Increased risk of non-alcoholic fatty liver disease in women with gestational diabetes mellitus: A population-based cohort study, systematic review and meta-analysis

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ABSTRACT

Aims: Non-Alcoholic Fatty Liver Disease (NAFLD) is one of the leading causes of liver transplantation in the West. This study seeks to examine whether women with gestational diabetes mellitus (GDM) are at increased risk of developing NAFLD compared to women without GDM.

Methods: We conducted a population-based retrospective matched-controlled cohort study utilising The Health Improvement Network (THIN), a large primary care database representative of the United Kingdom population, between 01/01/1990 to 31/05/2016 followed by systematic review of available literature. The study population included 9640 women with GDM and 31,296 controls without GDM, matched for age, body mass index (BMI) and time of pregnancy. All study participants were free from NAFLD diagnosis at study entry. Patients with GDM and patients developing NAFLD were identified by clinical codes.

Results: The median (range) follow-up duration was similar in women with and without GDM (2.95 (1.21–6.01) vs 2.85 (1.14–5.75) years respectively). Unadjusted incidence rate ratio (IRR) for NAFLD development in women with vs without GDM was 3.28 (95% CI 2.14–5.02), which remained significant after adjustment for wide range of potential confounders (IRR 2.70; 95% CI 1.744–4.19). The risk of NAFLD in GDM remained high (IRR 2.46: 95% CI 1.51–4.00) despite women being censored after they developed type 2 diabetes. The meta-analysis of 3 studies (including the current study) showed increased NAFLD risk in women with vs without GDM (OR 2.60; 95% CI 1.90–3.57, $I_2 = 0\%$). As our study is based on routine clinical diagnosis of NAFLD, this study could potentially have underestimated the risk of NAFLD development.

Conclusions: Women with GDM are at increased risk of developing NAFLD in their later life compared to women without GDM regardless of the development of type 2 diabetes. Clinicians should have a low threshold to investigate women with history of GDM for the presence of NAFLD. Further studies to identify screening strategies are needed.

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1. Introduction

Gestational Diabetes Mellitus (GDM) is common with a prevalence of 5.4% (3.8–7.8)[1] in Europe and rising to 19.19% (15.5–23.6) in other countries such as India.[2] The prevalence of GDM has increased over the last 20 years primarily fuelled by the obesity epidemic and the trend toward older maternal age.[3,4]

It is well established that GDM is associated with negative impact on maternal and fetal outcomes (fetal macrosomia, small for gestational age, pre-eclampsia, eclampsia, cesarean delivery etc.)[5,6] and increased risk of developing type 2 diabetes.[7,8] More recently, there has been an increasing interest in exploring the long-term consequences of GDM other than type 2 diabetes. Our group and others have recently reported that women with GDM were at increased risk of incident hypertension and cardiovascular disease.[9–11] However, other long-term consequences of GDM remain uncertain.

Non-alcoholic fatty liver disease (NAFLD) is a serious public health challenge with rising prevalence globally fuelled by the global increase in the prevalence of obesity and type 2 diabetes.[12–16] NAFLD is becoming the main cause of liver transplantation in the Western world.[13,17,18] GDM is associated with obesity, insulin resistance, dyslipidaemia, and type 2 diabetes; hence, it is plausible that the risk of developing NAFLD is increased in women with GDM. Our hypothesis is that women with GDM are at increased risk of incident NAFLD following delivery. This relationship has not been examined widely in the literature. Previous studies have identified that there is more than a two-fold increase in the risk of developing NAFLD following a diagnosis of GDM.[19],[20] However, these studies were of limited sample size, and failed to address key confounders.

To examine our hypothesis, we conducted a large population-based cohort study aimed at examining the relationship between GDM and incident NAFLD taking potential confounders into account. In addition, we conducted a systematic review and a meta-analysis of the available literature examining the risk of NAFLD development in women with GDM.

