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Long-term adverse multi-system health outcomes of gestational diabetes mellitus: an analysis of real-world cohort data

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ABSTRACT

Background: There is emerging evidence that gestational diabetes mellitus (GDM) increases the risk of multi-system long-term complications such as cancer and autoimmune disease, however this evidence is scarce and conflicting. Therefore, we aim to explore the long-term health implications of GDM.
Methods: We performed analyses using TriNetX in women ≥ 18 years who had a birth. Four cohorts were generated with a reference and GDM arm, and PSM 1:1 for factors including age, BMI, and cohort-specific risk factors. The cohort sizes were **metabolic** n = 72,014, **cancer** n = 88,131, **autoimmune** n = 96,110, and **gynaecological** n = 94,945.
Results: GDM increased the risk of 5-year incident clinical outcomes: **metabolic:** T2D (HR 18.42, p < 0.0001), hypertriglyceridemia (HR 2.47, p < 0.0001), obesity (HR 1.89, p < 0.0001), and sleep apnoea (HR 1.83, p < 0.0001); c**ancer:** thyroid cancer (HR 1.34, p = 0.036); **autoimmune:** type 1 diabetes (HR 12.32, p < 0.001), Grave's disease (HR 1.57, p=<0.0001), and psoriasis (HR 1.25, p = 0.007); and **gynaecological** PCOS (HR 1.97, p < 0.0001), uterine fibroids (HR 1.29, p < 0.0001), and endometriosis (HR 1.16, p = 0.018). At 10 years, there was a significantly increased risk of the composite 13 adiposity-related cancers (HR 1.18, p = 0.008).
Conclusion: Women with GDM are at risk of a myriad of long-term adverse health outcomes meriting targeted early intervention and long-term post-partum monitoring.

1. Introduction

Gestational diabetes mellitus (GDM), defined as glucose intolerance first detected during pregnancy whereby the pancreas can no longer maintain the increased insulin demands of pregnancy, complicates ~ 14% of pregnancies [1]. Important clinical risk factors include living with obesity, a family history of GDM or type 2 diabetes (T2D), a personal history of GDM, and increasing maternal age. Worldwide prevalence of GDM is increasing alongside alarming escalating rates of obesity and increasing maternal age [2,3].

GDM influences a range of maternal long-term health outcomes following the index pregnancy. Considering this rising prevalence, in the context of multiple adverse short and long-term implications for both mother and offspring, GDM is increasingly becoming a major public health concern. Short-term, GDM is associated with adverse pregnancy outcomes such as increased risk of pre-eclampsia and caesarean section,

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while longer-term GDM is an established strong risk factor for the future development of T2D. Studies report a 20–70% increased risk of T2D in the first decade after delivery [4], and an increased risk of long-term cardiovascular disease [4–6]. Some studies also suggest that women affected by GDM are high risk for developing type 1 diabetes (T1D) and other autoimmune conditions including thyroid autoimmunity [7,8]. The evidence around the risk of autoimmune disease is limited. One 23-year prospective cohort study reported a 5.7% risk of developing GDM during the first 7 years postpartum. However, this study did not report on relative risk, has poor generalisability, and small sample size of 391 participants [9]. Regarding autoimmune thyroid disease, there is only one retrospective cohort study reporting the risk of incident autoimmune thyroid disease and found GDM was associated with a 37% increased risk of Hashimoto's thyroiditis and 60% increased risk of hyperthyroidism [10].

GDM and PCOS are two of the most common metabolic conditions affecting women of reproductive age, with a well-documented association between them, considering their common pathophysiological and metabolic abnormalities. While the nature of the long-term health implications decades after PCOS has been clearly defined [11], the evidence about the magnitude and nature of the long-term maternal health implications of GDM after pregnancy is conflicting. Both obesity and T2D are recognised significant risk factors for cancer, including many gastrointestinal and reproductive cancers [12]. The association between T2D and cancer incidence may be causal, for example mediated by hyperinsulinaemia or hyperglycaemia, or cofounded by factors such as obesity [13]. It is therefore reasonable to infer that GDM, with a similar pathophysiological process and common risk factors, may also be associated with an increased risk of obesity-related cancers, with cohort studies suggesting an increased risk of breast [14], gynaecological [12], and pancreatic cancers [15]. However, a review comprising 23 studies (including 1207 patients) failed to demonstrate any overall association between GDM and incident breast, uterine and ovarian cancer [16].

With the lack of robust follow up data or large real-world analyses of long-term multisystem outcomes, this study aims to address the scarcity of, and somewhat conflicting evidence, using large real-world propensity-score matched data to characterise the magnitude of any increased risk of metabolic disease, cancer, autoimmune, and gynaecological disorders in patients with GDM.

2. Methods

2.1. Study design

We conducted a retrospective, observational study using anonymised data from TriNetX (TriNetX LLC, Cambridge, MA, USA), a global federated health research network with access to over 135 million electronic medical records from international healthcare organisations in North America and Western Europe. Further details on the network have been described elsewhere [17].

2.2. Cohorts

We identified all patients in TriNetX aged $\geq$ 18 years who had a birth (ICD-10-PCS:10E). Four cohorts were generated using following the same methodology for cohort creation as described elsewhere [18]. For each cohort, two arms were generated: **1) Reference arm** patients who had a childbirth without GDM, and **2) GDM arm**, patients who had a childbirth with a diagnosis of GDM (ICD-10-CM: O24.4) within the 9 months preceding the birth. Patients were excluded if they had a history of T1D (ICD-10 code E10) and T2D (ICD-10 code E11) identified through international classification of disease (ICD)-10 codes on their electronic medical records, prior to the diagnosis of GDM for all outcomes.

2.3. Index event

The baseline index event was the delivery ICD-10 code within the TriNetX platform.

2.4. Primary Outcomes

The primary outcomes of interest can be grouped into four main categories 1) Metabolic disease/complications, 2) cancer,including a composite of these 13 'adiposity-related cancers' in line with the European Society for Obesity reports, [19]; 3) autoimmune/autoinflammatory disease/organ-specific endocrine disorders, and 4) gynaecological. The risk for each outcome was assessed at 5 years and 10 years (Fig. 1). ICD-10 codes for each outcome are shown in **Supplementary Table S1**.

2.5. Secondary outcomes

The secondary outcomes of interest risk with and without obesity for metabolic outcomes.

2.6. Propensity Score Matching

For each outcome category, patients were propensity score matched (PSM) for relevant clinical risk factors prior to the index date based on the known risk associations between the exposure(s) and outcome(s), and potential for confounding rather than univariate statistical significance. This is consistent with published recommendations [20]. All cohorts were PSM for baseline demographic factors such as age and ethnicity, BMI, lifestyle and socioeconomic factors, markers of disease severity including HbA1c and renal function, adverse pregnancy outcomes and abortion, and group-specific variables which were selected based on biological plausibility, considered as contributory or causal, on the outcomes of interest. This strict PSM ensured that any differences in outcome did not reflect baseline differences or imbalances in characteristics/risk factors. The PSM criteria for each outcome are outlined in Table 1.

