HR 1.65, 95% CI 1.21-2.25).[110] Similarly, a Finish study found that among siblings positive for autoantibodies, reduced insulin secretion and higher insulin resistance predicted T1D development (HR, 95% CI: FPIR 10.9, 4.7-25.4 and HOMA-IR/FPIR 3.1, 1.8-5.3, respectively).[115] Furthermore, the Diabetes Prevention Trial of Type 1 Diabetes studies found that in both moderate (second-degree relatives of a T1D patient) and high-risk (first-degree relatives) populations, insulin resistance was strongly associated with T1D (HOMA-IR HR, 95% CI: 2.70, 1.45-5.06 and 1.83 1.19-2.82, respectively).[116]

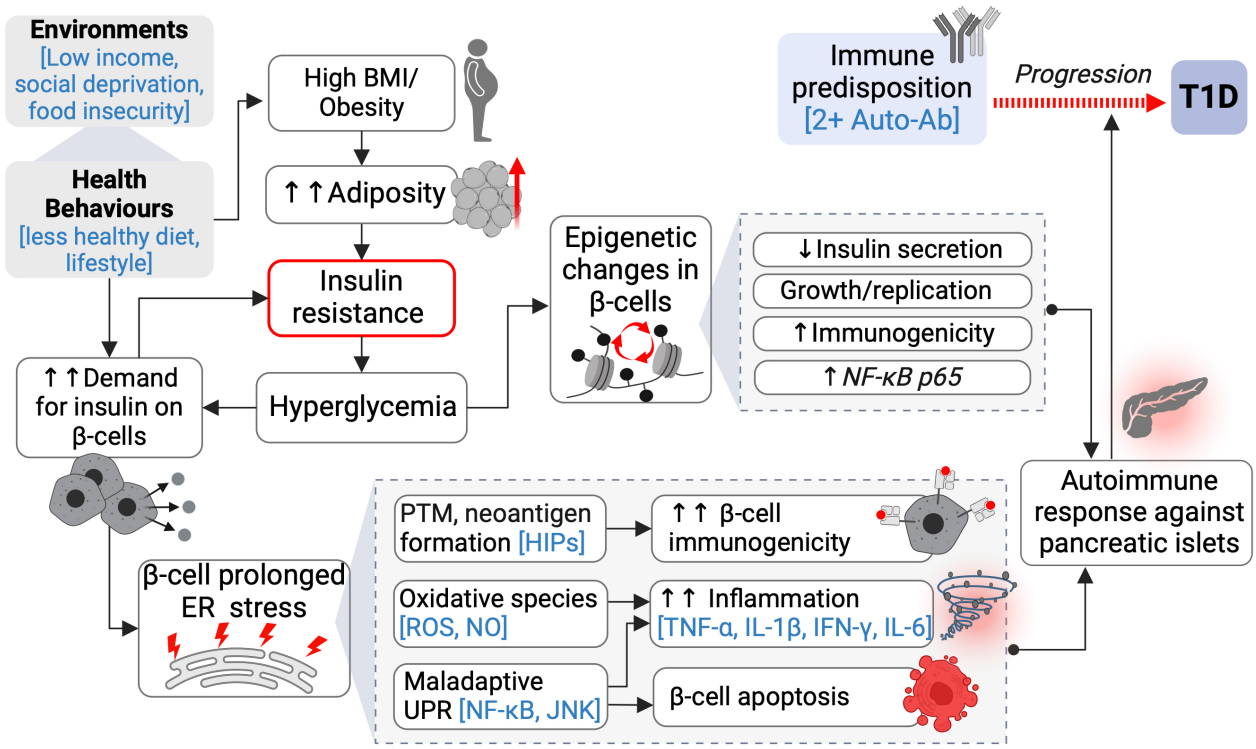
At the cellular level, insulin resistance resulting from high adiposity leads to hyperglycemia and a heightened demand for insulin from β-cells (**Figure 7**). This added stress on β-cells accelerates their apoptosis,[117] renders them more antigenic and triggers inflammatory responses, resulting in T1D progression.[118] β-cells dispose of a rapidly reactive secretory mechanism orchestrated by the endoplasmic reticulum (ER), the cellular core of protein synthesis, folding and processing. Under hyperglycemic conditions, the overstimulation of the

β-cell ER to meet the surge in insulin demand results in oxidative stress and the production of nitric oxide (NO) and reactive oxygen species (ROS). Both NO and ROS are targets of pro-inflammatory cytokines involved in T1D pathogenesis (IL-6, IL-1β, TNF-α, and IFN-γ). Inflammation exacerbates ER stress and leads to islet damage.[119] Another consequence of β-cell ER stress is a maladaptive unfolded protein response (UPR). Under acute stress, the UPR restores normal ER function by downregulating protein synthesis, recruiting chaperones and facilitating the degradation of misfolded proteins. However, in the context of persistent hyperglycemia and unresolved ER stress, the UPR activates the NF-κB and JNK pathways, both of which orchestrate inflammatory responses and β-cell apoptosis, leading to T1D progression.[120]

Finally, ER stress can increase β-cell immunogenicity through abnormal post-translational modifications of β-cell proteins involved in T1D, such as proinsulin, Chromogranin A,[121] and glutamic acid decarboxylase.[122] As these proteins undergo modifications distinct from those originally occurring in the thymus, T cells that recognize them could not have been eliminated during thymic selection. Said proteins become neo-antigens lacking immune tolerance, thus triggering an autoimmune response.[122] The most prominent example is hybrid insulin peptides (HIPs). Auto-reactive T cells with specificities against HIPs have been identified in pancreatic cells of diabetic mice and humans.[13]

In addition, hyperglycemia in the context of insulin resistance as in the context of *in utero* hyperglycemia (previously discussed in **section 2.2.4**) induces changes in gene expression within β-cells through epigenetic modifications. These include the downregulation of genes in the insulin secretion pathway and variations in the expression of genes governing β-cell regulation, growth, replication, and DNA damage response.[118] Such alterations in β-cell identity increase their immunogenicity by promoting the expression of antigens that activate autoreactive T cells with specificities against β-cells.[123] In addition, hyperglycemia-induced epigenetic marks have been identified at the proximal promoter region of the *NF-κB-p65* gene, resulting in its persistent upregulation.[124] As previously described, activation of the NF-κB pathway in β-cells has important implications for T1D progression.

Figure 7. Conceptual framework of possible underlying mechanisms for links between insulin resistance and T1D



Based on evidence supporting the link between maternal GDM/T2D with offspring T1D, as well as existing literature on the effects of *in utero* environment, genetics and insulin resistance-promoting factors, we assess for associations between GDM during pregnancy with an older sibling and diabetes development in a subsequent offspring. Our objective is to discern the relative importance of familial factors promoting insulin resistance (genetic predispositions, behaviours, and environmental influences) and pregnancy-specific factors (*in utero* hyperglycemia) in the associations between GDM and the onset of T1D in offspring.

3. Methods

3.1 Ethics Approval

The Research Ethics Board of the McGill University Health Centre (2019-5029; 2018/12/11) and the Quebec Access to Information Commission (1019371-S; 2019/11/18) approved procedures. We conducted our analyses at the *Institut de la statistique du Québec's* (ISQ) data centres. In compliance with ISQ confidentiality policies, we rounded frequencies to the nearest multiple of 5 and omitted any frequencies below five from reporting. Since we utilized deidentified data, our study did not require individual consent.

3.2 Study Design and Data Sources

We carried out this population-based retrospective cohort study in Quebec, Canada, a province with a population of 8.5 million. Quebec offers universal coverage for physician services and hospitalization. We used provincial health administrative (**section 3.2.1**) and vital statistics (**section 3.2.2**) databases. The ISQ maintains vital statistics databases and facilitates access to these and to health administrative data from the *Régie de l'Assurance Maladie du Québec* (RAMQ, see **section 3.2.1**) and the *Ministère de la Santé et des Services Sociaux* (MSSS). The ISQ links these databases through probability linkage (G-link software, Statistics Canada).

3.2.1 Health Administration Databases

The RAMQ and the MSSS systematically collect health administrative data in centralized provincial databases. For this study, we received access to information from files within the MSSS and RAMQ databases from April 1, 1990, to April 1, 2019: (i) The Hospital Discharge database, (ii) the Physician Service Claims database and (iii) The Public Health Insurance register (**Figure 6**).

(i) The Hospital Discharge database (referred to as the *Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière* [MED-ECHO]),[125] maintained by the MSSS, provided information on hospital admissions, diagnostic codes for inpatients and corresponding dates. Diagnostic codes for inpatients are based on the International Classification of Disease (ICD)-9 until April 1, 2006, and on the Canadian enhancement of the 10th revision (ICD-10-CA) thereafter.[126]

(ii) The Physician Service Claims database, maintained by the RAMQ, included procedural (*acte*)[127] and diagnostic codes[128] and the dates on which they were assigned. Procedural codes are used by physicians when carrying out a treatment or procedure on a patient. Diagnostic codes adhere to ICD-9 codes and are used during physician encounters, including outpatient visits. Both are employed for fee-for-service payment claims that health professionals submit to the RAMQ for remuneration.

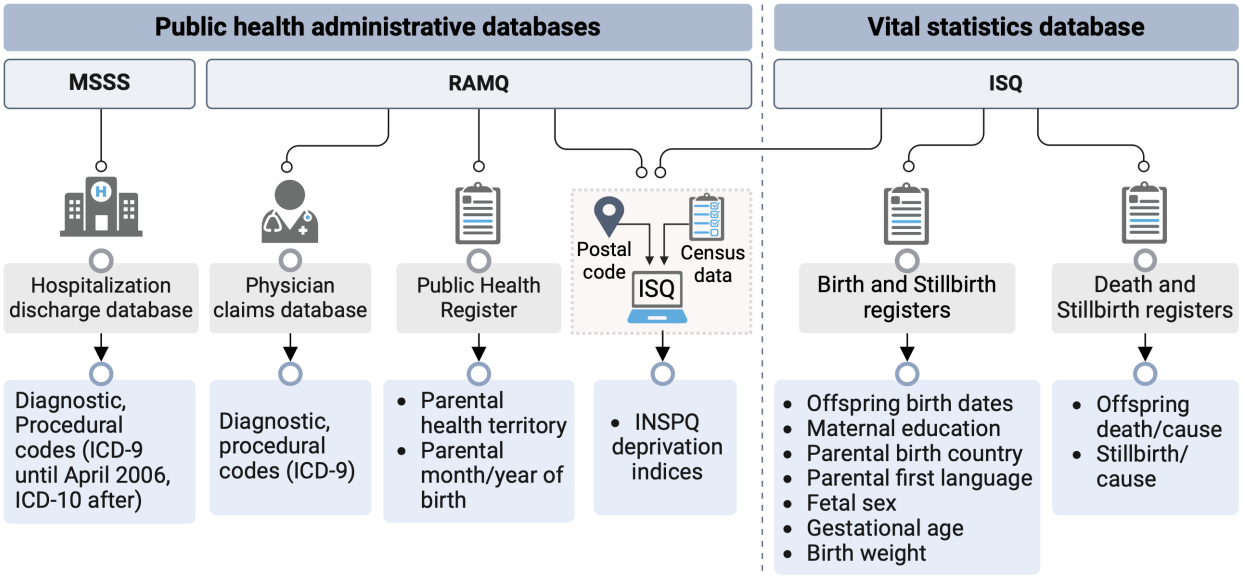
(iii) The Public Health Insurance Register (referred to as the *Fichier d'Inscription des Personnes Assurées* [FIPA]), maintained by the RAMQ, contains demographic and geographic information including parents' health territory, month/year of birth of parents

In addition, The RAMQ provided neighbourhood-level socioeconomic status indicators: the *Institut national de santé publique du Québec* (INSPQ) material and social deprivation indices. These are generated through an ISQ program that links 6-digit postal codes held by the RAMQ (not provided to us) to corresponding census dissemination areas (see **section 3.6.2**).[129]

3.2.2 Vitals Statistic Databases

Vital statistics databases held by the ISQ included the Quebec Birth, Stillbirth and Death registries (**Figure 8**). The ISQ's Quebec Birth and Stillbirth registries include data from the Declaration of Birth, which parents are legally obliged to complete within 30 days of the child's birth. Specifically, we collected information regarding years of maternal education, parental birth country and first language, the exact birth dates of offspring, fetal sex, gestational age at birth and birth weight. When relevant, death and cause of death of the offspring and/or their parents were determined through the Death and/or Stillbirth registries (ICD-9 codes until December 31, 1999; ICD-10 thereafter).

Figure 8. Data sources



3.3 Funding

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3.4 Study Population

Upon obtaining the necessary approvals, ISQ provided, at our request, data on families (mother, father, and offspring) insured under the RAMQ who had two consecutive singleton deliveries between 1990 and 2012. We obtained follow-up data until April 1st, 2019. Additionally, for the

parents, we had three years of data preceding the first delivery, including for those who delivered in 1990. We excluded families with missing gestational age information for either offspring, as it was required to define GDM and pre-existing diabetes (see 'Exposure').[130] We also excluded families in which the second pregnancy resulted in stillbirth, as the offspring under study could not develop the outcome of interest (diabetes).