2. Materials and methods

2.1. The population-based study

2.1.1. Research design

We conducted a population-based retrospective matched-controlled cohort study utilising The Health Improvement Network (THIN) database, which our group has utilised previously to conduct studies in the fields of GDM and NAFLD.[9,21]

2.1.2. Data source: The Health Improvement Network

The THIN database is a primary care database, representative of the United Kingdom population (in terms of demographics, mortality rates and major health conditions' prevalence)[22] and contains the electronic medical records of approximately 14 million patients from over 698 general practices in 2016.[23] Details of medical care such as history, examination, investigations, diagnoses and prescriptions are recorded utilising the Vision patient record software[24] in a hierarchical system known as Read codes.[25]

For primary care practices to be eligible for inclusion in the study they had to have used the electronic medical record (EMR) system for one year and have an acceptable mortality recording date. These conditions ensure the accuracy of data recording and that the practices included in the study were making full use of the EMR system.

2.1.3. Study population, inclusion and exclusion criteria

Incident cases of GDM diagnosed between 01 January 1990 to 31 May 2016 were identified by using Read codes, a hierarchical clinical coding system used in UK primary care system (Fig. 1A & Supplemental Table S1 of Appendix A in the online supplement). The date of diagnosis of GDM was assigned as the index date (i.e. study start date) of GDM cases.

The control group in this study were women without GDM by the time of delivery. The date at which pregnancy was first recorded was taken to be the index date for patients in the control arm.

Women were eligible for inclusion in the study following at least one year of registration with their primary care provider to ensure accurate co-morbidity recording. Women with GDM were matched to controls up to a ratio 1:4, for age ($\pm$1 year), time of pregnancy ($\pm$90 days) and BMI (($\pm$2 kg/m^2). Patients with type 1 or type 2 diabetes mellitus prior to pregnancy or a history of alcohol excess at any point during the study were excluded. A follow chart for the above process is presented in Fig. 1A.

2.1.4. Study outcomes and follow-up

The primary outcome of this study was NAFLD incidence following delivery during the follow up period. This was identified through Read codes (Supplemental Table S1 of Appendix A). A secondary outcome was to identify covariates contributing to NAFLD development in women with GDM. A sensitivity analysis was performed to assess the effect of incident type 2 diabetes on the relationship between GDM and incident NAFLD. This was done by censoring the pregnant women when they developed type 2 diabetes. Women who developed type 2 diabetes mellitus during follow-up were censored from analysis (Fig. 1A). Co-variates were identified at baseline and outcomes during the follow up period both using the Read codes (Supplemental Table S1 of Appendix A in the online supplement). The follow-up period began from the index date until the earliest of the following events (exit date); diagnosis of NAFLD, death, subject left the practice, or last data collection from practice.

2.1.5. Statistical analysis

Categorical variables were presented as frequencies and continuous variables were presented as mean and standard deviation (SD). The *p* values for the comparison in baseline characteristics between women with and without GDM were not calculated as per the guidelines for observational studies.[26,27]

NAFLD incidence was compared between the exposed and control groups using Poisson regression and incidence rate ratios (IRR) and 95% confidence intervals (95% CI). The following variables were adjusted for: age, smoking, BMI, Townsend deprivation score,[28] hypertension (ever-diagnosis), metformin use, polycystic ovarian syndrome (PCOS) (ever-diagnosis), hypothyroidism (ever-diagnosis) and lipid modifying medication use. These variables were chosen based on biological plausibility to affect the relationship between predictors and NAFLD. In this study, a $p < 0.05$ was considered significant. Statistical analysis was performed on Stata v14.0 software.[29]

2.2. Ethical approval

The THIN data collection scheme received multi-center research ethics committee (MREC) approval in 2003 with Scientific Review Committee approval (SRC Reference Number: 17THIN001) of this particular study in January 4, 2018 from 'IQVIA' (data provider).

2.3. The systematic review and meta-analysis

2.3.1. Aims

The primary aim was to assess the risk of NAFLD in patients with GDM. A secondary aim was to identify any co-variates that increased the risk of NAFLD in women with GDM.