2.7. Statistical analysis

Statistical analysis for cohort data was performed within the TriNetX platform. Normally distributed baseline characteristics are presented as mean and standard deviation (SD). PSM was performed using logistic regression. TriNetX uses 'greedy nearest-neighbour matching' with a caliper of 0.1 pooled standard deviations and difference between propensity scores < 0.1. We assessed covariate balance between groups using the standardised mean difference (SMD) with a SMD < 0.1 considered well matched. The reference arm (delivery) was considered the reference cohort (hazard ratio (HR) = 1) when compared against the 'exposure' (GDM) arm. Each cohort was generated by excluding both T1 and T2D at baseline, along with the outcomes of interest. A HR and log rank test were generated for each outcome using the R Survival package v3.2–3. The regression analysis performed within TriNetX operate on the available observed data without automatic statistical imputation for missing covariates. Missing data is handled on a complete-case analysis where records with missing values in model variables are excluded from the regression models. Additionally, for sensitivity analysis, we performed analysis by body mass index (presence or absence of obesity: ICD-10 coding (E66), or BMI $\geq$ 30 *vs.* $<$ 30 kg/m^2) for metabolic outcomes. All tests were two-tailed a p-values of ≤ 0.05 were considered statistically significant. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed in the reporting of this cohort study [21].

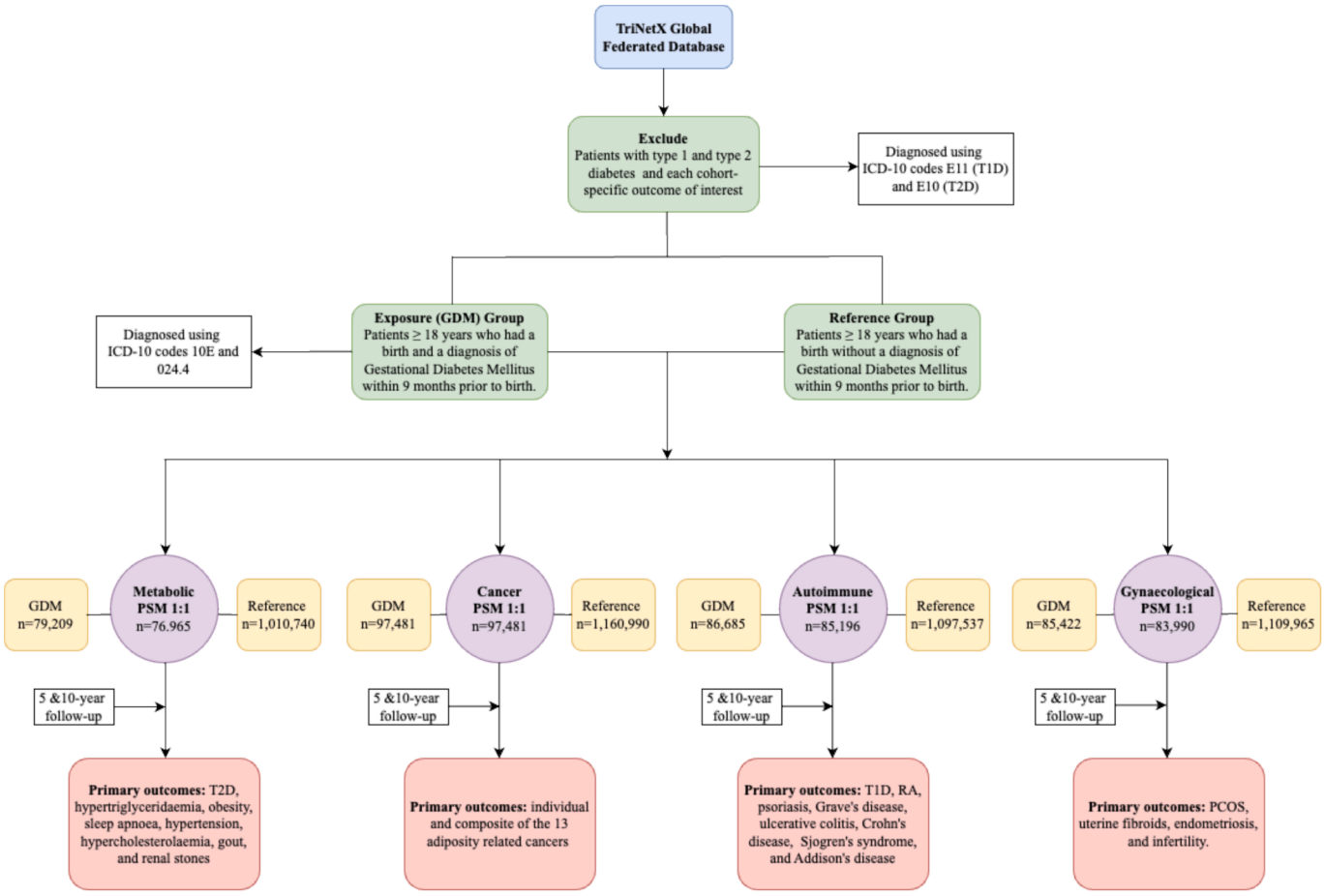

Fig. 1. Flow diagram of the metabolic (C1), cancer (C2), autoimmune (C3) and gynaecological (C4) cohort creation. *HCO, health care organisation; ICD, international classification of diseases; GDM, gestational diabetes mellitus; T1 and T2D, type 1 and type 2 diabetes; RA, rheumatoid arthritis; PCOS, polycystic ovarian syndrome.*

3. Results

3.1. Cohort 1, Metabolic outcomes

A total of 1,029,030 patients were identified: 954,743 (92.8%) in the reference delivery arm, and 74,287 (7.2%) in the exposure GDM arm. Cohort demographics before and after PSM matching, and PSM criteria are outlined within Table 1. After PSM, each cohort was deemed well matched. The total number of participants in each cohort was reduced to 72,014.

3.1.1. Risk at 5 years- Diabetes and metabolism

At 5 years, exposure to GDM significantly increased the risk of T2D (HR 18.42 [95% CI 16.06, 21.14], $p < 0.0001$), hypertriglyceridemia (HR 2.47 [1.95, 3.13], $p < 0.0001$), obesity (HR 1.89 [1.82, 1.95], $p < 0.0001$), obstructive sleep apnoea (HR 1.83 [1.59, 2.12], $p < 0.0001$), hypercholesterolaemia (HR 1.64 [1.42, 1.89], $p < 0.0001$), and renal stones (HR 1.55 [1.39, 1.74], $p < 0.0001$), and hypertension (HR 1.37 [1.30, 1.45], $p < 0.0001$). There was no difference in risk of gout between exposure and reference arms. HR are presented in Table 2, forest plots in Fig. 2**A and B,** and survival curves in Fig. 3.

3.1.2. Stratified analysis

Results are presented in **Supplementary Table S2 and S3.** At 10 years, exposure to GDM increases the risk of T2D, obesity, hypercholesterolaemia, and renal stones in patients without obesity (BMI < 30 kg/m^2) more than patients with obesity (BMI ≥ 30 kg/m^2). Conversely, the risk for hypertension, hypertriglyceridemia, and sleep apnoea is higher in patients with obesity. At 10 years, there was a significantly increased risk of all metabolic outcomes, including gout, following GDM. The HR, except for hypertension, were all lower at 10 years compared to 5 years.

3.2. Cohort 2, Cancer

A total of 1,208,242 patients were identified: 1,110,538 (91.9%) in the reference delivery arm, and 97,704 (8.09%) in the exposure GDM arm. Cohort demographics before and after PSM matching, and PSM criteria are outlined within Table 1. After PSM, each cohort was deemed well matched. The total number of participants in each cohort was reduced to 96,110.