3.5 Exposure

3.5.1 Maternal Pre-existing Diabetes (combination of T1D and T2D)

We defined pre-existing diabetes in the mothers using the validated Chronic Disease Surveillance System (CCDSS) diabetes definition for adults. This definition required one hospital discharge diagnostic code and/or two outpatient diagnostic codes assigned within two years of each other. The ICD diagnostic codes considered in this definition were 250, 648.0 and 648.8 (ICD-9) and E10-E14, O24.8 (ICD-10). This definition was validated in Quebec against self-reported diabetes amongst 3,506 individuals.[131] The sensitivity and specificity of the CCDSS definition were 84.3% (95% CI 79.3-88.5%) and 97.9% (97.4-98.4%), respectively. The positive (PPV) and negative predictive (NPV) values were 77.7 (72.4-82.4) and 98.7 (98.2-99.0), respectively.

Another study conducted in the provinces of Alberta and British Columbia also investigated the validity of this definition against physicians' charts. The authors reported a sensitivity of 92.3% (89.2-95.5), specificity of 96.9% (96.2-97.4), PPV of 77.2% (67.1-76.5), and NPV of 99.3% (99.0-100.0).[132] The time period we considered for this definition was the combination of the periods

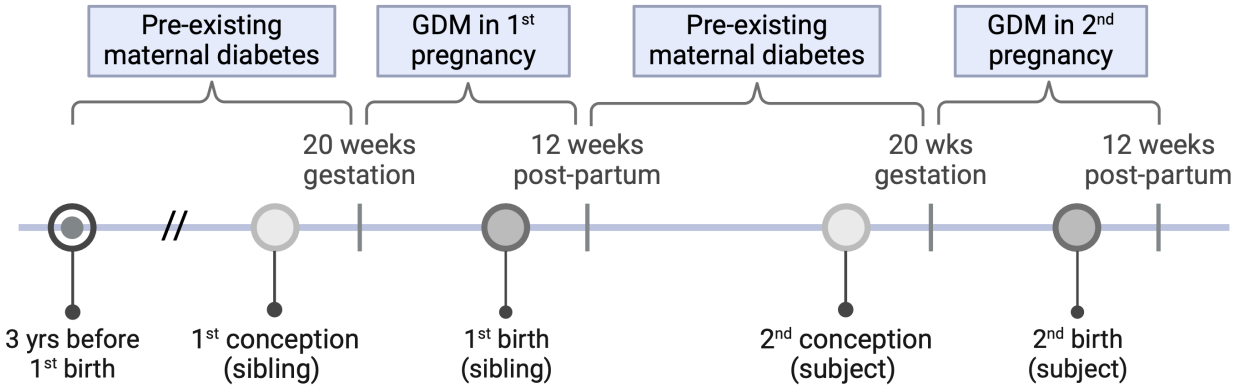
prior to and between the two pregnancies. The prior period occurred between the two years preceding the first child's birth and 20 weeks into that pregnancy. The period between pregnancies occurred from 12 weeks after the birth of the first child until 20 weeks into the second pregnancy. Women who experienced GDM during their first pregnancy and subsequently developed T2D between pregnancies were also included in this group, since at the second pregnancy—the primary focus of our study—these women had "pre-existing diabetes".(**Figure 9**).

3.5.2 GDM Definition

Among women without maternal diabetes (as defined above), we applied an adapted validated health administrative database definition to identify GDM.[133] The validation study was carried out in Ontario against glucose screening laboratory results. This study found that one hospital discharge and/or two outpatient visit diagnostic codes for diabetes assigned 120 days before delivery maximized specificity (99.5%, 95% CI 99.5-99.6) while maintaining sensitivity (94.1%, 95% CI 93.4%-94.8%). Since we had information on gestational age at birth, we considered the period between 20 weeks gestation and 12 weeks postpartum rather than 120 days before delivery (**Figure 9**). Screening for GDM is typically done at 20-24 weeks of gestation,[134,135] and diabetes diagnosed before 20 weeks is considered pre-existing diabetes.[136] The ICD codes captured in our adapted definition included both GDM-and diabetes-specific diagnoses: 250, 648.0, 648.8 (ICD-9) and E10-E14, O24.5-O24.8 (ICD-10). We decided to capture codes for any form of diabetes rather than only GDM-specific ones to account for physicians' coding errors. A validation study in Alberta demonstrated that physicians might apply general diabetes codes rather than GDM-specific ones during pregnancy, resulting in a high false-negative rate.[137] Because we excluded

mothers with diabetes diagnosed before pregnancy, any new diabetes captured within the aforementioned period is GDM.

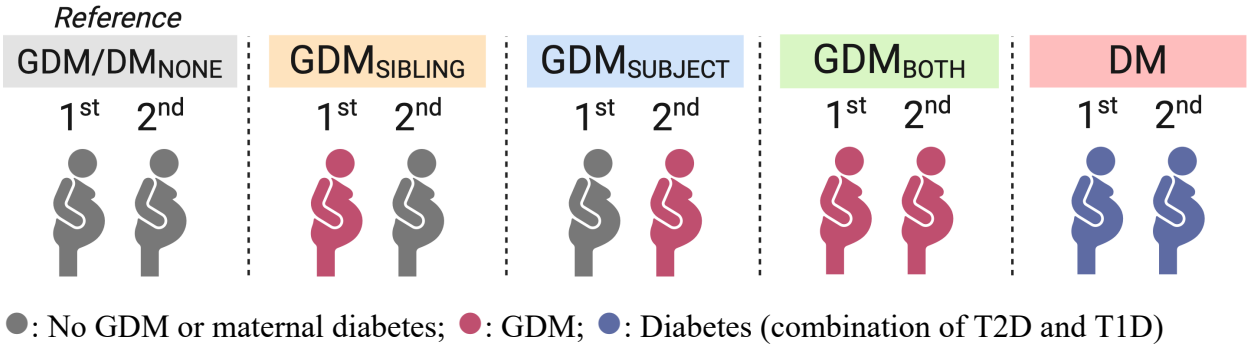
Figure 9. Timeline for maternal diabetes and GDM exposure definitions



3.5.3 Exposure Categories

We grouped maternal GDM/diabetes exposure into the following mutually exclusive categories. The reference group had no form of GDM/diabetes in either pregnancy (GDM_{NONE}). GDM occurring only in the first (sibling) pregnancy was indicated as $GDM_{SIBLING,}$ GDM in the second pregnancy (subject) as $GDM_{SUBJECT}$, and GDM in both pregnancies was labelled GDM_{BOTH}. Finally, maternal diabetes (T1D or T2D) diagnosed either prior to or between pregnancies was labelled as DM (**Figure 10**).

Figure 10. Exposure categories of GDM and maternal diabetes



●: No GDM or maternal diabetes; ●: GDM; ●: Diabetes (combination of T2D and T1D)

3.5.4 Secondary Exposures

We considered pre-existing paternal diabetes a key secondary exposure and defined it as any paternal diabetes that developed before the second pregnancy (between the two years preceding the first child's birth and 20 weeks into the second pregnancy). Paternal T1D is an established risk factor for offspring T1D,[6,138] and there is also evidence of an association between paternal T2D and offspring T1D.[8,11]

3.6 Covariates

We considered covariates and potential confounders for the parents and the offspring associated with GDM and offspring T1D.

3.6.1 Offspring

The offspring covariates included sex, macrosomia, preterm birth, birth through cesarean section for both the subject and their sibling, stillborn status in the sibling, as well as time between deliveries.

Macrosomia was defined as a birth weight higher than 4500 g and was considered an important secondary exposure for both offspring. A 2021 meta-analysis of 13 studies found that macrosomia increased the risk of T1D by 15% (pooled OR 1.15, 95% CI 1.05-1.26).[139] Another one found that a history of macrosomia was a predictor for future GDM (pooled OR 4.41, 95% CI 3.09-6.31).[140] Finally, a retrospective cohort study demonstrated that GDM during pregnancy significantly increased the risk for macrosomia (OR 1.53, 95% CI 1.12-2.08).[141] Macrosomia is a risk factor for both T1D in the offspring and future GDM in the mother. It is also a known adverse outcome of *in utero* hyperglycemia in pregnancies complicated by GDM (see **section 2.2.4**). As such, while it may act as a mediator along the causal pathway between GDM and offspring T1D, it may also independently influence both conditions, possibly acting as a confounding factor.

Preterm birth was defined as birth before 37 weeks of gestation. A 2014 meta-analysis of 18 studies found a significant association between preterm birth and T1D (pooled OR of 1.18, 95% CI 1.11-1.25).[142] Later, a large Swedish retrospective cohort found similar results in children and youth under 18 years old (adjusted HR 1.21, 95% CI 1.14-1.28).[143] The mechanisms underlying this association are explained in the discussion (**section 5.5**). Additionally, a history of preterm birth is associated with future GDM (pooled OR 1.93, 95% CI 1.21-3.07),[140] and women with GDM are at higher risk of giving birth preterm (OR 1.28, 95% CI 1.08-1.52).[144] Similar to macrosomia, preterm birth may act as a mediator and/or a confounder between GDM and offspring T1D.

Birth through cesarean section. We defined cesarean section as any procedural (acte) code (06912, 06913, 06946) assigned on the offspring's birth date. A 2019 meta-analysis revealed that offspring born via cesarean section had an increased risk of developing T1D (pooled OR 1.12, 95% CI 1.01-1.24).[145] This association may be attributed to the link between offspring macrosomia, a recognized T1D risk factor, and the necessity for cesarean section during delivery.[146]

Sibling stillborn status. Second-pregnancy stillbirths were excluded from the study, but we considered sibling stillbirth information. We obtained this variable from the Stillbirth registry and defined it using diagnostic codes 779.9 (ICD-9) or P95 and P96.9 (ICD-10) assigned on the date of birth. Although we did not find evidence of associations between a history of stillbirth and T1D in a subsequent child, maternal diabetes is a known risk factor of peri-natal mortality[147] and a potential marker of maternal health. In addition, a history of stillbirth may influence the decision

to pursue a second pregnancy[148] and elevate the risk of subsequent stillbirth,[149] thus affecting eligibility for inclusion in our cohort.

3.6.2 Parental / Familial

We examined parental age at birth of the subject, time between deliveries, parental ethnicity, maternal education at birth of the subject, and the social and material components of the INSPQ deprivation index assigned to the mother.

Parental age. Maternal and paternal ages at the birth of the subject (second-born offspring) were categorized as <25, 25 to <30, 30 to <35, ≥ 35 years old. A 2020 meta-analysis found that the risk of GDM increases linearly with successive age groups compared to the 20-25-year-old reference group, with the ≥ 40-year-old conveying the highest risk.[150] Similarly, a 2009 meta-analysis calculated a 5% increase in childhood T1D risk per 5-year increase in maternal age (OR 1.05, 95% CI 1.02-1.09).[151] Paternal age demonstrated a similar trend in various cohort studies with around 9% increase in T1D for each 5-year age increase and a 52% higher risk for offspring of fathers 35 years or older compared to those under 25 (RR 1.52, 95% CI 1.10-2.09).[152,153]

The time between deliveries. We categorized the time between first and second deliveries as less than three years and three or more years. We considered this variable as longer inter-delivery periods may heighten the probability of changes in the household environment and familial habits, impacting the risk for any form of diabetes.

Parental ethnicity. The parents' ethnicity was derived from their country of birth and/or birth language. Several studies have demonstrated a higher risk of GDM in non-Caucasian populations, as demonstrated in a meta-analysis.[154] Conversely, T1D has the highest incidence in Caucasian and Hispanic populations.[155] We classified this variable as 'Arab' if the parent's place of birth was the Arab League or if their birth language was Arabic. 'Asia' if their place of birth was West/East/Central/South/Southeast Asia or Pacific or if their birth language was Japanese, any Southeastern Asian language, Indo-Pakistani, language spoken in India, Chinese or other Asian dialects. 'African/Caribbean' if the parent's place of birth was West/Southern/East/Central Africa or the Caribbean and if their birth language was any African, Southwest Asian language or dialect or Creole. 'Europid' if the birth region was Canada/United States, Central/South America, East/South/West Europe, or Australia and if birth language was French, English, German, Austrian, Luxembourgish, Greek, Hungarian, Magyar, Italian, Flemish, Dutch, Polish, Romanian, Slovak, Russian, Swedish, Czech, Turkish, Ukrainian, Yiddish, Hebrew, Yugoslav, Spanish, or Catalan. 'Other' if first language was Indigenous or unspecified (collapsed because of low numbers in individual categories); or 'Different' if the parents did not share the same ethnicity, as defined above.