2.3.2. Search strategy and selection criteria

This systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

A

Women aged 15-50; registered with GP > 1 year (n=2,928,086)

↓

Read Codes for documented pregnancy(n=746,604)

→ Women with pre-existing Read Codes for diabetes and alcohol excess

↓

Read Codes for gestational diabetes mellitus documented (n=9,728)

→ Women with prescription of insulin at least 84 days before the date of GDM diagnosis indicating overt diabetes (n=68)

↓

Exposed population: Pregnant women with GDM (n=9,660) — Cases matched to controls on 1:4 basis / Pregnant women without GDM (n=31,318)

→ GDM exposed women with previous history of NAFLD (n=20); Control women with previous history of NAFLD (n=22)

↓

Poisson regression: the risk of NAFLD in GDM cohort (GDM: n=9,640, Non-GDM: n= 31,296)

Sensitivity analysis: Censoring of patients developing diabetes (n=15) during follow-up

B

Identification

230 articles found
- Medline & Embase (English)
- Reference list screening

→ Removed duplicates: 32

→ Abstracts not pertaining to topic: 168

↓

Screening

30 articles screened

Letters, Review, Editorials: 3
Basic Science: 5
Treatment of NAFLD: 1
NAFLD in Pregnancy: 7
Other: 11

↓

Inclusion

3 full text articles identified

← Current Cohort Study

↓

4 studies eligible for systematic review

↓
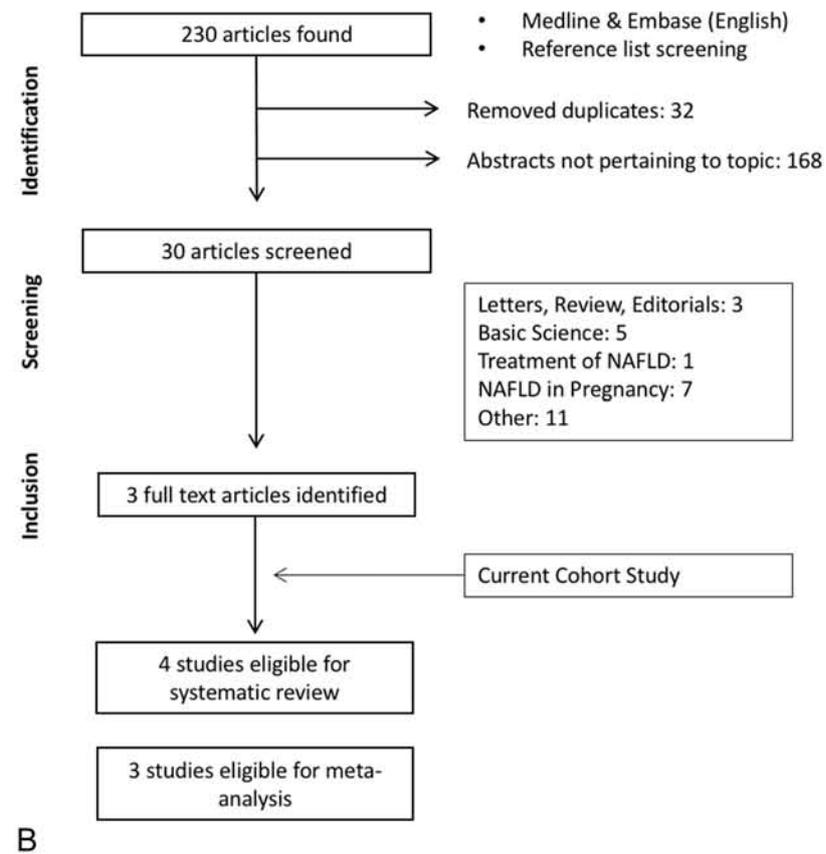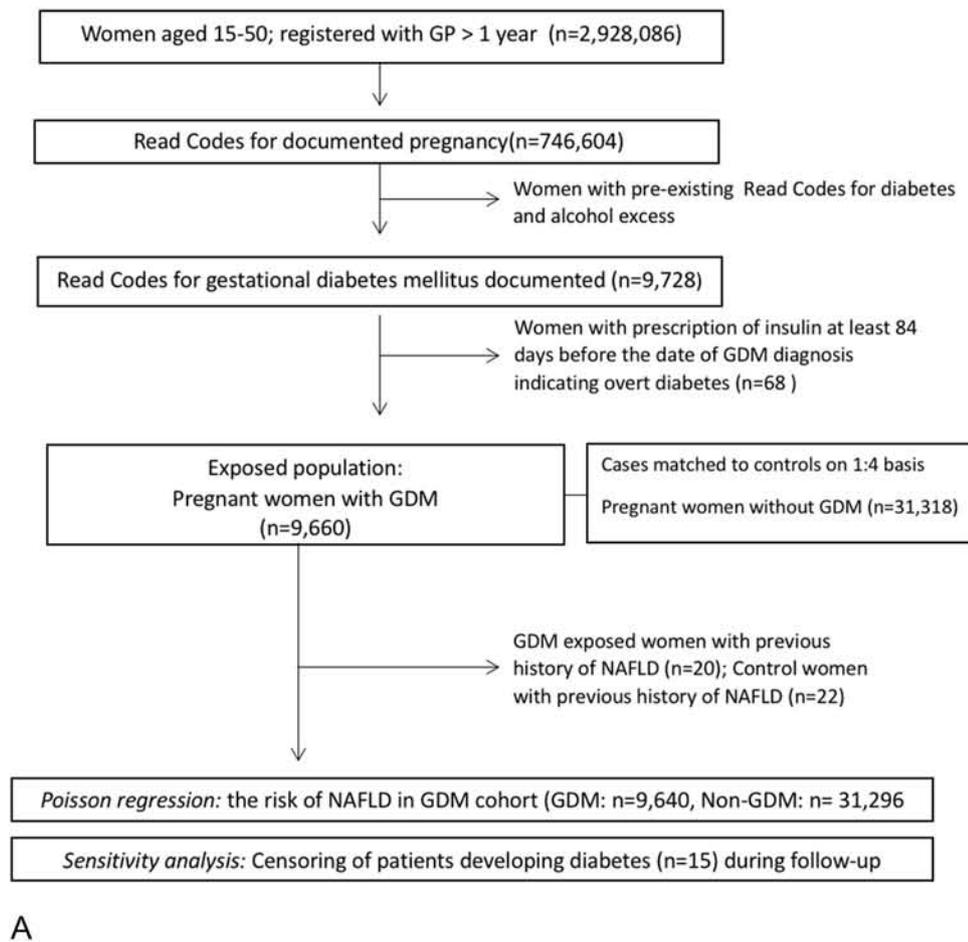
3 studies eligible for meta-analysis