3.2.1. Risk at 5-years- Cancer

At 5 years, exposure to GDM significantly increased the risk of thyroid cancer (HR 1.34 [1.02, 1.75], $P = 0.036$). There was no increased risk of 13 adiposity-related cancers, oesophageal, stomach, colorectal, liver and bile duct, gallbladder, pancreatic, breast, uterine, ovarian, renal, brain, thyroid, or myeloma cancers. HR are presented in Table 2, forest plots in Fig. 2C, and survival curves in Fig. 4**A and B**.

3.2.2. Stratified analysis

Results are presented in **Supplementary Table S2.** At 5 years, the risk of thyroid cancer was higher in patients with obesity (HR 2.27 [1.44, 3.60], $p < 0.0001$) than without obesity (HR 1.19 [0.78, 1.83], $p = 0.419$). At 10-years, GDM increased the risk of 13 adiposity-related cancers (HR 1.18 [1.04, 1.34], $p = 0.008$), and thyroid cancer (HR

Table 1
Baseline demographics before and after propensity score matching at 5 years for the metabolic, cancer, autoimmune and gynaecological cohorts.

	Before propensity score matching				After propensity score matching			
Characteristic	**Exposure**	**Reference**	**SMD**	**P-value**	**Exposure**	**Reference**	**SMD**	**P-value**
Diabetes and metabolism								
Demographics								
Numbers (n)	77,286	954,743			72,014	72,014		
Age (years)	31.2 ± 5.6	29.0 ± 6.2	0.382	<0.001	31.2 ± 5.6	31.3 ± 6.3	0.017	0.001
Ethnicity, white (%)	48.2%	48.3%	0.001	0.751	48.2%	48.4%	0.004	0.480
Socioeconomic hazards (%)	5.1%	2.6%	0.134	<0.001	5.0%	5.0%	0.001	0.876
Anthropometrics,0.001								
Mean Body mass index (kg/m^2)	31.6 ± 6.2	29.3 ± 5.5	0.401	0.001	31.5 ± 6.1	31.3 ± 6.0	0.044	<0.001
Biochemistry								
Mean Glomerular filtration rate (ml/min/1.73 m^2)	125.2 ± 33.3	124.5 ± 34.3	0.020	0.001	125.2 ± 33.3	123.8 ± 32.7	0.043	0.043
Cholesterol LDL (mg/dL)								
Mean cholesterol	102.2 ± 30.8	95.8 ± 29.8	0.213	<0.001	102.0 ± 30.6	98.7 ± 29.4	0.112	<0.001
102.2 ± 30.8	8.5%	5.8%	0.107	<0.001	8.4%	8.5%	0.031	<0.001
130–159	1.5%	0.7%	0.082	<0.001	1.5%	1.2%	0.025	<0.001
≥160	0.5%	0.2%	0.053	<0.001	0.5%	0.4%	0.018	<0.001
Triglyceride (mg/dL)								
Mean	113.2 ± 77.8	88.2 ± 53.1	0.317	<0.001	112.3 ± 77.2	99.9 ± 64.1	0.174	<0.001
<150	8.3%	6.0%	0.092	<0.001	8.3%	7.4%	0.031	<0.001
150–199	1.5%	0.5%	0.097	<0.001	1.4%	1.2%	0.025	<0.001
200–499	1.3%	0.3%	0.105	<0.001	1.2%	0.9%	0.028	<0.001
≥500	0.1%	0.0%	0.027	<0.001	0.0%	0.0%	0.012	0.020
Blood pressure systolic (mm[Hg])	116.3 ± 13.9	115.2 ± 13.9	0.080	<0.001	116.2 ± 13.8	115.9 ± 14.5	0.025	<0.001
Blood pressure diastolic (mm]Hg])	70.8 ± 11.2	70.0 ± 11.4	0.067	<0.001	70.7 ± 11.1	70.4 ± 11.7	0.025	<0.001
Comorbidity (%)								
Nicotine dependence	5.3%	4.1%	0.053	<0.001	5.2%	4.9%	0.015	0.005
Alcohol-related disorders	0.9%	0.7%	0.019	<0.001	0.8%	0.7%	0.019	<0.001
Pregnancy with abortive outcome	8.8%	5.4%	0.133	<0.001	8.7%	8.1%	0.021	<0.001
Complications of labour and delivery	50.9%	33.4%	0.358	<0.001	50.5%	50.9%	0.008	0.110
Hypertensive disease	1.7%	0.0%	0.177	<0.001	0.6%	0.5%	0.013	0.013
Ischaemic heart disease	0.3%	0.2%	0.021	<0.001	0.2%	0.2%	0.008	0.130
Cerebrovascular disease	0.2%	0.2%	0.017	<0.001	0.2%	0.3%	0.005	0.311
Diseases of respiratory system	22.2%	16.3%	0.152	<0.001	21.9%	21.5%	0.010	0.052
Heart failure	0.1%	0.1%	0.010	0.006	0.1%	0.1%	0.009	0.077
Other peripheral vascular disease	0.2%	0.2%	0.001	0.936	0.2%	0.3%	0.012	0.027
Diseases of liver	1.2%	0.4%	0.085	<0.001	1.1%	0.9%	0.018	<0.001
Diseases of circulatory system	7.5%	4.2%	0.137	<0.001	6.4%	5.9%	0.023	<0.001
Cancer cohort								
Demographics								
Numbers (n)	97,704	1,110,538			96,110	96,110		
Age (years)	31.2 ± 5.6	28.7 ± 6.04	0.378	<0.0001	31.2 ± 5.6	31.2 ± 5.9	0.0008	0.511
Ethnicity, white (%)	51.1%	49.7%	0.029	<0.0001	51.1%	51.1%	<0.001	0.790
Socioeconomic hazards (%)	7.0%	3.3%	0.167	<0.0001	7.0%	7.0%	0.002	0.630
Anthropometrics								
Mean Body mass index (kg/m^2)	33.1 ± 7.1	30.5 ± 6.4	0.395	<0.0001	33.1 ± 7.1	32.9 ± 7.0	0.039	<0.0001
Biochemistry								
Mean Glomerular filtration rate (ml/min/1.73 m^2)	124.5 ± 33.1	125.2 ± 34.9	0.019	0.0001	124.5 ± 33.1	123.6 ± 32.9	0.028	<0.0001
Comorbidity (%)								
Neoplasms	9.6%	6.0%	0.135	<0.0001	9.6%	9.2%	0.014	0.009
Complications of labour and delivery	54.3%	36.6%	0.359	<0.0001	54.2%	54.5%	0.006	0.066
Pregnancy with abortive outcome	9.9%	6.1%	0.143	<0.0001	9.9%	9.2%	0.025	<0.0001
Alcohol related disorders	1.0%	0.8%	0.017	<0.0001	1.0%	0.7%	0.026	<0.0001
Nicotine dependence	6.4%	5.0%	0.064	<0.0001	6.4%	6.0%	0.020	<0.0001
Autoimmune disease cohort								
Demographics								
Numbers (n)	96,522	1,098,547			94,945	94,945		
Age (years)	31.2 ± 5.6	29.0 ± 6.2	0.379	<0.001	31.2 ± 5.6	31.2 ± 5.9	0.003	0.003
Ethnicity, white (%)	50.9%	49.5%	0.028	<0.001	50.9%	51.1%	0.003	0.003
Socioeconomic hazards (%)	7.0%	3.3%	0.168	<0.001	7.0%	7.1%	0.005	0.005
Anthropometrics								
Medial body mass index (kg/m^2)	33.2 ± 7.1	30.5 ± 6.4	0.397	<0.001	33.2 ± 7.1	32.9 ± 6.9	0.033	0.033
Biochemistry								
Median glomerular filtration rate (ml/min/1.73 m^2)	125.0 ± 33.1	124.4 ± 34.0	0.018	<0.001	125.0 ± 33.1	123.5 ± 32.2	0.047	0.047
Comorbidity (%)								
Nicotine dependence	6.4%	4.9%	0.064	<0.001	6.4%	6.1%	0.012	0.012
Alcohol related disorders	1.0%	0.8%	0.016	<0.001	1.0%	0.7%	0.024	0.024
Pregnancy with abortive outcome	9.9%	6.0%	0.143	<0.001	9.9%	9.4%	0.017	0.017
Complications of labour and delivery	54.1%	36.4%	0.361	<0.001	54.1%	54.4%	0.006	0.006
Disorders of thyroid gland	8.0%%	4.3%	0.156	<0.001	8.0%	7.7%	0.011	0.011
Rheumatoid arthritis	0.1%%	0.0%	0.027	<0.001	0.1%%	0.1%	0.012	0.012
Systemic connective tissue disease	0.5%	0.4%	0.019	<0.001	0.5%	0.3%	0.023	0.023
Autoinflammatory syndromes	0.0%	0.0%	0.007	0.021	0.0%	0.0%	<0.001	<0.001
Gynaecological								
Demographics								