Maternal education. Maternal years of education, an indicator of socio-economic status, potentially complementary to deprivation levels was captured at birth of the subject and categorized as less than 12, 12 to 14, 14 to 18 and 18 or more years. A 2019 meta-analysis found that a high maternal education level is associated with a decreased risk of GDM compared to low education (pooled OR 0.68, 95% CI 0.57-0.80).[156]

Maternal INSPQ material and social deprivation indices. The ISQ computes the INSPQ deprivation indices through a program that links 6-digit postal codes to corresponding census dissemination areas.[129,157,158] The material deprivation component is based on the proportion of individuals in the dissemination area without a high school diploma, the employment/population ratio, and the average income. The social deprivation component is based on the proportion living alone, divorced, separated, or widowed and the proportion of single-parent families. Deprivation index components are assigned as quintiles from least (Q1) to most (Q5) deprived individuals. We recorded this variable for the mother at birth of the subject or one year before/after delivery if the value at birth was missing. Various studies have found associations with higher social and material deprivation and GDM.[159,160]

3.6.3 Parental Co-morbidities

Maternal hypertension (HTN) and gestational hypertension (GH) at either pregnancy were defined using the CCDSS definitions and the time periods described for pre-existing diabetes and GDM, respectively. GH was sub-categorized as occurring with or without preeclampsia (PEE). The codes for both HTN and GH were 401-405, 642 (ICD-9) and I10-I13, I15, O10-O11, O13-O16 (ICD-10). PEE has been associated with the risk of offspring T1D in a number of studies.[161] In addition, there is evidence for associations between pre-existing HTN and GDM (OR 1.20, 95% CI 1.09-1.33),[162] between GDM and GH[163] and between GDM and PEE [163,164] (pooled RR 1.77, 95% CI 1.14-2.75).[165]

Parental autoimmune conditions included for their association to offspring T1D were thyroid diseases, autoimmune nerve diseases, muscular conditions, ophthalmological conditions, asthma, rheumatoid arthritis, inflammatory bowel disease, skin diseases, connective tissue disorders, other arthritis, vasculitis, inflammatory arthritis and enthesopathy.[166-168] We identified them in the mother and father separately through any code: 24xx, 34xx, 35xx, 55xx, 69xx, 70xx, 71xx (ICD-9) or G7xx, J45xx, J9xx, K5xx, L1xx, L40x, M0xx, M31x, M79xx (ICD-10) assigned between the two years preceding the first child's birth and 20 weeks into that pregnancy. Associations between parental autoimmunity and offspring T1D are described in the discussion (**section 5.5**)

3.7 Outcome

The primary outcome was diabetes in the subject, diagnosed from birth to 22 years of age. We defined it as one hospital discharge and/or four or more outpatient diagnostic codes within two years of one another. In a prior study, we demonstrated a sensitivity of 100% and specificity of 93% in youth, specifically for the outpatient diagnostic code component of this definition.[169] We set the event time as the date corresponding to the first of the diagnostic code(s) that fulfilled the definition. Although the RAMQ coding system for diabetes does not reliably distinguish T1D from T2D, we considered diabetes in the offspring to be T1D, given that most incident diabetes in children and youth under 22 is T1D. In an Ontario study, 94.8% of diabetes cases in pediatric diabetes centers were T1D.[170] In the United States, T1D accounted for 98% of all cases of diabetes in children under ten and over 87% of all cases in youth between 10-19 years of age in 2015.[171] Finally, worldwide, it is estimated that 85% of diabetes diagnosed before 20 years of age is T1D.[14] Our follow-up period started at the birth of the index offspring. It ended at the incidence of

diabetes, death if applicable, reaching 22 years of age or April 1, 2019 (the end of our study period), whichever occurred first.

3.8 Statistical Analysis

We used SAS (version 9.4) to compute baseline characteristics for the offspring and parents and calculate incidence rates of diabetes in the second-born (number/10,000 person-years). Incidence rates were computed for the overall period of birth to 22 years as well as for children (birth to 12 years old) and youth (12 to 22 years old) separately. We used RStudio to generate Kaplan-Meier curves and performed log-rank tests to assess differences in event-free survival across GDM/maternal diabetes exposure groups. Log-rank p-values for were considered significantly different at $p \leq 0.05$, slightly similar survival $0.1 \geq p > 0.05$, and highly similar at $p > 0.1$. We also generated KM curves for paternal diabetes. To evaluate the association between GDM/maternal pre-existing diabetes and T1D in the second-born (subject), we constructed Cox proportional hazards (PH) models using the SAS PROC PHREG function. We first assessed for correlation through pairwise comparisons between covariates/confounders (variables were considered correlated at Cramer's $V \geq 0.5$; PROC FREQ CHISQ function). We verified the proportionality of hazards by examining Kaplan-Meier curves and generating Schoenfeld residuals (requiring $p > 0.05$ for valid PH assumption).

We originally planned to examine offspring from birth to 22 years of age within a single model. However, when we considered this full age range together, the GDM/pre-existing maternal diabetes exposure variable did not meet PH assumptions. To mitigate this issue, we constructed

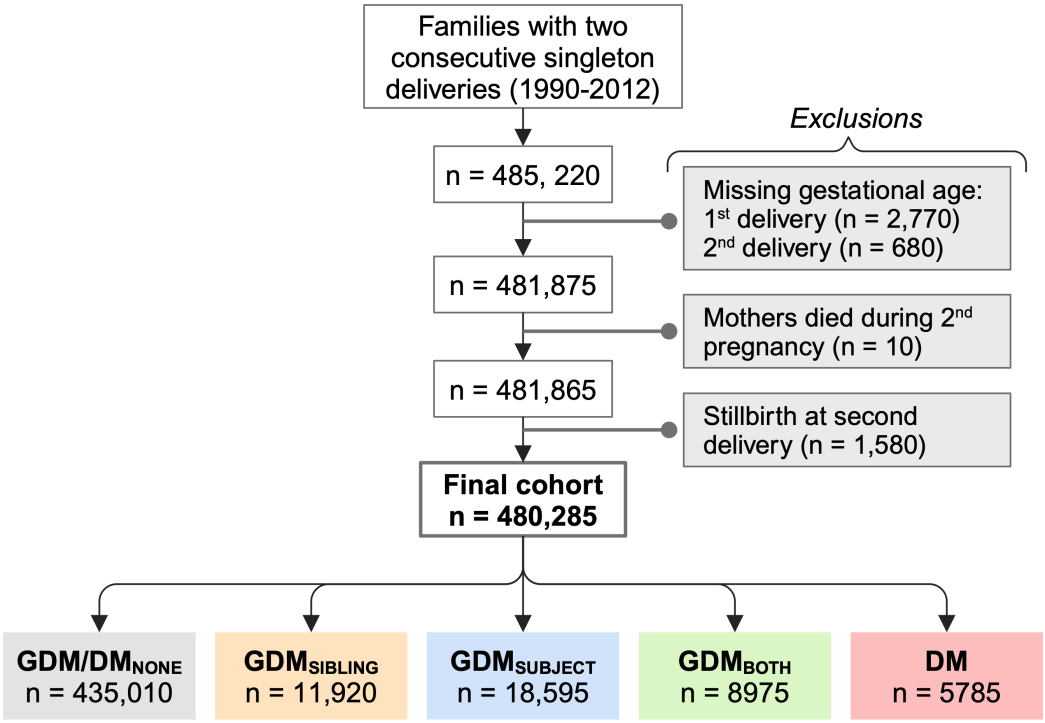
separate models for childhood (birth until 12 years) and youth (12 to 22 years) periods. In addition to meeting PH assumptions, this approach aligns with the results from our previous study, which demonstrated differences in magnitude of associations between GD in index pregnancy and offspring diabetes development between these groups.[7] Separate models are also justified by puberty-related differences in T1D risk described in other studies.[172,173] We set the 12-year cut-off according to the age of puberty (11-14 years)[174,175] and by evaluating PH validity for different ages within this range. The youth cohort excluded offspring who developed diabetes before age 12. We forced selected variables into the models based on their demographic and clinical importance: maternal and paternal ages, offspring macrosomia, subject sex, and deprivation levels. To ensure fulfillment of the PH assumption for these variables, we included maternal age as a spline function, incorporated subject sex with a time interaction in the youth model, and retained social but not material deprivation as the SES indicator. In terms of offspring size, we included macrosomia. Size for gestational age (i.e., including large, appropriate, and small for gestational age categories) did not meet PH assumptions. The literature does not indicate an association between small for gestational age and type 1 diabetes.[176] For all other variables, we excluded those that did not fulfill PH assumptions and with $p > 0.25$ at the univariate level. We then performed backward model selection, retaining variables significant at $p \leq 0.05$ and that minimized Bayesian Information Criteria (BIC) values (**Appendix Table 2)**. GDM/DM_{NONE} was the reference category in the main models for GDM/maternal diabetes exposure. In additional models, we directly compared the $GDM_{SIBLING}$, $GDM_{SUBJECT}$, GDM_{BOTH}, and DM exposure groups by alternating the reference categories in our models, adjusting for the same covariates. We also compared paternal pre-existing diabetes against its absence regarding T1D risk in the second-born.

4. Results

4.1 Descriptive Statistics

Of the initial 485,220 families, 480,285 (99.0%) families met our eligibility criteria. We excluded 3,450 families due to missing gestational age at either delivery, 10 because the mother died giving birth to the subject (second born), and 1,580 families in which the subject died at birth (**Figure 11**). Of the remaining 480,2855, 435,010 (90.6%) families classified as GDM/DM_{NONE} (the reference group), 11,920 (2.48%) as $GDM_{SIBLING}$, 18,595 (3.87%) as $GDM_{SUBJECT}$, 8,975 (1.87%) as GDM_{BOTH} and 5,785 (1.20%) as DM. The prevalence of GDM in our cohort (in either or in both pregnancies) was 39,490 (8.14%).

Figure 11. Study cohort



Overall, 400,710 (83.4%) were from European background, 16,510 (3.44%) from Arab-speaking regions, 12,800 (2.67%) were of Asian background, and 8105 (1.69%) were of African-Caribbean background. The proportion of European background was highest in the control group (84.4%). Compared to controls, for both offspring, the average gestational age at birth was about one week shorter in the DM group; proportions of preterm birth were higher in the GDM exposure groups and more than double in the DM group; proportions of macrosomia were double in the GDM exposure groups and triple in the DM group. Proportions of cesarean section were higher in the GDM groups and highest in the DM group (**Table 3**). Paternal diabetes and maternal but not paternal autoimmunity were more frequent in exposure groups compared to controls. The proportion of families with maternal hypertension and gestational hypertension at either pregnancy was about two times higher in GDM exposure groups and five times higher in the DM group. Parents in exposure groups were, on average, 1-2 years older than parents in the control arm. Mothers in exposure groups had fewer years of education and were more socially and materially deprived.

Table 3. Baseline characteristics of offspring and parents by maternal diabetes status

	GDM/DM_{NONE} (n = 435,010)	$GDM_{SIBLING}$ (n = 11,920)	$GDM_{SUBJECT}$ (n = 18,595)	GDM_{BOTH} (n = 8975)	DM (n = 5785)
Subject (second-born) characteristics					
Sex (female)	211,790 (48.7%)	5720 (48.0%)	9005 (48.4%)	4310 (48.0%)	2780 (48.1%)
Gestational age, weeks, mean (SD)	39.0 (1.6)	38.8 (1.7)	38.6 (1.5)	38.5 (1.6)	38.1 (1.8)
Preterm birth	19,715 (4.5%)	685 (5.8%)	1305 (7.0%)	645 (7.2%)	665 (11.5%)
Birth weight, g, mean (SD) *	3386.6 (521.1)	3413.3 (534.6)	3381.8 (622.3)	3396.4 (550.1)	3402.1 (655.8)
Macrosomia *	5165 (1.2%)	210 (1.8%)	425 (2.3%)	190 (2.1%)	215 (3.7%)
Cesarean section	76,900 (17.7%)	2675 (22.4%)	4635 (24.9%)	2390 (26.6%)	2180 (37.7%)
Sibling (first-born) characteristics					
Sex (female)	211,235 (48.6%)	5845 (49.0%)	8970 (48.2%)	4200 (46.8%)	2810 (48.6%)
Gestational age, weeks, mean (SD)	39.1 (1.9)	38.9 (1.7)	38.8 (2.5)	38.6 (1.7)	38.2 (2.3)
Preterm birth	26385 (6.1%)	850 (7.1%)	1835 (9.9%)	790 (8.8%)	740 (12.8%)
Birth weight, g, mean (SD) †	3393.0 (507.9)	3406.0 (543.1)	3403.3 (570.8)	3407.3 (556.7)	3406.2 (625.2)
Macrosomia †	5265 (1.2%)	235 (2.0%)	380 (2.0%)	215 (2.4%)	195 (3.4%)
Cesarean section	78,830 (18.1%)	2680 (22.5%)	4425 (23.8%)	2250 (25.1%)	1960 (33.9%)
Stillbirth	2120 (0.5%)	35 (0.3%)	305 (1.6%)	40 (0.5%)	85 (1.5%)
Parental co-morbidities					
Father diabetes	2865 (0.7%)	100 (0.8%)	210 (1.1%)	135 (1.5%)	110 (1.9%)
Mother autoimmunity	61,285 (14.1%)	1905 (16.0%)	2785 (15.0%)	1525 (17.0%)	1305 (22.6%)
Father autoimmunity	47,840 (11.0%)	1295 (10.9%)	1985 (10.7%)	1075 (12.0%)	710 (12.3%)
Mother hypertension	5395 (1.2%)	270 (2.3%)	395 (2.1%)	275 (3.1%)	335 (5.8%)
Gestational hypertension during subject pregnancy					
Without pre-eclampsia	14,470 (3.3%)	590 (5.0%)	1345 (7.2%)	695 (7.8%)	700 (12.1%)
With pre-eclampsia	6795 (1.6%)	280 (2.4%)	560 (3.0%)	275 (3.1%)	295 (5.1%)
Gestational hypertension during sibling pregnancy					
Without pre-eclampsia	13,640 (3.1%)	615 (5.2%)	995 (5.4%)	560 (6.2%)	435 (7.5%)
With pre-eclampsia	17,040 (3.9%)	680 (5.7%)	1275 (6.9%)	590 (6.6%)	525 (9.1%)
Mother characteristics					
Mother age, years, mean (SD)	29.9 (4.5)	30.9 (4.7)	31.6 (4.8)	32.0 (4.7)	32.0 (4.7)
Years of education at subject delivery ‡					
<12	90,685 (20.9%)	2765 (23.2%)	4545 (24.4%)	2100 (23.4%)	1375 (23.8%)
12-14	76,215 (17.5%)	2200 (18.5%)	3285 (17.7%)	1550 (17.3%)	980 (16.9%)
14-18	203,360 (46.8%)	5290 (44.4%)	8145 (43.8%)	4020 (44.8%)	2590 (44.8%)
≥18	43,220 (9.9%)	1090 (9.1%)	1725 (9.3%)	840 (9.4%)	535 (9.3%)
Social deprivation index ¶					
Q1 = least deprived	95,110 (21.9%)	2470 (20.7%)	3575 (19.2%)	1880 (21.0%)	1125 (19.5%)