Fig. 1. A: Identification of patients with GDM and overview of analysis in the retrospective cohort study. 1B: Study identification and selection process for inclusion in the systematic review and meta-analysis.

A systematic literature search was conducted on Medline (1946 to March 2018) and Embase (1974 to March 2018) for studies assessing the risk of developing NAFLD subsequent to a diagnosis of GDM. The detailed search strategy was developed with the assistance of an information specialist and is presented in Appendix B, Supplemental Fig. S1 of the online supplement. The reference lists of all relevant articles were also included in the literature research. Two reviewers (T.T and A.L) independently screened the initial search results for abstract and titles pertaining to the research question.

Randomised controlled trials or cohort studies were suitable for inclusion if they reported any of the following: the raw number of patients, risk ratio in the form of odds ratio or hazard ratio, or incidence rate in person years describing the occurrence of NAFLD in patients with a previous history of GDM. Randomised controlled trials or cohort studies assessing risk factors associated with the development of NAFLD in the GDM cohort were also eligible for inclusion.

Studies were excluded if they did not report original data or if their investigation was a laboratory-based investigation. Discrepancies between the reviews were resolved in conjunction with third party experts: K.N. and A.T. The flow chart for the above process is presented in Fig. 1B.

2.3.3. Data extraction and statistical analysis

The data extracted included: the first author, study design, study setting, study period, maternal characteristics, follow-up duration, definition of exposure and modalities of determining primary outcome (Appendix B, Supplemental Table S1 of the online supplement). Metabolic and anthropometric measurements collected over the course of each study were also extracted (Appendix B, Supplemental Table S2 of the online supplement). The raw number of patients in the exposed and non-exposed cohort in each study as well as odds ratio (OR) and 95% CIs with and without adjustment for confounding factors were also extracted. Data on whether each study adjusted for the following variables were also collected: age, parity, baseline BMI, waist circumference, HOMA–IR, high density lipoprotein (HDL), low density lipoprotein (LPL), triglycerides (TG), hypertension, Townsend deprivation scale, smoking, lipid controlling drugs, use of metformin, PCOS, hypothyroidism, and incident diabetes mellitus. Risk of bias assessment of studies included was performed using a modified version of the Cochrane Collaboration endorsed Newcastle-Ottawa Quality Assessment Scale (Appendix B, Supplemental Table S3 in the online supplement).