(*continued on next page*)

Table 1 (*continued*)

	Before propensity score matching				After propensity score matching			
Characteristic	**Exposure**	**Reference**	**SMD**	**P-value**	**Exposure**	**Reference**	**SMD**	**P-value**
Numbers (n)	89,648	1,056,938			88,131	88,131		
Age (years)	31.0 ± 5.6	28.8 ± 6.2	0.377	<0.001	31.0 ± 5.6	31.1 ± 6.0	0.015	0.002
Ethnicity, white (%)	50.8%	49.2%	0.031	<0.001	50.8%	50.2%	0.012	0.015
Socioeconomic hazards (%)	7.1%	3.2%	0.173	<0.001	7.1%	7.3%	0.011	0.023
Anthropometrics								
Median Body mass index (kg/m^2)	33.1 ± 7.1	30.4 ± 6.4	0.394	<0.001	33.1 ± 7.1	32.8 ± 6.9	0.031	0.031
Biochemistry								
Median Glomerular filtration rate (ml/min/1.73 m^2)	125.9 ± 33.4	125.1 ± 34.3	0.024	<0.001	125.9 ± 33.4	124.4 ± 32.5	0.047	0.047
Comorbidity (%)								
Hypertensive disease	5.3%	1.0%	0.179	<0.001	5.3%	4.7%	0.030	0.030
Complications of labour and delivery	53.5%	35.6%	0.365	<0.001	53.5%	52.8%	0.013	0.006
Pregnancy with abortive outcome	9.1%	5.5%	0.137	<0.001	9.1%	8.4%	0.024	<0.001
Alcohol related disorders	1.0%	0.8%	0.016	<0.001	1.0%	0.7%	0.024	<0.001
Nicotine dependence	6.3%	4.9%	0.063	<0.001	6.3%	5.8%	0.022	<0.001

1.44 [1.13, 1.84], p = 0.003).

3.3. Cohort 3, Autoimmune disease

A total of 1,195,069 patients were identified: 1,098,547 (91.9%) in the reference delivery arm, and 96,522 (8.08%) in the exposure GDM arm. Cohort demographics before and after PSM matching, and PSM criteria are outlined within Table 1. After PSM, each cohort was deemed well matched. The total number of participants in each cohort was reduced to 94,945.

3.3.1. Risk at 5 years- autoimmune disease

At 5 years, exposure to GDM significantly increased the risk of T1D (HR 12.32 [8.23, 18.25], p < 0.0001), p = 0.031), Grave's disease (HR 1.24 [1.02, 1.51], p = 0.035), and psoriasis (HR 1.25 [1.06 1.48], p = 0.007). Conversely, the risk of Sjogren's syndrome was significantly lower in the GDM group (HR 0.52 [0.35, 0.77], p = 0.001). No increased risk was observed for RA, Crohn's disease, ulcerative colitis, autoimmune thyroiditis (Hashimoto's disease), multiple sclerosis, or Addison's disease. HR are presented in Table 2, forest plots in Fig. 2, and survival curves are presented in Fig. 4**C-E**. After excluding all oral hypoglycaemic agents at baseline, the risk at 5 years was less (HR 6.28 [5.78, 6.83], p < 0.0001).

3.3.2. Stratified analysis

Results are presented in **Supplementary Table S2**. The risk of T1D, psoriasis, Grave's disease, and RA was also significantly increased at 10 years. However, for T1D and psoriasis, the HR were lower at 10 years. After excluding all oral hypoglycaemic agents at baseline to minimise potential for data misclassification, the risk of T1D at 5 years was less (HR 7.38 [4.85, 11.22], p < 0.0001).

3.4. Cohort 4, Gynaecological

A total of 1,146,586 patients were identified: 1,056,938 (92.2%) in the reference delivery arm, and 89,648 (7.8%) in the exposure GDM arm. Cohort demographics before and after PSM matching, and PSM criteria are outlined within Table 1. After PSM, each cohort was deemed well matched. The total number of participants in each cohort was reduced to 88,131.

3.4.1. Risk at 5 years- gynaecological

At 5 years, exposure to GDM was associated with an increased risk of PCOS (HR 1.97 [1.76, 2.19], p < 0.0001), uterine fibroids (HR 1.29 [1.17, 1.42], p < 0.0001), and endometriosis (HR 1.16 [1.03, 1.32], p = 0.018). No difference in risk was observed for infertility between the exposure and reference arms. Hazard ratios are presented in Table 2, forest plots in Fig. 2, and survival curves are presented in Fig. 4**F**−**H**.

3.4.2. Stratified analysis

Results are presented in **Supplementary Table S2**. The risk at 10 years was significantly greater in the GDM arm for PCOS, uterine fibroids, and endometriosis. However, for PCOS and uterine fibroids, the HR was lower at 10 years than at 5 years. Stratified analysis at 10 years also yielded no increased risk of infertility in the exposure arm.

4. Discussion

In this large real-world cohort study, we demonstrate that women with GDM, when compared to women with normoglycaemic pregnancies, had an increased risk of multiple long-term complications including T2D and T1D, obesity and related metabolic complications, a composite of 13 adiposity-related cancers and thyroid cancer, autoimmune disease, and gynaecological disorders.

4.1. Risk of T2D after GDM

The finding that women with GDM are more likely to develop T2D than those with a normoglycaemic pregnancy is consistent with the reported literature. One *meta*-analysis of 20 studies, involving 1,332,373 patients, reported a 10-fold higher increased risk of T2D in patients with previous GDM, whilst another study reported the lifetime risk of T2D to be up to 20 fold higher [22]. In keeping with the literature, we also found the risk of T2D to be highest in the first 5 years after pregnancy [4], perhaps partly explained by increased screening following a pregnancy complicated by GDM. The magnitude of the increased risk is consistent with shared risk factors such as obesity and weight gain, and inherent defects such as insulin resistance and pancreatic beta cell dysfunction [23,24]. Studies have reported that future risk of T2D in patients with GDM is higher in those living with obesity, highlighting the importance of considering obesity in T2D prevention in patients with a history of GDM [24,25]. However, out findings suggest the relationship between GDM and T2D may be stronger in sub-groups with traditionally low risk of T2D. In addition to higher risk of T2D, we found that women with GDM are also at higher risk of obesity, hypertension, and dyslipidaemia which have been translated into large retrospective cohort studies investigating cardiovascular risk after GDM [22,26].