Q2	92,850 (21.3%)	2430 (20.4%)	3685 (19.8%)	1760 (19.6%)	1145 (19.8%)
Q3	88,905 (20.4%)	2390 (20.1%)	3810 (20.5%)	1735 (19.3%)	1175 (20.3%)
Q4	80,840 (18.6%)	2330 (19.6%)	3680 (19.8%)	1855 (20.7%)	1155 (20.0%)
5 = most deprived	70,010 (16.1%)	2115 (17.7%)	3510 (18.9%)	1600 (17.8%)	1090 (18.8%)
Material deprivation index §					
Q1 = least deprived	86,785 (20.0%)	2145 (18.0%)	3200 (17.2%)	1600 (17.8%)	990 (17.1%)
Q2	91,280 (21.0%)	2455 (20.6%)	3690 (19.8%)	1755 (19.6%)	1140 (19.8%)
Q3	86,900 (20.0%)	2330 (19.6%)	3595 (19.3%)	1685 (18.8%)	1220 (21.1%)
Q4	82,925 (19.1%)	2345 (19.7%)	3710 (20.0%)	1780 (19.9%)	1080 (18.7%)
Q5 = most deprived	79,825 (18.4%)	2460 (20.6%)	4065 (21.9%)	2010 (22.4%)	1265 (21.9%)
Father characteristics					
Father age, years, mean (SD)	32.8 (5.3)	33.5 (5.5)	34.4 (5.7)	34.7 (5.7)	34.8 (5.7)
Different fathers	31,140 (7.2%)	680 (5.7%)	1770 (9.5%)	370 (4.1%)	460 (7.9%)
Other characteristics					
Time between deliveries ≥ 3 years	113,730 (26.1%)	3060 (25.7%)	7050 (37.9%)	2495 (27.8%)	2065 (35.7%)
Parent ethnicity					
Europid	367,025 (84.4%)	9405 (78.9%)	13,680 (73.6%)	6285 (70.0%)	4315 (74.6%)
Arab	13,790 (3.2%)	580 (4.9%)	1195 (6.4%)	640 (7.1%)	305 (5.3%)
African, Caribbean	6885 (1.6%)	245 (2.1%)	490 (2.6%)	260 (2.9%)	225 (3.9%)
Asian	10,190 (2.3%)	565 (4.7%)	1105 (5.9%)	685 (7.6%)	255 (4.4%)
Other	9475 (2.2%)	380 (3.2%)	745 (4.0%)	395 (4.4%)	220 (3.8%)
Different between parents	27,645 (6.4%)	750 (6.3%)	1380 (7.4%)	710 (7.9%)	465 (8.0%)

Data are n (%) or mean (SD). *566 subjects missing birth weight, also required to derive macrosomia. †564 siblings missing birth weight also required to derive macrosomia. ‡23,770 missing social deprivation for the mother at subject birth and birth +/-1 year. ¶8,048 missing material deprivation at subject birth and birth +/-1 year.

4.2 Survival Analysis and Incidence Rates

Overall, 1845 second-born offspring developed T1D over an average time of 11.7 years (SD 6.2) for the entire cohort (birth to 22 years). A total of 960 children (birth until 12 years) developed T1D over an average time of 6.67 years (SD 3.36). A total of 865 youth (12 to 22 years) developed T1D at an average age of 17.3 years (SD 3.1). Overall, the average follow-up time (which ended

at diabetes diagnosis, death or reaching 22 years) was 15.5 years (SD 5.4). There were 1810 who died before the end of follow-up (1455 children and 355 youth). Among children, incidence rates per 100,000 person-years were similar in the control GDM/DM_{NONE} (1.74) and $GDM_{SIBLING}$ groups (1.51), higher in the $GDM_{SUBJECT}$ (2.39) and GDM_{BOTH} (2.55) groups, and highest in the DM group (5.04). In youth, rates were lowest in the control group (3.70), higher and similar to one another in the $GDM_{SIBLING}$ (5.32) and $GDM_{SUBJECT}$ groups (6.02), even higher in the GDM_{BOTH} group (8.70), and highest in the DM group (17.7) (**Table 4**).

Table 4. Incidence rates per 100,000 person-years of diabetes second-born offspring by maternal diabetes status

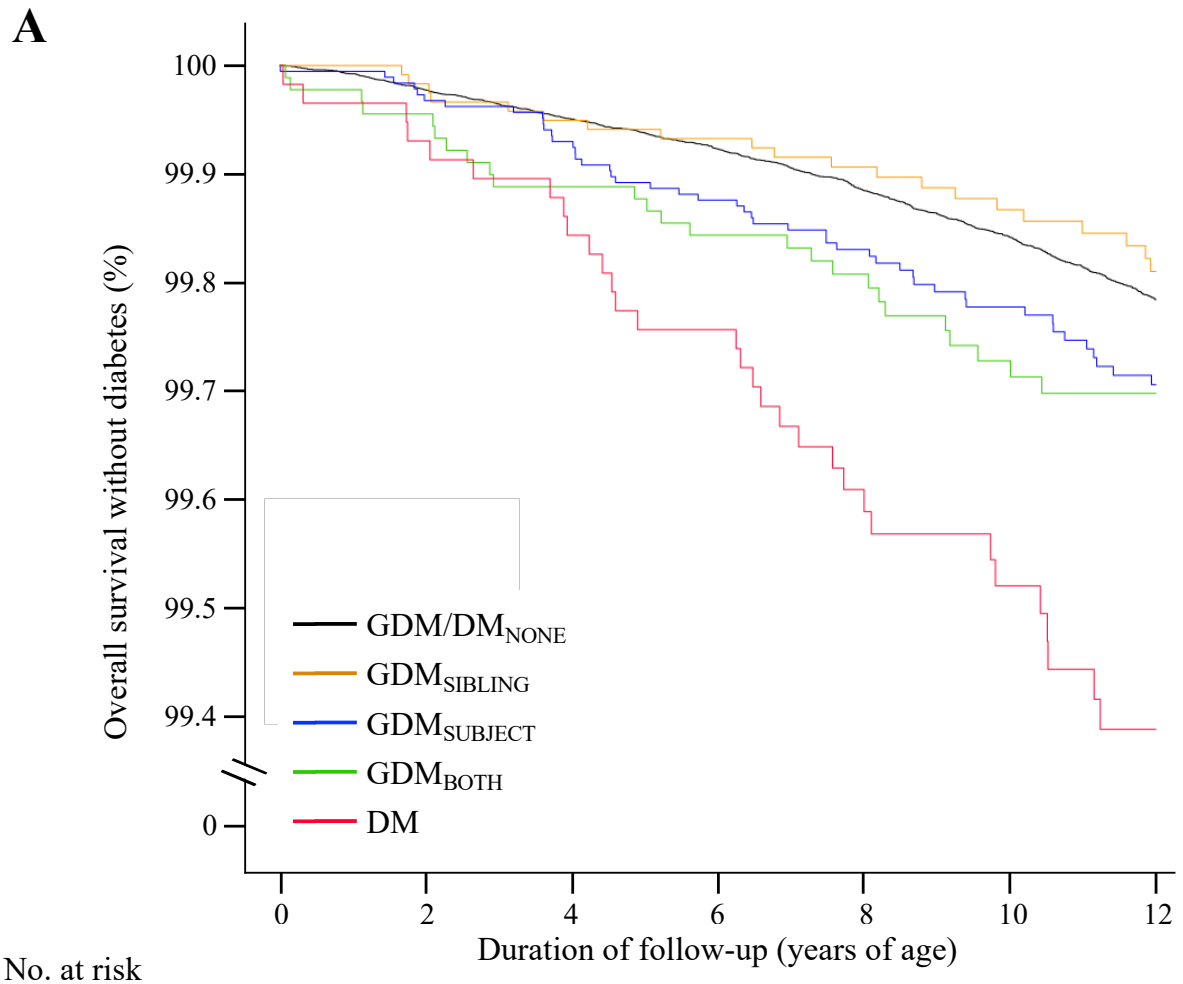
		GDM/DM_{NONE}	**$GDM_{SIBLING}$**	**$GDM_{SUBJECT}$**	**GDM_{BOTH}**	**DM**
Children	Person-years	4,811,139	132,475	200,833	98,003	61,523
	Events	835	20	50	25	30
	Incidence rate	**1.74**	**1.51**	**2.39**	**2.55**	**5.04**
Youth	Person-years	1,960,878	56,433	74,766	36,802	19,204
	Events	725	30	45	30	35
	Incidence rate	**3.70**	**5.32**	**6.02**	**8.70**	**17.7**

Incidence rates are per 100,000 person-years at risk.

The Kaplan-Meier curves were consistent with these incidence rates (**Figure 12**). Pairwise log-rank comparisons between curves (**Table 5**) indicate strong similarities in event-free survival between the GDM/DM_{NONE} and $GDM_{SIBLING}$ groups ($p = 0.5$) in children and the $GDM_{SUBJECT}$ and $GDM_{SIBLING}$ groups in youth ($p = 0.5$) as well as for the $GDM_{SUBJECT}$ and GDM_{BOTH} in youth ($p = 0.2$). All other comparisons demonstrated statistically different survival ($p < 0.05$) except the three GDM exposure groups (**$GDM_{SIBLING}$, $GDM_{SUBJECT}$, and** GDM_{BOTH} groups) in children, which were similar (p-values between 0.07 and 0.08). Overall log ranks in both age groups demonstrate

significant differences ($p < 0.001$). Survival without T1D in the offspring of fathers with diabetes also declined much faster than that of offspring of fathers without (**Figure 13**).

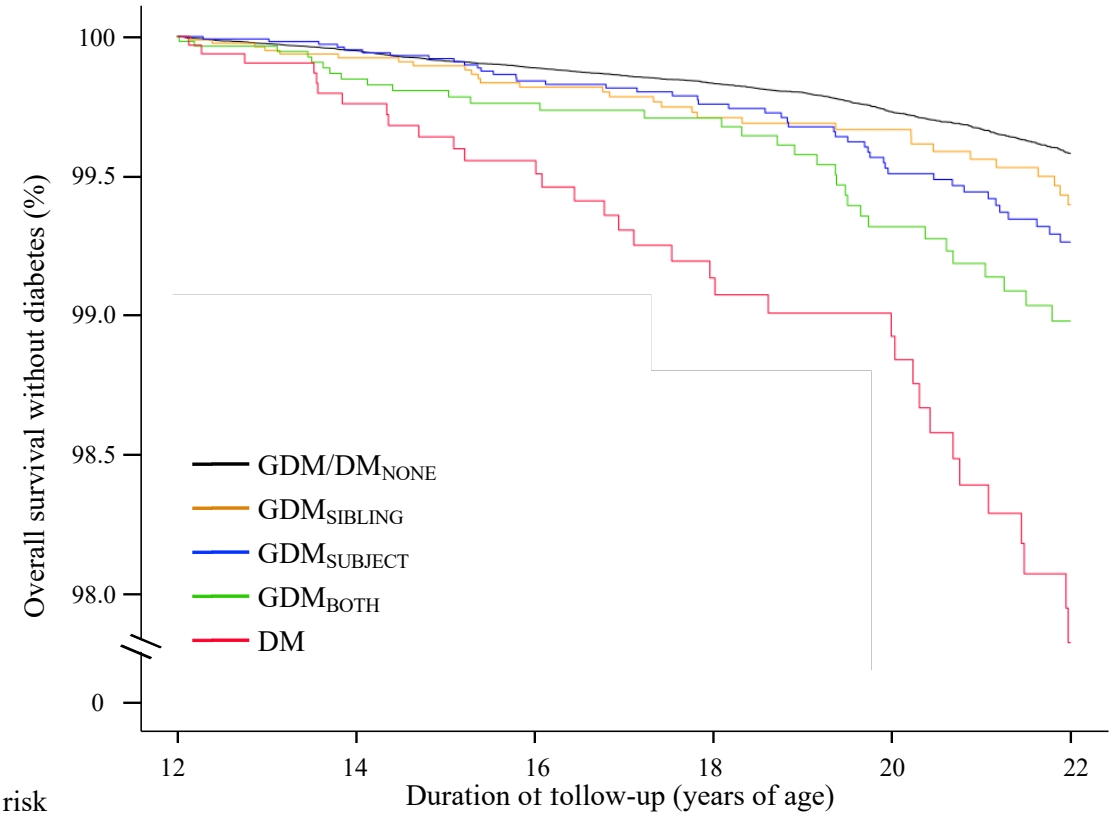
Figure 12. Overall survival without diabetes in the second-born offspring by maternal diabetes status in (A) children and (B) youth