The primary outcome of the meta-analysis was the risk of NAFLD in patients with a previous diagnosis of GDM. Pooled ORs and 95% CIs were derived using the random effects model described by DerSimonian and Laird.[30] Adjusted ORs were used in the meta-analysis to incorporate confounding variables. Heterogeneity was assessed through the I_2 statistic with values >50% indicative of significant heterogeneity. The secondary outcome was to screen for potential risk factors that were associated with NAFLD development in the GDM cohort. The protocol for the systematic review was uploaded to the PROSPERO registry (CRD42018088569) in February 2018.[31]

3. Results

3.1. The population-based study

3.1.1. Study population characteristics

There were 9640 patients diagnosed with GDM matched to 31,296 controls within the THIN database (Table 1). The median follow-up duration in exposed and control groups was similar; 2.95 (1.21–6.01) and 2.85 (1.14–5.75) years respectively. The study population consisted mainly of young women below the age of 40 who were overweight or had grade 1 obesity. The GDM cohort had a higher proportion of patients with PCOS (3.56% vs 1.89%) compared to controls. The control population had a higher proportion of current smokers (19.26% vs 15.81%) in comparison to the patients with GDM. Only a minority of

the study population (<3%) were prescribed metformin, or lipid-lowering treatment. Study population characteristics are presented in Table 1.

3.1.2. GDM and incident NAFLD

Women in the exposed group (i.e. with GDM) had a greater risk of incident NAFLD (IRR: 3.28, 95% CI 2.14–5.02, $p < 0.0001$) (Table 2), which remained significant after adjustment for potential confounders (IRR: 2.70, 95% CI 1.74–4.19, p < 0.0001) (Table 2). NAFLD also occurred earlier during the follow up in the GDM group compared to the control group (median (IQR): 3.64 (1.44–6.46) years vs 5.12 (2.68–9.58), $p = 0.0505$).

3.1.3. Risk factors for NAFLD in the GDM cohort

In women with GDM: older age (IRR 1.06 (95% CI 1.00–1.12), $p = 0.0384$), obesity (IRR 16.28 (95% CI 2.20–120.57), $p = 0.006$), hypothyroidism (IRR 2.94 (95% CI 1.43–6.08), $p = 0.004$) and PCOS (IRR 3.24 (95% CI 1.60–6.56), $p = 0.001$) predicted incident NAFLD during the follow-up. Use of lipid-lowering drugs and use of metformin were not predictors of incident NAFLD in women with GDM (Appendix A, Supplemental Table S2 of the online supplement).

3.2. Sensitivity analysis

Women with GDM remained at a higher risk of NAFLD compared to the control population (IRR 2.46; 95% CI 1.51–4.00, $p < 0.0001$) despite censoring of patients who developed type 2 diabetes mellitus during follow-up. Out of the 44 women who developed NAFLD only 12 had preceding diagnosis diabetes (Fig. 1A).

3.3. Systematic review and meta-analysis

3.3.1. Search results

Out of 198 unique studies identified by the search strategy, only 3 studies fulfilled the inclusion criteria for the systematic review,[19,20,32]

Table 1
The Health Improvement Network gestational diabetes mellitus cohort and matched control group characteristics.