4.2. Risk of T1D after GDM

We found a 12-fold increased risk of incident T1D after GDM at both 5 and 10 years, with highest risk observed at 5 years. To the best of our knowledge, this is the first large cohort study to suggest a link between GDM and T1D risk. Our findings are in keeping with previous studies suggesting that women with GDM with pancreatic beta cell autoantibodies are pre-disposed to postpartum development of T1D [27–29]. Prospective cohort studies over 6 and 24 years have shown that islet cell autoantibody and glutamic acid decarboxylase autoantibody positivity

Table 2
Hazard ratios and 95% confidence intervals at 5 years for metabolic, cancer, autoimmune, and gynaecological outcomes.

Outcome	Sample size	Outcome (n)	Incidence per 1000 people	5-year survival probability (%)	Hazard ratio (95% confidence interval)	Long-rank test	P-value	E-value
Metabolic Cohort								
Type 2 diabetes								
GDM	72,014	3,741	52.0	89.7	18.42 (16.16, 21.14)	3347.4	<0.0001	36.18
Reference	72,014	215	3.0	99.3				
Hypertension								
GDM	72,014	2,980	41.4	91.9	1.37 (1.30, 1.45)	128.5	<0.0001	2.07
Reference	72,014	2,222	30.9	94.1				
Hypertriglyceridemia								
GDM	72,014	232	3.2	99.3	2.47 (1.95, 3.13)	60.0	<0.0001	4.38
Reference	72,014	97	1.4	99.7				
Hypercholesterolaemia								
GDM	72,014	489	6.8	98.5	1.64 (1.42, 1.89)	47.0	<0.0001	2.56
Reference	72,014	308	4.3	99.0				
Sleep apnoea								
GDM	72,014	521	7.2	98.4	1.83 (1.60, 2.12)	71.2	<0.0001	3.05
Reference	72,014	294	4.1	99.1				
Renal stones								
GDM	72,014	761	10.6	97.8	1.55 (1.39, 1.74)	59.3	<0.0001	2.36
Reference	72,014	504	7.0	98.5				
Gout								
GDM	72,014	18	0.2	100.0	1.85 (0.85, 4.00)	2.5	0.11	3.09
Reference	72,014	10	0.1	100.0				
Obesity								
GDM	72,014	8,152	113	78.7	1.89 (1.82, 1.95)	1220.6	<0.001	3.15
Reference	72,014	4,604	63.9	87.0				
Cancer Cohort								
13 obesity-related cancers								
GDM	96,110	378	3.9	99.2	1.14 (0.99, 1.34)	3.25	0.071	1.45
Reference	96,110	337	3.5	99.2				
Oesophageal cancer								
GDM	96,110	0	n/a	100	n/a	1.00	0.318	n/a
Reference	96,110	10*	0.1	100				
Stomach cancer								
GDM	96,110	10*	0.1	100.0	4.02 (0.45, 36.00)	1.82	0.178	7.49
Reference	96,110	10*	0.1	100.0				
Colorectal cancer								
GDM	96,110	24	0.2	99.4	0.79 (0.46, 1.35)	0.76	0.383	1.75
Reference	96,110	31	0.3	99.9				
Liver and bile duct cancer								
GDM	96,110	15	0.2	100.0	3.05 (1.11, 8.40)	5.18	0.506	5.55
Reference	96,110	10*	0.1	100.0				
Gallbladder cancer								
GDM	96,110	10*	0.1	100.0	1.02 (0.063, 16.23)	0.00	0.992	1.16
Reference	96,110	10*	0.1	100.0				
Pancreatic cancer								
GDM	96,110	10*	0.1	100.0	2.52 (0.49, 12.97)	1.31	0.253	4.48
Reference	96,110	10*	0.1	100.0				
Breast cancer								
GDM	96,110	162	1.7	99.6	0.97 (0.78, 1.20)	0.106	0.745	1.20
Reference	96,110	172	1.8	99.6				
Uterine cancer								
GDM	96,110	10*	0.1	100.0	5.09 (0.60, 43.57)	2.74	0.098	9.64
Reference	96,110	10*	0.1	100.0				
Ovarian cancer								
GDM	96,110	18	0.2	100.0	1.32 (0.65, 2.62)	0.55	0.457	1.98
Reference	96,110	14	0.1	100.0				
Kidney cancer								
GDM	96,110	13	0.1	100.0	1.48 (0.63, 3.45)	0.812	0.368	2.28
Reference	96,110	10*	0.1	100.0				
Brain cancer								
GDM	96,110	17	0.2	100.0	1.44 (0.9, 3.01)	0.939	0.332	2.22
Reference	96,110	12	0.1	100.0				
Thyroid cancer								
GDM	96,110	121	1.3	99.8	1.34 (1.02, 1.75)	4.42	0.036	1.99
Reference	96,110	92	1.0	99.8				
Myeloma								
GDM	86,224	10*	0.1	100.0	2.02 (0.51, 8.07)	1.029	0.310	3.47
Reference	86,224	10*	0.1	100.0				
Autoimmune Cohort								
Type 1 Diabetes								
GDM	94,945	328	3.5	99.3	12.32 (8.32, 18.25)	259.5	<0.0001	16.12
Reference	94,945	27	0.3	99.9				
Rheumatoid Arthritis								

(*continued on next page*)

Table 2 (*continued*)

Outcome	Sample size	Outcome (n)	Incidence per 1000 people	5-year survival probability (%)	Hazard ratio (95% confidence interval)	Long-rank test	P-value	E-value
GDM	94,945	127	1.3	99.7	1.23 (0.95, 1.59)	2.41	0.121	1.00
Reference	94,945	105	1.1	99.8				
Psoriasis								
GDM	94,945	320	3.4	99.3	1.25 (1.60, 1.48)	7.29	0.007	2.32
Reference	94,945	259	2.7	99.4				
Crohn's disease								
GDM	94,945	81	0.9	99.8	1.17 (0.85, 1.62)	0.96	0.327	1.00
Reference	94,945	70	0.1	99.9				
Ulcerative Colitis								
GDM	94,945	92	1.0	99.8	1.18 (0.87, 1.59)	1.16	0.282	1.00
Reference	94,945	79	0.8	99.8				
Sjogren's syndrome								
GDM	94,945	37	0.4	99.9	0.52 (1.25, 1.97)	11.20	0.001	1.71
Reference	94,945	73	0.8	99.8				
Grave's disease								
GDM	94,945	191	2.0	99.6	1.57 (1.21, 1.94)	15.35	<0.0001	1.00
Reference	94,945	123	1.3	99.7				
Autoimmune thyroiditis								
GDM	94,945	826	8.7	98.5	0.95 (0.87, 1.05)	0.964	0.326	1.00
Reference	94,945	866	9.1	98.4				
Addison's disease								
GDM	94,945	42	0.4	99.9	1.58 (0.97, 2.56)	3.50	0.061	1.00
Reference	94,945	27	0.3	99.9				
Multiple Sclerosis								
GDM	94,945	91	1.0	99.8	1.27 (0.93, 1.72)	2.27	0.132	1.00
Reference	94,945	73	0.8	99.8				
Gynaecological Cohort								
PCOS								
GDM	88,131	935	10.6	97.8	1.97 (1.76, 2.19)	152.53	<0.0001	2.84
Reference	88,131	489	5.5	98.8				
Uterine fibroids								
GDM	88,131	944	10.7	97.7	1.29 (1.17, 1.42)	27.50	<0.0001	1.64
Reference	88,131	753	8.5	98.1				
Endometriosis								
GDM	88,131	531	6.0	98.7	1.16 (1.03, 1.32)	5.60	0.018	1.23
Reference	88,131	471	5.3	98.8				
Infertility								
GDM	88,131	521	5.9	98.7	1.09 (0.97, 1.24)	1.98	0.159	1.46
Reference	88,131	491	5.6	98.8				