No. at risk

GDM/DM$_{NONE}$	435,010	433,955	433,725	433,515	391,600	344,205	297,010
GDM$_{SIBLING}$	11,920	11,890	11,880	11,875	10,795	9590	8390
GDM$_{SUBJECT}$	18,595	18,555	18,540	18,530	16,055	13,600	11,590
GDM$_{BOTH}$	8975	8955	8950	8940	7935	6780	5830
DM	5785	5750	5745	5740	4895	4070	3305

B



No. at risk

GDM/DM$_{NONE}$	297,005	253,670	214,730	176,155	137,620	97,215
GDM$_{SIBLING}$	8390	7265	6205	5090	3990	2860
GDM$_{SUBJECT}$	11,590	9900	8275	6590	5070	3400
GDM$_{BOTH}$	5830	4885	4035	3235	2480	1685
DM	3305	2635	2115	1635	1190	785

Figure 13. Overall survival without diabetes in the second-born offspring by paternal diabetes status in (A) children and (B) youth

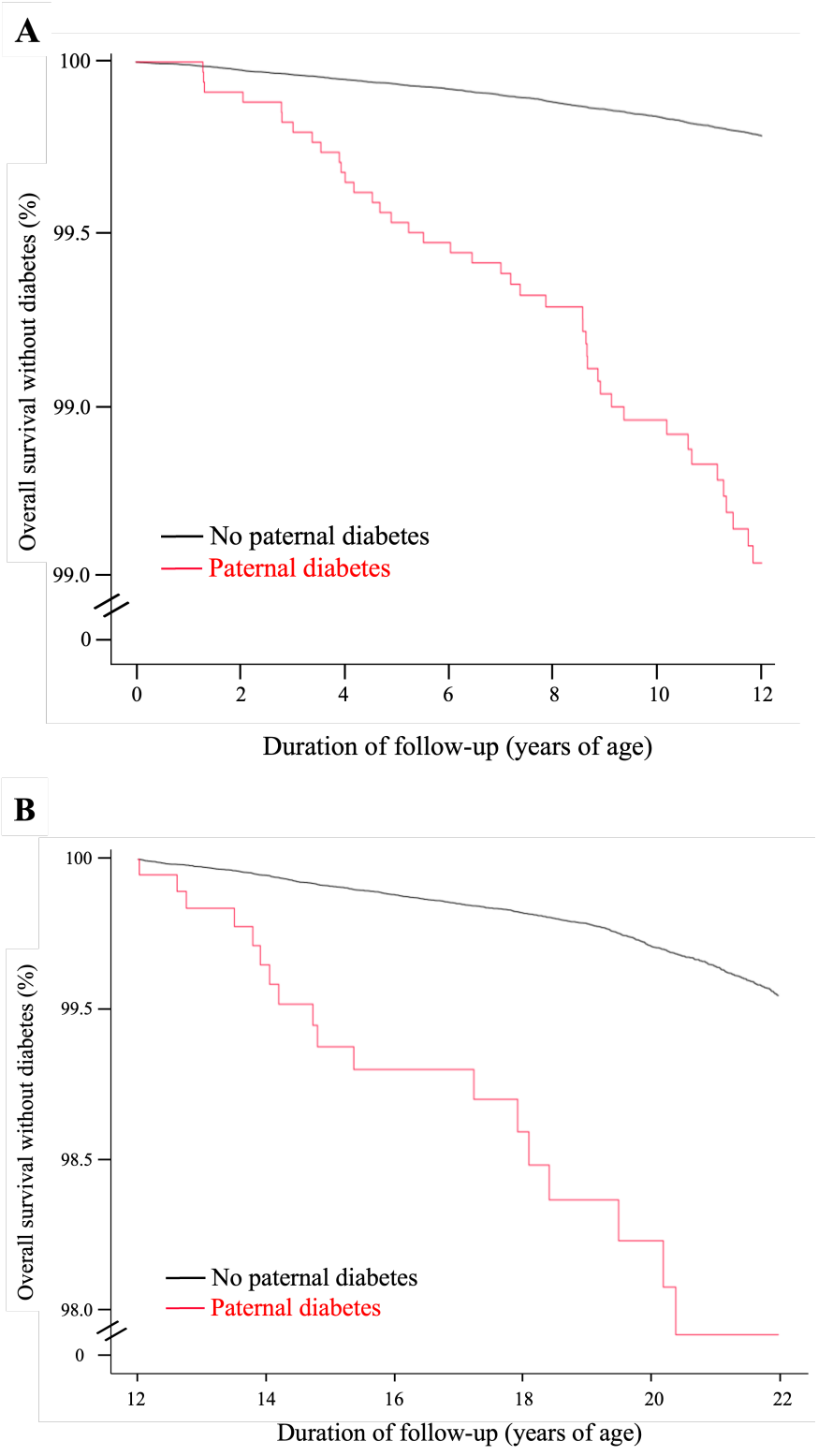


Table 5. Pairwise log-rank comparisons between survival without diabetes curves by GDM/maternal diabetes exposure

Children	GDM/DM_{NONE}	$GDM_{SIBLING}$	$GDM_{SUBJECT}$	GDM_{BOTH}
$GDM_{SIBLING}$	0.5			
$GDM_{SUBJECT}$	0.03	0.08		
GDM_{BOTH}	0.05	0.07	0.08	
DM	<0.001	<0.001	<0.001	<0.001
Youth	GDM/DM_{NONE}	$GDM_{SIBLING}$	$GDM_{SUBJECT}$	GDM_{BOTH}
$GDM_{SIBLING}$	0.05			
$GDM_{SUBJECT}$	0.001	0.5		
GDM_{BOTH}	<0.001	0.04	0.2	
DM	<0.001	<0.001	<0.001	<0.001

p-values for pairwise log-rank comparisons were considered significantly different at $\mathbf{p \leq 0.05}$ (unshaded), slightly similar survival $\mathbf{0.1 \geq p > 0.05}$ (●) and highly similar at $\mathbf{p > 0.1}$ (●)

4.3 Cox Proportional Hazards Models

After applying our model selection criteria, the variables adjusted for in the final models were subject age, sex, subject and sibling macrosomia, parental age groups, ethnicity, social deprivation, subject preterm birth, maternal autoimmunity, and maternal GH with PEE in the first pregnancy (only in the children model); and time between deliveries (only in the youth model). The only strongly correlated covariates were cesarean section in the subject and in the sibling ($p > 0.6$) (**Appendix Figure 1**). Sibling stillbirth was not significant in either the children or youth models at the univariate level ($p > 0.25$) and was therefore removed from both. We removed cesarean section at first delivery and material deprivation from the children and youth models, respectively, as they violated the PH assumption (**Appendix Table 1**). The remaining variables not retained

were removed according to our multivariable model selection criteria (see **section 3.8**; **Appendix Table 2**). Amongst essential variables to be forced into the models, maternal age categories and subject sex violated PH assumptions in the youth model (**Appendix Table 1**). Maternal age could not be included as a continuous variable due to non-linearity according to martingale residuals. Therefore, we included this variable as a spline function and applied a time interaction to the subject sex variable in the final youth model.

4.3.1 Children (birth up to 12 years old)

In children, neither $GDM_{SIBLING}$ (HR 0.77, 95% CI 0.48-1.25; **Figure 13**) nor $GDM_{SUBJECT}$ (HR 1.18, 95% CI 0.85-1.64) were conclusively associated with diabetes in the subject. For GDM_{BOTH}, associations were also inconclusive, although the lower limit of the 95% CI was above 0.9 (HR 1.40, 95% CI 0.93-2.11). DM demonstrated a greater than doubling of hazards compared to the control group (HR 2.38, 95% CI 1.60-3.53). DM was conclusively associated with higher hazards of offspring diabetes in the subject compared directly to $GDM_{SIBLING}$ (HR 3.07, 95% CI 1.66-5.67) and to $GDM_{SUBJECT}$ (HR 2.02, 95% CI 1.22-3.33) but not conclusively different from the GDM_{BOTH} group (**Figure 14**).

4.3.2 Youth (12 to 22 years old)

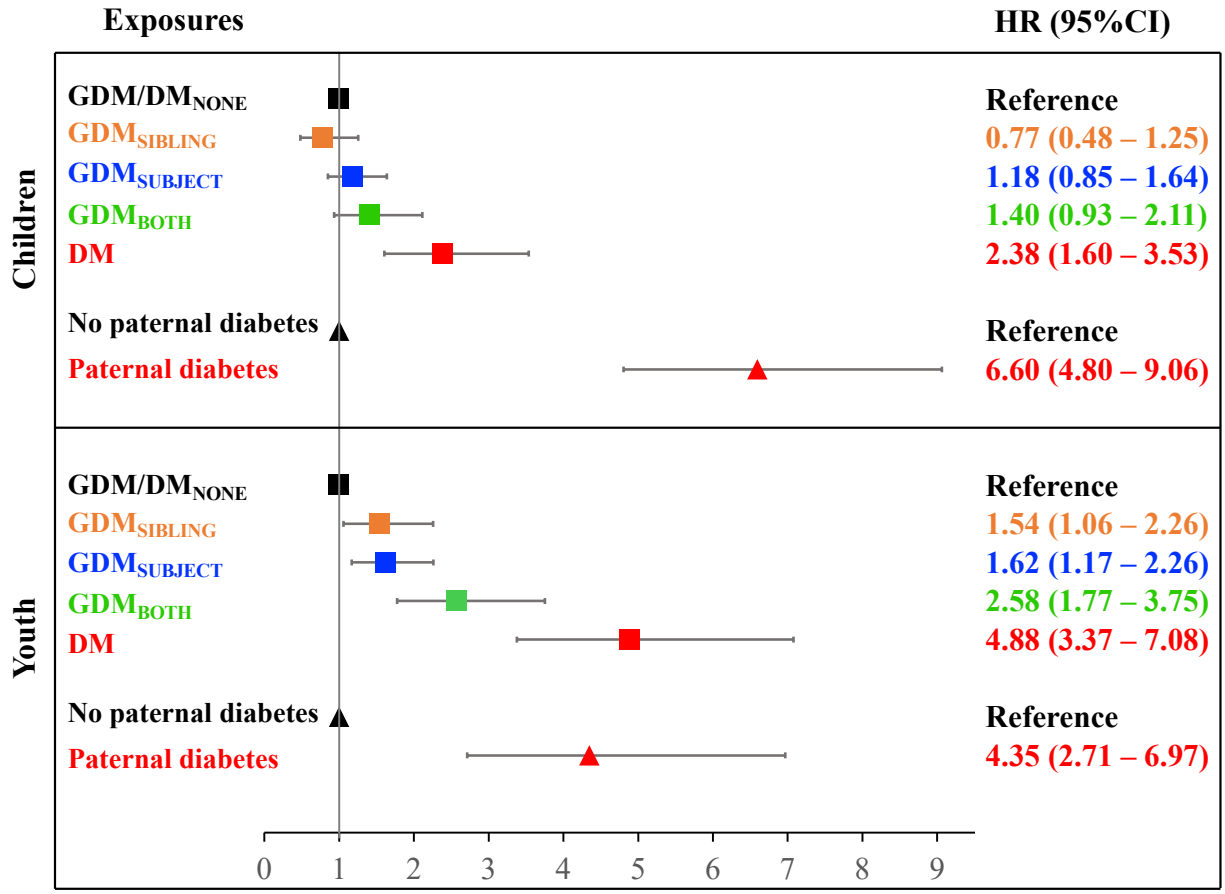
In youth, $GDM_{SIBLING}$ was associated with a 54% increase in hazards for second born diabetes (HR 1.54, 95% CI 1.05-2.25; **Figure 14**). $GDM_{SUBJECT}$ was associated with a 63% hazard increase (HR 1.62, 95% CI 1.17-2.26). GDM_{BOTH} was associated with a 2.58-fold hazard increase (HR 2.58,

95% CI 1.77-3.75). DM was associated with a nearly five-fold hazard increase (HR 4.88, 95% CI 2.71-6.97). Consistent with these analyses, in youth, $GDM_{SIBLING}$ and $GDM_{SUBJECT}$ groups compared directly were not conclusively different from one another ($GDM_{SIBLING}$ reference, HR 1.05, 95% CI 0.64-1.71). In addition, GDM_{BOTH} appeared to be associated with higher hazards than $GDM_{SUBJECT}$ (HR 1.59, 95% CI 0.98-2.57) and $GDM_{SIBLING}$ (HR 1.67, 95% CI 0.99-2.81). DM was associated with higher hazards than all other exposure groups (**Figure 15**).