	Gestational Diabetes Mellitus	Control
Number of patients	9640	31,296
Person years of follow-up (median, IQR)	2.95 (1.21–6.01)	2.85 (1.14–5.75)
Age	32.87 (5.58)	32.55 (5.27)
Body mass index (median, IQR)	29 (24.4–34.2)	27.6 (23.7–32.00)
Smoking status		
Current	1524 (15.81%)	6029 (19.26%)
Former	1816 (18.84%)	5854 (18.71%)
Never	6099 (63.27%)	18,994 (60.69%)
Missing	201 (2.09%)	419 (1.34%)
Alcohol intake		
No intake	2905 (30.13%)	7137 (22.80%)
Active intake	5198 (53.92%)	19,946 (63.73%)
Missing	1537 (15.94%)	4213 (13.46%)
Lipid lowering drugs	6 (0.06%)	30 (0.10%)
Current metformin use	249 (2.58%)	11 (0.04%)
Hypertension	553 (5.74%)	1000 (3.20%)
Polycystic ovarian syndrome	809 (8.39%)	1578 (5.04%)
Hypothyroidism	562 (5.83%)	1301 (4.16%)
Townsend Index		
1	1638 (16.99%)	5741 (18.34%)
2	1504 (15.60%)	5356 (17.11%)
3	1898 (19.69%)	6173 (19.72%)
4	1873 (19.43%)	5603 (17.90%)
5	1521 (15.78%)	4102 (13.11%)
Not available	1206 (12.51%)	4321 (13.81%)

Table 2
The risk of developing non-alcoholic fatty liver disease in the gestational diabetes cohort (Poisson Regression model with adjustment for confounding variables).

	Gestational Diabetes mellitus	Control
Number of outcomes	44 (0.46%)	41 (0.13%)
Person-years	40,718	124,520
Incidence rate (per 100,000 person-years)	108.06	32.93
Incidence rate ratio (95% CI) (unadjusted)	3.28 (2.14–5.02)	
p-Value	<0.0001	
Incidence rate (95% CI) (adjusted)[a]	2.70 (1.74–4.19)	
p-Value	<0.0001	

[a] Adjusted for age, smoking, BMI, Townsend deprivation score, hypertension, metformin use, polycystic ovarian syndrome and hypothyroidism.

The current retrospective cohort study was subsequently included, resulting in a total of four studies for the systematic review. Three studies provided sufficient data including odds ratio to be included in the meta-analysis to assess the risk of developing NAFLD subsequent to a diagnosis of GDM (including the current study).[19,20] Foghsgaard et al.[32] was not included in the meta-analysis as it did not compare the risk of developing NAFLD in the GDM cohort to a non-GDM cohort. However, it was included in the systematic review as it assessed risk modulators of NAFLD in women with GDM. The main characteristics of this study are described in the online supplement. In summary, a total of 103 cases of NAFLD were diagnosed in 9874 patients with a previous history of GDM compared to118 cases of NAFLD in 32,400 control patients.

3.3.2. Characteristics of included studies

The characteristics of all included studies are presented in (Appendix B, Supplemental Table S4 of the online supplement). Forbes et al.[20] and Ajmera et al.[19] were both cohort studies. Forbes et al. comprised of patients with GDM that were retrospectively identified through use of the National Health Service (NHS) antenatal database.[20] Ajmera et al. selected participants from the pre-existing Coronary Artery Risk Development in Young Adults (CARDIA) cohort.[19] Patients were recruited to this cohort from four cities across the United States of America between 1985 and 1986. Patients with at least one delivery and no history of diabetes prior to the delivery were included in this study. Both Forbes et al. and Ajmera et al. utilised imaging; ultrasonography (US) and computed tomography (CT) respectively, to identify the outcome of hepatic steatosis. Foghsgaard et al.[32] compared the baseline characteristics of NAFLD and non-NAFLD patients in the GDM cohort. These patients were sourced from a randomised, placebo-controlled, double blind intervention trial assessing the effect of a glucagon-like peptide-1 receptor agonist on glucose tolerance in women with previous GDM.[33]

3.4. Quality of included studies

The median Newcastle-Ottawa quality score for the included studies was 8 (range, 8–9); all studies were considered of high quality (Appendix B, Supplemental Table S3 of the online supplement). Adjustment for confounders was heterogenous across the included studies. However, all studies adjusted for BMI. Both Ajmera et al. and the current study adjusted for age and hypertension.