was associated with higher risk of subsequent T1D, with additional risk factors including insulin treatment and age under 30 years [28]. However, it could also be suggested that women with undetected T1D could be misdiagnosed with GDM, whereby glucose intolerance is caused by autoimmune destruction of pancreatic beta cells following the expression of T1D autoantibodies, instead of placentally-mediated insulin resistance [30]. Our data suggest that risk of T1D diagnosis increases linearly over many years, so is less likely to be explained by increased testing during pregnancy. After excluding all patients on oral hypoglycaemic agents with a separate cohort, the risk of subsequent T1D is still almost 10-fold at 5 years. This suggests the impact of misclassification, T1D being miscoded as T2D, is only limited, and potentially mediated by the aforementioned mechanisms. Studies have shown that T1D accounts for less than 10% of all diabetes cases suggesting that autoimmunity is not a major factor in the aetiology of GDM. While our data suggest that increased surveillance in women with GDM might be useful, this would be very challenging in practice since routine screening for T1D autoantibodies is not widely recommended in GDM clinical care pathways. Autoantibody testing could be considered in women diagnosed with GDM who have features suggestive of an autoimmune-like phenotype for example, younger age, low BMI, early insulin therapy, presence of autoimmune risk factors, and presence of ketonaemia [9]. Precision approaches to GDM pathophysiology may guide improved risk profiling and new individualised screening strategies.

4.3. Risk of cancer after GDM

Our study found an increased risk of a composite of the 13-adiposity-related cancers and thyroid cancer in patients with GDM. T2D is a recognised as a significant risk factor for several types of cancer including colorectal, pancreatic, gallbladder, breast, and endometrial cancer [12], and cancer now represents the leading cause of excess deaths in patients with T2D [31]. From 1990 to 2019, all cancer combined incidence rates have increased, with the greatest increase in the 25–49 (22%) age group, and rates are projected to continually rise in the coming decades [32]. The prevalence of T2D and GDM has also increased globally, with rates of younger-onset T2D also increasing disproportionately [33,34]. Indeed, the observed increased cancer risk in GDM may be driven by subsequent development of T2D and obesity, however several other pathophysiological mechanisms have been proposed. For example, increased growth factor bioavailability: insulin and insulin-like growth factor 1, increased hormones such as oestrogen, altered adipocytokine levels, and low-grade inflammation and oxidative stress affecting growth-promoting cytokines [35]. Although the evidence for cancer risk in GDM is scarce and conflicting, cohort studies have suggested an increased risk of breast [14,36], gynaecological [12], and pancreatic cancers [14,15]. In keeping with our findings, a systematic review and *meta*-analysis of 17 observational studies also reported an increased risk of thyroid cancer, and additionally breast, liver, and stomach cancer [37]. As the global burden of GDM, T2D rises, and obesity rises, it is likely that their synergistic effects will continue to increase the rates of cancer, particularly in younger people.

4.4. Risk of gynaecological conditions after GDM

We found an increased risk of incident PCOS, endometriosis, and

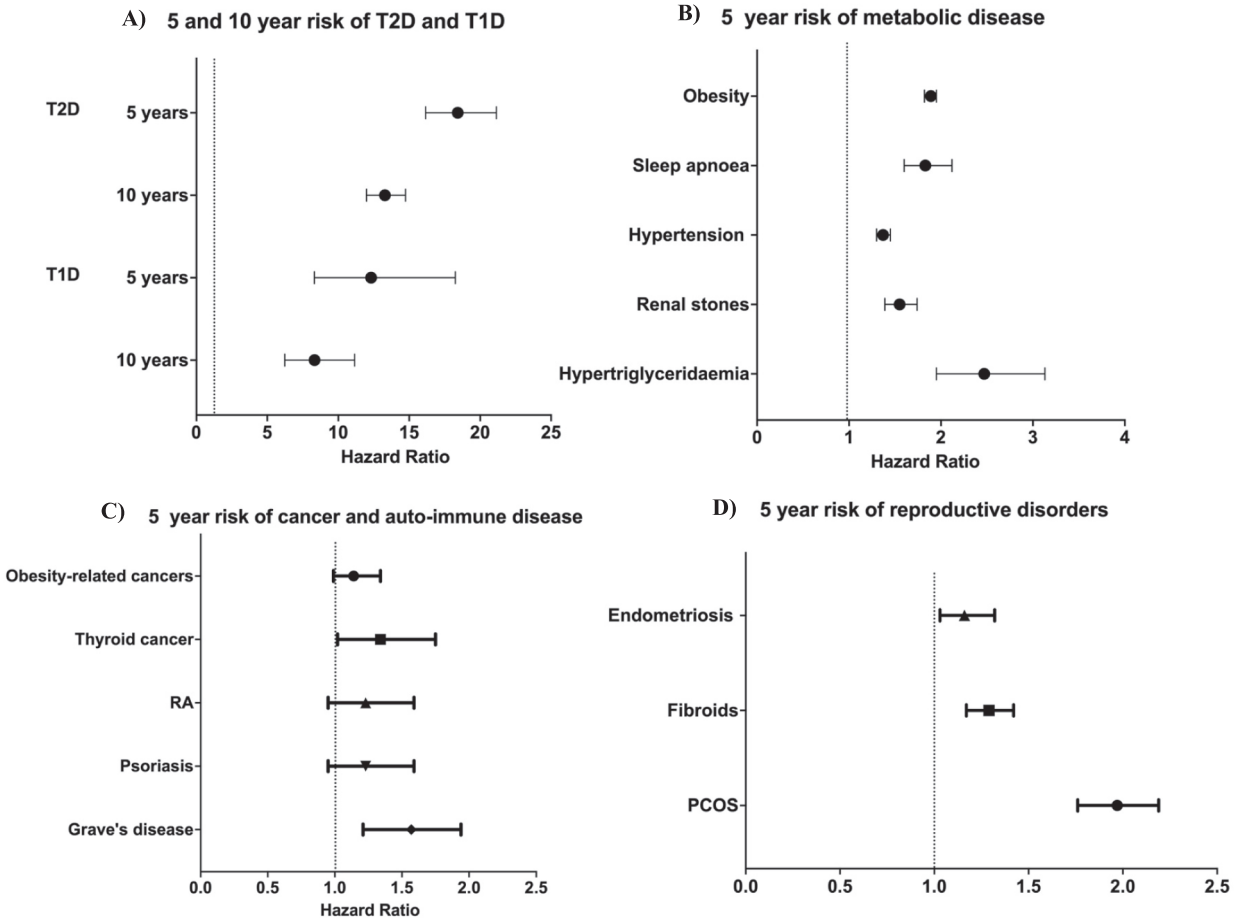

Fig. 2. Forest plots demonstrating mean and 95% confidence interval for **A)** type 2 and type 1 diabetes, **B)** metabolic disease, **C)** cancer and autoimmune disease, and **D)** reproductive disorders.