4.3.3 Paternal Diabetes

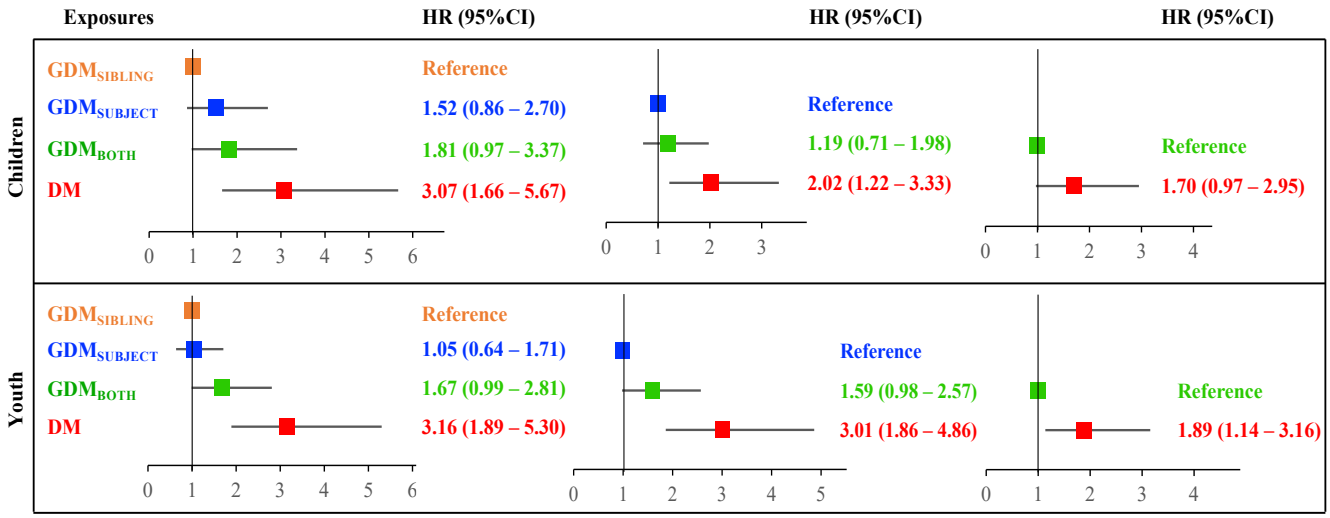
In children, paternal diabetes had a stronger association with second born diabetes than any maternal diabetes exposure category, with over 6-fold higher hazards compared to the absence of paternal diabetes (HR 6.60, 95% CI 4.80-9.06; **Figure 14**). In youth, paternal diabetes also demonstrated a strong association, but the magnitude (HR 4.35, 95% CI 2.71-6.97) was similar to that of pre-existing maternal diabetes.

Figure 14. Associations between maternal/paternal diabetes status and diabetes in the second-born offspring, in childhood and youth



The forest plots illustrate HR for maternal diabetes status depicted as squares, HR for paternal diabetes status depicted as triangles, and 95% CI depicted as lines. The GDM/maternal diabetes exposures were compared with the absence of GDM or maternal pre-existing diabetes (GDM/DM_{NONE}), and paternal pre-existing diabetes exposure was compared to its absence.

Figure 15. Associations between maternal diabetes status and diabetes in the second-born offspring, comparing maternal diabetes categories with one another



4.3.4 Other Covariates

Other covariates that demonstrated significant associations with diabetes in children were subject preterm birth (HR 1.49, 95% CI 1.147-1.94), GH with PEE during the first pregnancy with the sibling (HR 1.503, 95% CI 1.147-1.969) and maternal autoimmunity (HR 1.29, 95% CI 1.08-1.53). In youth, time between deliveries three years or higher also demonstrated conclusive associations (HR 1.30, 95% CI 1.11-1.52), and the Asian ethnicity was protective (HR 0.26, 95% CI 0.11-0.62) (**Appendix Table 3**).

5. Discussion

5.1 Summary of Findings

Our analyses confirm an association between GDM and offspring diabetes in youth and indicate a dose-dependent relationship between the burden of GDM and the incidence of offspring diabetes. Specifically, we demonstrated that GDM in a first pregnancy and GDM in a second pregnancy are each similarly associated with diabetes occurrence between 12 and 22 years of age. Further, they appear to have multiplicative effects, as GDM in both pregnancies demonstrated an even stronger association. We did not observe these associations during childhood among such families with at least two consecutive pregnancies, in contrast to a previous study in which we did not impose a two-pregnancy specification. Additionally, we demonstrated pre-existing diabetes in mothers and in fathers diagnosed before the second pregnancy to be individually associated with diabetes development during both childhood and youth periods. Paternal diabetes was a stronger risk marker than pre-existing maternal diabetes in childhood, but both were similar in youth.

5.2 GDM in second pregnancy and offspring diabetes in the second born

We detected an association between GDM in a second pregnancy and offspring diabetes in the second born during youth but not childhood. Among studies involving children under 15 years old, four studies, including my research group's previous one, found conclusive associations,[7,10,11,177] while four,[178-181] like the present one, did not (**Table 2**). In their previous retrospective cohort, my supervisor and team identified a 43% increased risk from birth to age 12 (HR 1.43; adjusted for

gestational age, macrosomia, sex, demographic factors, history of prior pregnancy and maternal autoimmunity).[7]

On the other hand, two large retrospective studies did not detect increased hazards.[178,179] One of these focused on offspring under six years of age.[178] The age restriction in this young cohort might explain the lack of association, as the follow-up period may have been too short for T1D to develop. In addition, these younger children may be less susceptible to insulin resistance-related factors. The two other studies reporting inconclusive findings were case-controls of 112 and 1142 children.[180,181] The smaller sample sizes in these studies might have limited their ability to detect conclusive associations.

The absence of an association during childhood in the current analysis may be related to our restriction to families with at least two deliveries. Women with more severe GDM and challenged by glycemic management may have opted not to have a second pregnancy.[182] They would thus have been excluded from our study cohort, lowering the background diabetes risk in our population. This may partly explain the inconclusive nature of the associations we observed in children. Moreover, our point estimates for HR in children were above 1, and we did observe differences in the incidence rates for second-born children exposed to GDM, indicating that a larger sample size may have allowed us to detect conclusive associations. Further study is required for this age group.

In contrast to children, youth have a higher baseline diabetes risk due to puberty-related increases in insulin resistance, driven by growth hormone, C-peptide, insulin-like growth factor levels,[172]

and changes in diet and physical activity.[173] They are also more likely to develop obesity,[183] both associated with T1D.[110,111] Consistent with this, a 2013 case-control study[184] and my team's previous retrospective cohort[7] found conclusive associations (OR 5.1 and HR 2.53, respectively). Importantly, the latter reported stronger associations in this older age group than in the under-12. Supporting these risk differences between children and youth, a case-control study found that higher maternal insulin resistance accompanying GDM was associated with later age at diagnosis of T1D for the offspring.[185]

5.3 GDM in a first pregnancy and diabetes in the second born

We not only confirmed an association between GDM and offspring diabetes in youth, but also detected an association between GDM in the first pregnancy and diabetes development in the second born. This association was similar in magnitude to the association between second-pregnancy GDM and second-born diabetes in youth. Specifically, compared to the absence of any form of maternal diabetes, first-pregnancy GDM was associated with a 54% increase in hazards of diabetes in the second born and second-pregnancy GDM, with a 62% increase. Direct risk comparisons between these two exposure categories demonstrated no conclusive differences, further supporting their similarity. Thus, the mechanisms behind these associations are less likely to be related to pregnancy-specific factors and the *in utero* environment. Instead, they may be attributable to familial factors that affect both offspring similarly, regardless of which pregnancy was complicated by GDM. GDM in both pregnancies was associated with a higher 2.58-fold increase in hazard in youth. This indicates that GDM in two pregnancies likely signals an even

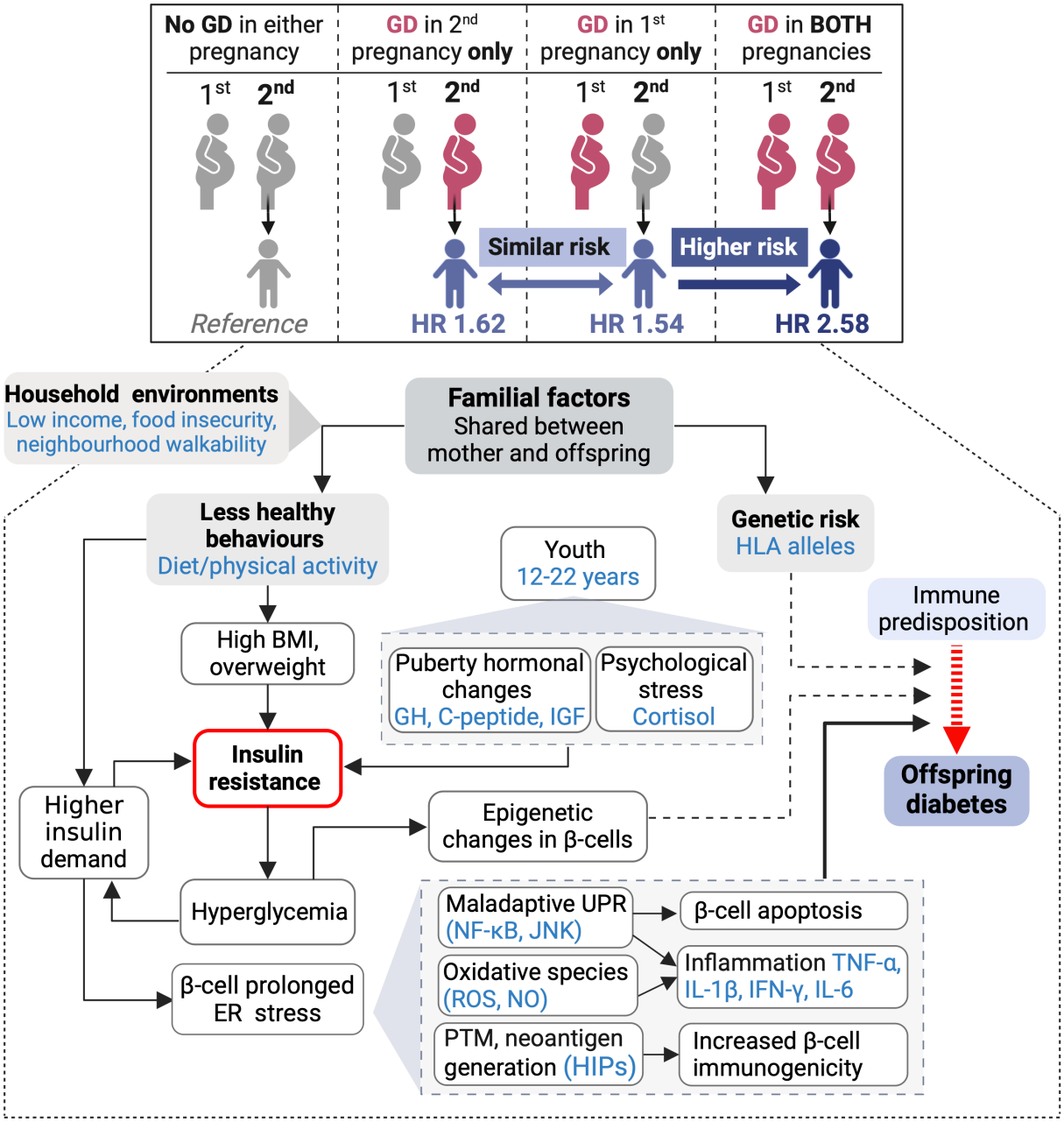
higher burden of familial factors driving GDM and offspring T1D associations. Such familial factors include genetics, household environments, and behavioural patterns.

With respect to genetic factors, various studies, including a meta-analysis, have identified associations between known T1D *HLA* risk alleles and GDM (see **section 2.2.3**).[36,85] Mothers carrying such genetic vulnerability could transmit it to either offspring, irrespective of which pregnancy was directly complicated by GDM. However, the rise in T1D incidence in the past decades is not reflected by changes in *HLA* allele population frequencies,[186] and most of the rising incidence of T1D occurs in individuals without a genetic risk, suggesting the growing importance of environmental factors.[187,188] In fact, T1D incidence is more closely matched by the rising incidence rates of obesity, which have increased 3-fold in the past five years,[56] and of insulin resistance.[189] Therefore, shared genetic susceptibility may not be the primary driver of the association between GDM and offspring T1D. Instead, behavioural and environmental factors related to insulin resistance and overweight likely play a more significant role.

Mothers who develop GDM frequently have dietary and physical activity habits that promote the development of insulin resistance. Either offspring may model these behaviours, and both share environments that could lead to them (low income, food insecurity, low neighbourhood walkability, beliefs).[190] While insulin resistance has traditionally been linked to T2D and GDM, emerging evidence suggests that it also hastens the progression of T1D in individuals with autoantibodies against β-cells, a phenomenon called the 'Accelerator Hypothesis'. The evidence supporting this theory is detailed in **section 2.2.4**. As previously stated, youth have a higher baseline risk for diabetes and insulin resistance due to puberty-related hormonal changes.[191]

Further supporting our results in this age group, human and animal studies demonstrate an increase in psychological stress and cortisol levels during puberty,[192-194] both of which are associated with insulin resistance.[195,196] We provide a conceptual schematic for possible mechanisms underlying associations between GDM at either pregnancy and T1D in the second-born offspring during youth (**Figure 16)**.

Figure 16. Conceptual framework for possible mechanisms underlying associations between first- and second-pregnancy GDM and second-born diabetes in youth



As previously discussed, T1D diagnosis is often delayed until DKA occurs.[26] Patients, caregivers, and clinicians often dismiss the earlier symptoms of thirst and increased urination as non-specific and/or unimportant. The novel association we have identified between GDM during an older sibling pregnancy and offspring T1D development during youth constitutes an additional risk marker that could improve appreciation of early diabetes symptoms. Our findings also add to a growing body of literature supporting the importance of household environments and behaviours that promote insulin resistance in T1D development.