uterine fibroids after GDM, which may be explained by shared clinical risk factors, increased rates of detection following regular ultrasonography during pregnancy, or both. Although the association between PCOS and subsequent increased risk of GDM is well documented, our findings support a potential bidirectional relationship. Although the GDM and subsequent PCOS risk may be explained by obesity and associated insulin resistance, this does not explain our findings considering the baseline BMI matching of all participants in our cohort. Clinical data relating to the relationship between GDM, and uterine fibroids is scarce. Hyperinsulinemia, induced by insulin resistance, with upregulation of insulin-like growth factor 1 (IGF1) and epidermal growth factor levels, may enhance ovarian hormone secretion or directly promote myometrial smooth muscle proliferation [38,39]. Similarly, there is scarce and contradictory literature surrounding the link between GDM or T2D and endometriosis. Some studies have shown a potential association between laparoscopically diagnosed endometriosis and subsequent risk of GDM [40,41]. We hypothesise that the observed risk of incident endometriosis after GDM may be driven by systemic hyperinflammation with several inflammatory markers (C-reactive protein IL-1, IL-6, and TNF-α) raised in women with endometriosis [42,43].

4.5. Risk of autoimmune disorders after GDM

For the first time, we demonstrate an increased risk of incident rheumatoid arthritis, psoriasis, and Grave's disease following a diagnosis of GDM. Patients with diabetes have an altered number and function of innate immune system cells, in particular autoimmunity defined by loss of self-tolerance and chronic excess B and T cell reactivity. Similarly, research has suggested that the pathophysiology of GDM is also fuelled by inflammatory processes [44].

The increased production of cytokines characterising the chronic inflammatory state of T2D destroys pancreatic beta cells resulting in the release of antigens which further promote autoimmune activation and subsequent hyperglycaemia. Although no studies have yet explored the risk of incidence autoimmune thyroid disease in GDM, studies have found an increased prevalence of thyroid dysfunction and thyroid autoimmunity in patients with GDM [7,8,45,46]. The link between GDM and incident rheumatoid arthritis and psoriasis could be explained by increased levels of IL-6 and raised C-reactive protein (CRP) in patients with both RA and T2D [47,48], and in psoriasis, TNF-α plays an important role in insulin resistance through inhibiting tyrosine-kinase activity of the insulin receptor. Nevertheless, further clinical, and mechanistic studies are required to explore the relationship between GDM, autoimmune thyroid disease, psoriasis, and RA.

4.6. Strengths and limitations

Our study has several strengths. TriNetX is a large, federated database which allows for large sample sizes covering a range of healthcare settings and geographic regions which increases generalisability and enhances statistical power. Additionally, ICD-10 codes are internationally recognised classifications that enable robust cohort selection and examination of a broad range of clinically relevant outcomes at a population level. We minimised the effect of residual bias through rigorous outcome-specific confounder selection and inclusion in PSM. Finally, we examined outcomes at 5 and 10 years to provide novel data on both

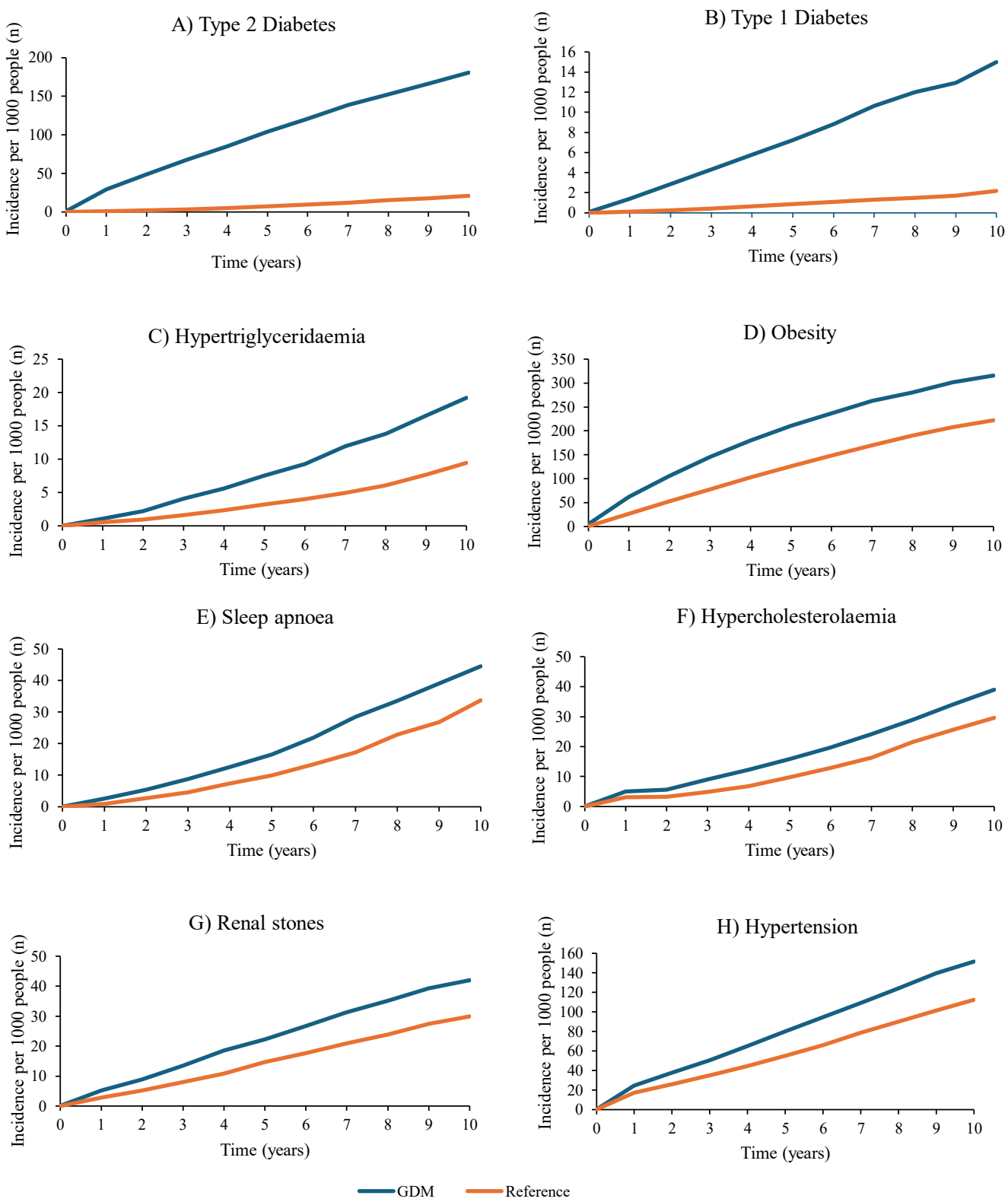

Fig. 3. Incidence per 1000 people for **A)** type 2 diabetes, **B)** type 1 diabetes, **C)** hypertriglyceridaemia, **D)** obesity, **E)** sleep apnoea, **F)** hypertriglycaeidaemia, **G)** renal stones, and **H)** hypertension.

medium and long-term risks after GDM.