5.4 Parental pre-existing diabetes and offspring diabetes

While our primary focus was on GDM, we also examined the relationships between pre-existing parental diabetes and offspring diabetes. We demonstrated conclusive associations during both childhood and youth periods for both maternal and paternal pre-existing diabetes. We did not have information on the date of onset of pre-existing diabetes in parents. However, the parents in our study averaged 30 to 32 years; at this age, pre-existing diabetes is essentially T2D but also includes T1D. Parental T1D is a well-established risk marker for offspring T1D,[138] and emerging evidence suggests that parental T2D is another risk marker,[8] likely due to behavioural and environmental factors like those driving the associations between GDM and offspring T1D, as we have described.

In our analysis of children under 12 years old, the 6.6-fold increase in risk conferred by paternal diabetes was much higher than the 2.38-fold increase in risk from maternal diabetes (compared to their respective absence). Consistent with this, a recent review summarized studies demonstrating stronger associations for paternal than for maternal T1D with offspring T1D.[138] This difference in

parental contributions to offspring T1D risk has also been reported in the context of parental T2D in several studies (the risk estimates are detailed in **section 2.2.2**).[8,11,197] Different mechanisms have been proposed to explain the discrepancy between maternal and paternal diabetes (**Figure 17**).

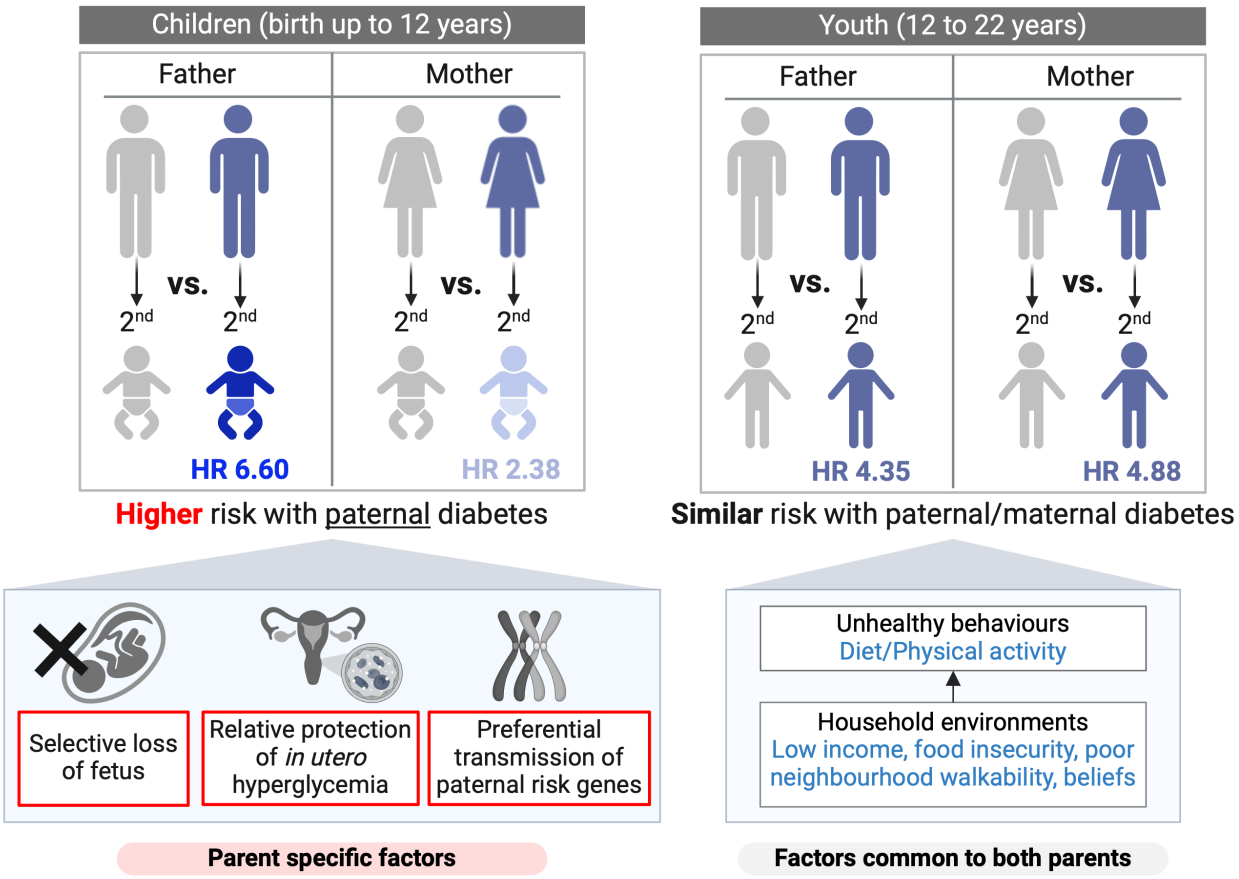
One possibility is the preferential genetic transmission of T1D risk alleles of the *HLA* gene from fathers with T1D[198] and fathers with T2D.[199] Given that the *HLA* loci are autosomal, the mechanisms behind this preferential transmission are likely epigenetic and involve some form of maternal imprinting on regulatory regions.[200,201] Another theory suggests that the selective loss of fetuses in women with pre-existing diabetes may be at play. Perinatal mortality is more than four times as frequent in offspring of women with T1D or T2D than in the general population.[202,203] This suggests that if offspring of mothers with severe hyperglycemia during pregnancy and at the highest risk of impaired β-cell development are selectively lost and therefore excluded from the study population, children born to fathers with diabetes may hence show greater susceptibility to T1D.

Finally, some studies suggest a relative protective effect of *in utero* hyperglycemia against T1D autoimmunity. As discussed earlier, exposure to elevated glucose levels from the mother increases self-antigen expression in developing β-cells. Studies have found that such an early increase in β-cell immunogenicity can render the immune system more tolerant to pancreatic antigens by enhancing negative thymic selection of developing T cells that react to these antigens, thereby protecting against autoimmunity later in life. The BABYDIAB study found that offspring of mothers with moderate hyperglycemia (HbA1c 5.7-7%) had a lower risk of islet autoantibodies

(HR 0.35, 95% CI 0.13-0.92) compared to those of mothers with low HbA1c < 5.7%. However, the risk was higher if the mother had severe hyperglycemia HbA1c > 7% (HR 2.76, 95% CI 1.11-6.87).[42] A possible explanation for this is that maternal hyperglycemia may stimulate fetal β-cell growth and maturation when moderate, resulting in a relatively lower risk in offspring of mothers compared to fathers with diabetes but can potentially lead to their exhaustion upon reaching a higher threshold.[138]

We did not, however, observe such a difference in strength of parental associations among youth. Childhood-onset diabetes may involve an autoimmune response that is influenced both by a genetic component, particularly from the father's side and by the effects of *in utero* hyperglycemia. In contrast, during youth, the impact of perinatal environments and genetics which differ between parents may diminish. Instead, factors such as insulin resistance-related habits and household environments, which are likely similar between parents,[204] may become more critical in establishing the link between parental and offspring diabetes.

Figure 17. Conceptual framework for possible mechanisms underlying differential contributions of paternal and maternal diabetes to offspring T1D risk in childhood



5.5 Secondary Findings: Other Covariates

We also identified associations between preterm birth and diabetes in the second-born offspring. This has been previously reported in multiple studies, including a 2014 meta-analysis that calculated a pooled increased risk of 18% (pooled OR 1.18, 95% CI 1.11-1.25) based on 18 studies.[142] Similarly, a large 2020 cohort found a 1.2-fold increase in the risk for T1D in children under 18 years born preterm.[143] Possible mechanisms underlying these associations may involve

interruptions in β-cell maturation, which occurs predominantly during the third trimester of pregnancy. Preterm birth during this critical period may disrupt this process, leading to reduced β-cell counts and/or impaired β-cell function, increasing the risk for T1D later in life. Animal studies on sheep have demonstrated that induced preterm birth results in a 65% reduction of β-cell mass and impaired insulin secretion later in life.[205] Similarly, human studies have found evidence of decreased insulin sensitivity in children born preterm.[176] This may be due to the rapid catch-up growth that follows preterm birth, leading to increased adiposity and consequent insulin resistance.[176]

Maternal autoimmunity was also associated with diabetes development during childhood. A large Swedish retrospective cohort reported associations between the risk of T1D in the offspring and various parental autoimmune conditions.[168] The shared genetic risks among these autoimmune disorders may explain their associations. Genetic studies have found that the T1D-associated *HLA-DR* and *-DQ* genes are also implicated in rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease.[206] The T1D risk *PTPN22* variant (1858C>T) was found to be associated with rheumatoid arthritis[207] and the CTLA-4 gene with autoimmune thyroid disease.[208]

5.6 Strengths and Limitations

5.6.1 Strengths

In a universal healthcare system like the one in Quebec, health administrative data offer large samples with minimal biases related to selection, recall, or non-response and extended follow-up period, permitting detection of associations that are difficult to capture in prospective cohort studies. While prospective studies provide investigators with some control over data collection, they typically have smaller in numbers, are less heterogeneous, and are conducted over shorter periods.[126] Data linkage in our retrospective cohort study between health administrative data and vital statistics databases allowed us to obtain valuable information on demographic factors, gestational age, birth weight, and sex. Quebec is the only jurisdiction in which the collection of demographic information at birth is mandatory.

Although we conducted our study at the provincial level (rather than national), Quebec has over 8.5 million people. Similar important studies have been conducted in Finland and Denmark, with country-wide populations of around 5 and 6 million, respectively. In addition, while Scandinavian countries are well known for their breakthrough research on T1D due to the high incidence of the condition in these populations,[20] GDM is far less common in these countries than it is in North America. It affects around 2-4% of pregnancies in Denmark,[209,210] about 1% in Finland and Sweden,[211,212] compared to more than 10% in Quebec.[213] This may explain why some studies, such as the Swedish retrospective cohort previously described

(**section 2.2.2**), had a combined exposure to GDM/maternal T2D. The high incidence of GDM and T1D in Quebec allowed us to investigate associations between T1D and GDM thoroughly.

5.6.2 Limitations

While our data sources provided these advantages, the validated diabetes definitions we applied were not specific to diabetes type, and we had no laboratory data on maternal hemoglobin A1c or on offspring autoantibodies and C-peptide levels. We inferred that new-onset diabetes before 22 years of age was T1D, based on the epidemiology of diabetes in most parts of Canada. A similar rationale has been used in other studies using comparable data sources, including the previously discussed Swedish study that examined a combined exposure category of maternal T2D or GDM.[8]

We did not request data on medication because the pharmaceutical insurance program in Quebec consists of both private and public insurance plans, and we would not have been able to access private plan data. Moreover, among individuals under 65 years (all of our study subjects), enrollment in public and private plans varies over time based on employer plans. Since we only have access to public databases, the information would have been incomplete; hence, we opted not to include it. In addition, we did not have information on pre-pregnancy maternal body mass index, obesity, weight gain, physical activity, or smoking which are important risk factors for both maternal and offspring diabetes. However, we did include offspring macrosomia in our models, which is closely associated with maternal obesity, and arguably more relevant in assessing offspring outcomes.[214]

5.7 Conclusions

Our study confirms the association between maternal GDM and diabetes in offspring between 12 and 22 years of age. Additionally, we highlight that in families with multiple children, both first- and second-pregnancy GDM independently increase the risk of diabetes in second-born offspring during youth, with cumulative effects. These findings support the use of GDM history as a risk marker to detect T1D, a condition notorious for its subtle early symptoms that often go unnoticed until life-threatening complications such as DKA occur, affecting a quarter of those ultimately diagnosed with T1D. While parental history of pre-existing diabetes is also a risk factor, GDM presents a more prevalent clinical signal within a broader population. Our research supports the potential impact of insulin resistance in triggering T1D and emphasizes the interplay between maternal health during pregnancy, familial diabetes history, and the risk of T1D development in offspring. By identifying and addressing these factors, we can take proactive steps to reduce the burden of diabetes in vulnerable youth, advance preventive healthcare initiatives, and enhance long-term health outcomes. The effectiveness of such interventions requires further investigation through interventional studies aimed at identifying successful preventive strategies related to health behaviours such as diet and physical activity.

5.8 My Personal Journey

At around 9 p.m. on March 4, 2021, I was clad to my lab coat, incubating cells under the bright laboratory lights. Despite weeks of dizziness and fatigue, my determination to carry out my experiments pushed me forward. However, eventually overcome by my symptoms, I nearly collapsed. A few minutes later, I was hooked up to an IV for three days, on the verge of a coma.

I had long been intrigued by the immune system because of its impact on my family. Several family members had diagnoses of Lupus and hypothyroidism, including my pet dog Koko. This prompted me to pursue a Bachelor's degree in the Honors in Immunology program at McGill in 2016.

During the summer of 2017, I launched my research journey in Dr. Constantin Polychronakos' lab, which focuses on the molecular genetics and immunology of T1D. Over the next four years, I worked on multiple genomics and animal studies, including a large prospective screening study on monogenic causes of T1D and a murine model on the impact of PTPN22 variants on antigen-presenting cells and T cells. I concurrently completed my honours project in Dr. Ciriaco Piccirillo's lab, investigating the role of the *Helios* gene in T regulatory cells.

Fascinated by my university studies and research, I felt as though my life and career were on an unstoppable train. But this train derailed on the evening of March 4, 2021. As the "healthy" child of the family or as a pre-med student, I had only seen one side of the hospital curtain. Therefore, lying on that emergency bed, my first reaction was "I can't be away from the lab, who is going to take care of the diabetic mice?" Little did I know I was on the verge of DKA, facing my own T1D

diagnosis. I suspect that my workload and the pandemic led to less healthy eating habits and a more sedentary lifestyle, unmasking a predisposition for T1D that I did not know I had. Discouraged by the irony of my situation, I realized that despite my deep understanding of the biology of my disease, I knew nothing about its daily challenges. But I soon realized the potential for growth, deepening my connection to research and medicine.

My diagnosis of T1D catalyzed my decision to pursue a master's degree in diabetes at the McGill Program of Experimental Medicine. With a solid foundation in basic research, I sought to delve deeper into epidemiology and clinical research to come closer in my research work to the now very personal experience of this condition. I discovered Dr. Dasgupta's work, met with her, and felt an immediate connection to her and her research. I now have a 360-degree view of T1D, its immunology, its epidemiology, and its lived experience.

Throughout my master's journey, I have not only deepened my passion for a career in health and medicine but have also been fortunate to encounter remarkable role models like Dr. Dasgupta and my fellow lab partners, who have supported me as a student and patient. Conducting this project has imbued my academic career with newfound purpose and determination. It has become a driving force for me to continue working in research aimed at finding a cure for myself and countless others affected by T1D and other autoimmune conditions.

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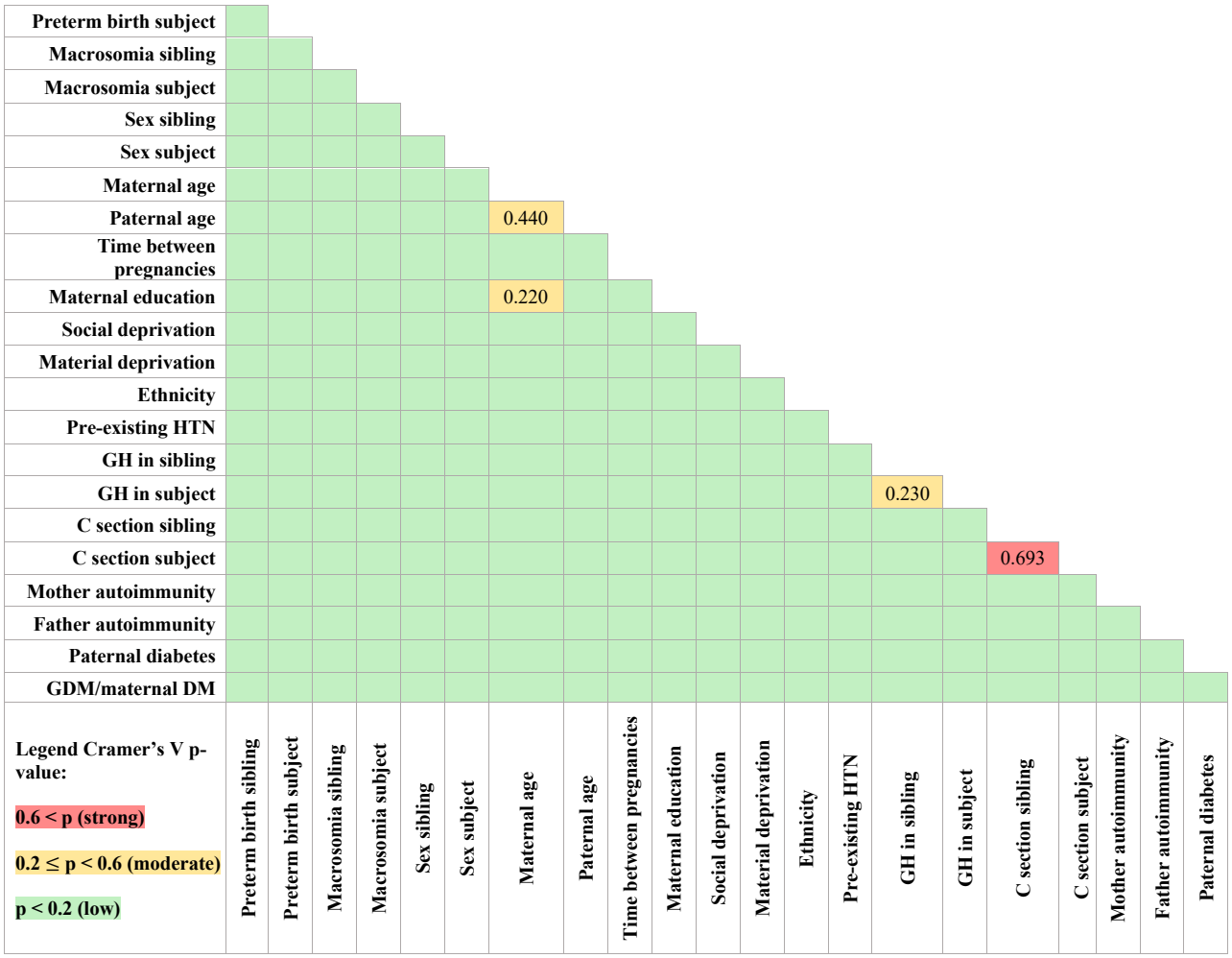
Appendix

Appendix Figure 1. Cramer's V correlation matrix



Appendix Table 1. PH Assumption Schoenfeld residuals

		Children	Youth
Covariate	**Levels**	**p-value**	**p-value**
GDM/ maternal diabetes status	GDM_{NONE}	**Reference**	**Reference**
	$GDM_{SIBLING}$	0.6329	0.7542
	$GDM_{SUBJECT}$	0.4361	0.1979
	GDM_{BOTH}	0.1272	0.4420
	DM	0.2708	0.1713
Paternal diabetes	Yes	0.3228	0.1305
Subject preterm birth	Yes	0.4297	0.6773
Sibling preterm birth	Yes	0.6666	0.4237
Subject macrosomia	Yes	0.9705	0.5514
Sibling macrosomia	Yes	0.5542	0.7735
Maternal HTN or GH in 2nd pregnancy	No	**Reference**	**Reference**
	Without pre-eclampsia	0.4620	0.5771
	With pre-eclampsia	0.1344	0.6903
GH in 1st pregnancy	No	**Reference**	**Reference**
	Without pre-eclampsia	0.3000	0.9114
	With pre-eclampsia	0.5512	0.2538
Pre-existing maternal HTN	Yes	0.6000	0.4438
Subject sex	Female	0.3601	**0.0020**
Social deprivation index	Q1 = least deprived	**Reference**	**Reference**
	Q2	0.1984	0.3380
	Q3	0.3561	0.3470
	Q4	0.0985	0.6101
	Q5 = most deprived	0.1609	0.2273
Material deprivation index	Q1 = least deprived	**Reference**	**Reference**
	Q2	0.0982	0.2528
	Q3	0.2847	0.6408
	Q4	0.9466	**0.0434**
	Q5 = most deprived	0.5371	**0.0007**
Parental ethnicity	Europid	**Reference**	**Reference**
	African/ Caribbean	0.4166	0.5584
	Arab	0.2619	0.3248
	Asia	0.1892	0.2198
	Other	0.8029	0.7095
	Different between parents	0.3621	0.1504
Maternal age groups	<25	**Reference**	**Reference**
	25-<30	0.5777	**0.0003**
	30-<35	0.9113	**<.0001**
	≥35	0.1787	**<.0001**
Paternal age groups	<25	**Reference**	**Reference**

	25-<30	0.5177	0.7993
	30-<35	0.5170	0.9239
	≥35	0.2654	0.4158
Maternal autoimmunity	Yes	0.6125	0.1531
Paternal autoimmunity	Yes	0.7863	0.0673
Cesarean section 2nd birth	Yes	0.0676	0.3118
Cesarean section 1st birth	Yes	**0.0049**	0.6000
Time between deliveries	<3 years	**Reference**	**Reference**
	≥3 years	0.5928	0.4077

PH assumption considered not met for variables significant at **p < 0.05**

Appendix Table 2. BIC Criteria stepwise and backward variable selection

		Children			
		AIC		BIC (or SBC)	
STEPWISE	Step	Without Covariates	With covariates	Without Covariates	With covariates
AIC and BIC value at each step in the stepwise selection process	1	22381.180	22297.516	22381.180	22302.283
	2	22381.180	22284.091	22381.180	22307.928
	3	22381.180	22276.017	22381.180	22309.388
	4	22381.180	22264.764	22381.180	22321.972
	5	22381.180	22258.509	22381.180	22320.485
	6	22381.180	22252.987	22381.180	22319.730
BACKWARDS	Step	Without Covariates	With covariates	Without Covariates	With covariates
AIC and BIC value at each step in the backwards selection process	0	22381.180	22275.140	22381.180	22461.067
	1	22381.180	22269.727	22381.180	22441.351
	2	22381.180	22266.083	22381.180	22428.172
	3	22381.180	22264.375	22381.180	22421.697
	4	22381.180	22262.745	22381.180	22415.300
	5	22381.180	22258.018	22381.180	22391.504
	6	22381.180	22254.002	22381.180	22368.418
	7	22381.180	22252.910	22381.180	22362.559
	8	22381.180	22252.384	22381.180	22357.266
	9	22381.180	22251.953	22381.180	22352.067
	10	22381.180	22251.580	22381.180	22346.927
	11	22381.180	22251.483	22381.180	22342.062
	12	22381.180	22250.872	22381.180	22327.149
	13	22381.180	22251.821	22381.180	22323.331
	14	22381.180	22252.987	22381.180	22319.730

		Youth			
		AIC		BIC (or SBC)	
STEPWISE SEL	Step	Without Covariates	With covariates	Without Covariates	With covariates
AIC and BIC value at each step in the stepwise selection process	1	18800.439	18739.774	18800.439	18758.385
	2	18800.439	18684.380	18800.439	18716.950
	3	18800.439	18660.304	18800.439	18697.526
	4	18800.439	18629.788	18800.439	18690.276
	5	18800.439	18626.250	18800.439	18691.390
	6	18800.439	18623.229	18800.439	18706.981
BACKWARDS SEL	Step	Without Covariates	With covariates	Without Covariates	With covariates
AIC and BIC value at each step in the backwards selection process	0	18800.439	18635.021	18800.439	18779.260
	1	18800.439	18633.041	18800.439	18772.627
	2	18800.439	18630.248	18800.439	18760.528
	3	18800.439	18627.254	18800.439	18748.228
	4	18800.439	18625.888	18800.439	18742.210
	5	18800.439	18624.898	18800.439	18736.567
	6	18800.439	18623.969	18800.439	18730.985
	7	18800.439	18623.302	18800.439	18725.665
	8	18800.439	18623.156	18800.439	18720.866
	9	18800.439	18622.378	18800.439	18715.435
	10	18800.439	18622.035	18800.439	18710.440
	11	18800.439	18623.229	18800.439	18706.981

NOTE: in both stepwise and backward selection, the same variables are retained

Appendix Table 3. Associations between covariates included in the final models and diabetes in the second-born offspring

		Children		Youth	
Covariate	**Level**	**HR**	**95% CI**	**HR**	**95% CI**
Subject preterm birth	Yes	1.49*	1.15-1.94	..	..
Subject macrosomia	Yes	1.29	0.77-2.16	1.31	0.79-2.18
Sibling macrosomia	Yes	0.80	0.43-1.51	1.29	0.77-2.18
Gestational hypertension in 1st pregnancy	No	**Reference**		..	
	Without pre-eclampsia	1.38*	1.00-1.90		
	With pre-eclampsia	1.50*	1.15-1.97		
Subject sex †	Female	0.92	0.80-1.05	0.82	0.66-1.03
Social deprivation index	Q1 = least deprived	**Reference**		**Reference**	
	Q2	0.99	0.81-1.05	1.01	0.81-1.25
	Q3	1.00	0.82-1.21	0.94	0.76-1.18
	Q4	0.85	0.82-1.21	1.16	0.93-1.44
	Q5 = most deprived	0.92	0.68-1.05	1.37	0.84-2.23
Parental ethnicity	Europid	**Reference**		**Reference**	
	African/Caribbean	0.63	0.33-1.17	1.14	0.83-1.56
	Arab	1.35	0.98-1.87	0.85	0.52-1.41
	Asia	0.46*	0.26-0.81	0.25*	0.10-0.62
	Other	0.58	0.33-1.00	2.11*	1.54-2.90
	Different between parents	1.10	0.84-1.45	1.08*	1.03-1.13
Maternal age groups ‡	<25	**Reference**		..	
	25-<30	0.92	0.72-1.16		
	30-<35	0.94	0.73-1.22		
	≥35	0.94	0.69-1.27		
Paternal age groups	<25	**Reference**		**Reference**	
	25-<30	1.41	0.96-2.07	0.92	0.70-1.22
	30-<35	1.24	0.83-1.84	0.78	0.57-1.06
	≥35	1.40	0.92-2.12	0.91	0.64-1.27
Maternal autoimmunity	Yes	1.29*	1.08-1.53	..	
Time between deliveries	<3 years	..		**Reference**	
	≥3 years			1.30*	1.11-1.52

*: Conclusive associations. †: Sex was included with a time interaction in the birth-12-year-old group to fulfill the PH assumption. ‡: Maternal age was included as a spline function in the 12-22-year-old group to fulfill the PH assumption. Maternal and paternal diabetes groups were omitted from the table but were included in these models.