However, there are limitations to our work which must be addressed. Firstly, as with any real-world data, comparisons are not randomised or controlled, and are therefore unable to prove causation. Also, the retrospective observational nature may be associated with unmeasured residual bias due to limitations in coding for potential cofounding variables (e.g. physical activity and nutrition), and a lack of biochemical data quantifying GDM severity and associated metabolic abnormalities. For GDM specifically, there is international heterogeneity in the criteria for screening and diagnosis. Secondly, as data are extracted from pooled

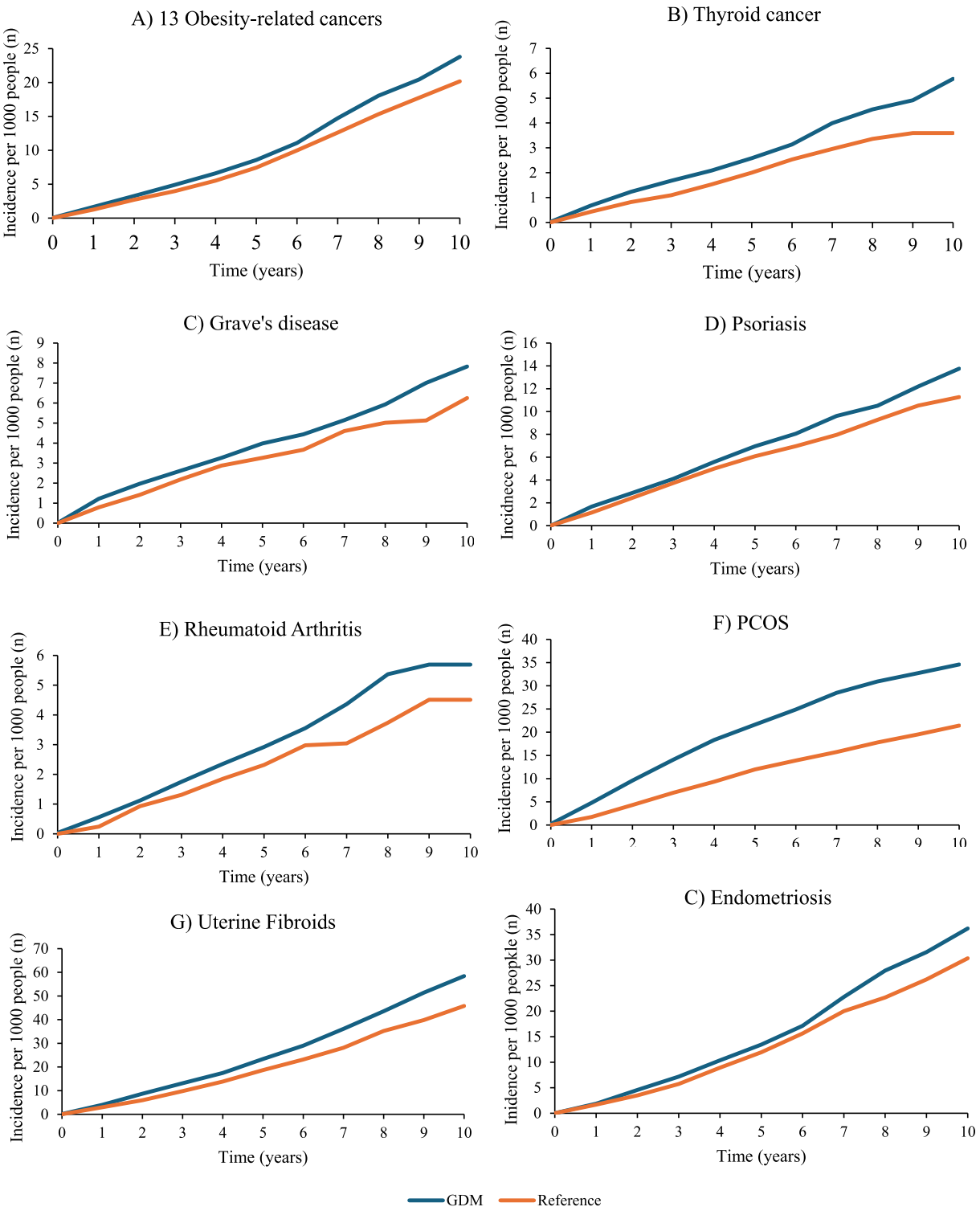

Fig. 4. Incidence per 1000 people for **A)** 13 obesity-related cancers, **B)** thyroid cancer, **C)** Grave's disease, **D)** psoriasis, **E)** rheumatoid arthritis, **G)** PCOS, and **H)** endometriosis.

electronic health records from an administrative database, there is a potential for missing data with data unavailable if patients move to another HCO not part of the global collaborative network. There may be some variability in diagnostic and coding practices between HCOs influencing its accuracy. Our relatively short follow-up time of 5 and 10 years may be insufficient to detect even longer-term consequences of GDM. Finally, we were not able to discern whether patients with GDM were treated with glucose-lowering medications during the index pregnancy or subsequent follow-up period.

4.7. Relevance to clinical care and policy

Women with GDM are at an increased risk of multiple long-term conditions and therefore represent a key population to target for disease prevention measures. Health intervention studies for women after GDM are of great importance given increasing prevalence of GDM

internationally, with relevance for future T2D risk. Our data suggest that non-obese women with GDM are also at risk, highlighting the potential limitations of a strategy which focuses on obesity alone. Despite the magnitude of subsequent diabetes risk, attendance for postpartum HbA1c screening is sub-optimal in Europe, the United States, and Canada [49–51]. Although international guidelines recommending testing for glycaemic status every 1–3 years post-partum, women are often not tested with diffusion of responsibility for screening between primary or secondary care [22,52]. Furthermore, guidelines make few recommendations for screening for other complications such as cardiovascular disease. Barriers to screening includes poor communication between clinical teams and patients, and between primary and secondary healthcare, inadequate education raise awareness of T2D risk, and time restrictions due to maternal duties [53]. Raising awareness for the importance of implementing patient-centred strategies and addressing reported barriers may help improve screening uptake. Our findings provide clear rationale for further research to investigate the impact of subsequent development of T2D and obesity on long-term outcomes, and the efficacy of screening, lifestyle, and pharmacological interventions to improve maternal outcomes after GDM.

5. Conclusions

In this retrospective cohort study, we found that GDM is associated with an increased risk of T2D and T1D, cardiometabolic disorders, adiposity-related cancers and thyroid cancer, autoimmune disease, and gynaecological disorders. Thus, GDM represents a severe disease phenotype with a myriad of complications, for which early intervention is warranted to minimise or prevent these long-term health risks.

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CRediT authorship contribution statement

Megan O. Heague: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Alex E. Henney:** Writing – review & editing, Methodology. **David R. Riley:** Writing – review & editing. **Matthew Anson:** Writing – review & editing. **Claire L Meek:** Writing – review & editing, Writing – original draft, Supervision. **Uazman Alam:** Writing – review & editing, Writing – original draft. **Daniel J. Cuthbertson:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

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Declaration of competing interest

DJC has recieved investigator-initated grants from Astra Zeneca and Novo Nordisk, support for education from Perspectum and consultency fees from Madrigal with any financial remuneration from pharmaceutical company consultation made to the University of Liverpool. He serves as the Topic Advisor for Type 2 Diabetes medications for the National Institute for Health and Care Excellence (NICE), UK. U.A has received honoria from Procter & Gamble, Viatris, Grunenthal, and Sanofi for educational meetings and funding for attendance at an educational meeting from Diiachi Sankyo. U.A has also received investigator-led funding from Procter & Gamble and is a council member of the Royal Society of Medicine's Vascular, Lipid & Metabolic Medicine section. All other authors declare that there are no financial relationships or activities that may bias, or be percieved to bias, their contribution to this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2026.113171.

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