3.4.1. The risk of non-alcoholic fatty liver disease in GDM

All three studies included in the meta-analysis showed a significantly increased risk of developing NAFLD subsequent to a diagnosis of GDM. The meta-analysis showed that women with GDM are at a higher risk of developing NAFLD in comparison to patients without a previous diagnosis of GDM; OR 2.60 (95% CI 1.90–3.57), ($p < 0.0001$) (Fig. 2A). The results showed minimal heterogeneity ($I^2 = 0\%$). This

was also reflected in the crude analysis; OR 3.11 (95% CI 2.30–4.20), $p < 0.0001$ (Fig. 2B). A multivariable logistic regression model was computed for the current retrospective cohort study to produce an odds ratio. The IRR previously calculated and odds ratio were similar (IRR 2.70 (95% CI 1.74–4.19), $p < 0.0001$ compared to OR 2.60 (95% CI 1.90–3.57), $p < 0.0001$. The odds ratio analysis was used in the meta-analysis.

3.4.2. Risk factors for NAFLD in women with GDM

In addition to our current study, another study by Foghsgaard et al.[32] presented a significant univariate association between increase in BMI and development of NAFLD in the GDM cohort; OR 1.24 (95% CI 1.11–1.41), $p = 0.0005$. However, this did not remain statistically significant following multivariate logistic regression including: weight, waist circumference, HDL cholesterol, VLDL cholesterol, triglycerides, visceral fat mass, android to gynoid fat ratio, total fat mass, ALT, AST, Matsuda Index, $HOMA2_{IR}$, FLI and glucagon tAUC. Our retrospective cohort study showed that increasing age, obesity, hypothyroidism, and PCOS confers an increased risk of NAFLD within the GDM cohort. Other studies pooled GDM and non-GDM patients in assessment of NAFLD and hence did not seek to investigate the role of BMI in development of NAFLD in the GDM cohort.

3.5. Sensitivity analysis

We conducted a sensitivity analysis for incident diabetes mellitus of the three included studies in the meta-analysis, which showed that the GDM cohort remained at a higher risk of NAFLD compared to the non-GDM cohort (OR 2.24; 95% CI 1.60–3.13) (Fig. 2C).

4. Discussion

In this paper we present the findings of a large population-based study that assessed the risk of postpartum NAFLD development in women with GDM. This study found that women with GDM were at significantly increased risk of incident NAFLD during the follow up period independent of potential confounders and the occurrence of type 2 diabetes. In addition, NAFLD manifested earlier in women with GDM compared to women without GDM. Finally, we identified additional risk factors for NALFD development within the GDM cohort; previous diagnosis of PCOS or hypothyroidism. This is consistent with previous findings in the literature however this relationship has not been previously shown in the GDM cohort.[34,35]

Our systematic review showed that only two other published studies provided extractable evidence to answer our research question.[19,20] Our cohort study results were consistent with the previous two studies and the meta-analysis confirmed that women with GDM were at an increased risk of NAFLD compared to women without GDM. However, our study was much larger than the other two reported studies (Appendix B, Supplemental Table S4 of the online supplement) and more generalizable since we utilised a population-based primary care database. THIN data is representative of the UK population demographics (age and sex structure), co-morbidities and mortality rates.[22] This dataset has been previously used for studies involving GDM[9] and NAFLD.[21] In addition, the current study population were very well characterized which allowed us to adjust for several confounders that were not considered in previous studies. A previous study utilised self-reporting to identify GDM diagnosis making it prone to recall bias, in contrast this study has identified GDM diagnosis through reporting by physicians.[19]

There are several potential mechanisms linking GDM to NAFLD development. GDM results from the inability to adapt to complex metabolic needs during gestation and leads to an increased risk of metabolic syndrome[36] and type 2 diabetes development in later life.[37,38] GDM has been linked to subsequent lipid abnormalities, hyperinsulinaemia/insulin resistance and increased systematic inflammation especially in overweight or obese women.[39–41] On the other hand, there is the potential

A: The risk of NAFLD in the GDM cohort (Adjusted meta-analysis)
B: The risk of NAFLD in the GDM cohort (Unadjusted meta-analysis)
C: Sensitivity analysis - the risk of NAFLD in the GDM cohort (adjusted for incident diabetes mellitus)
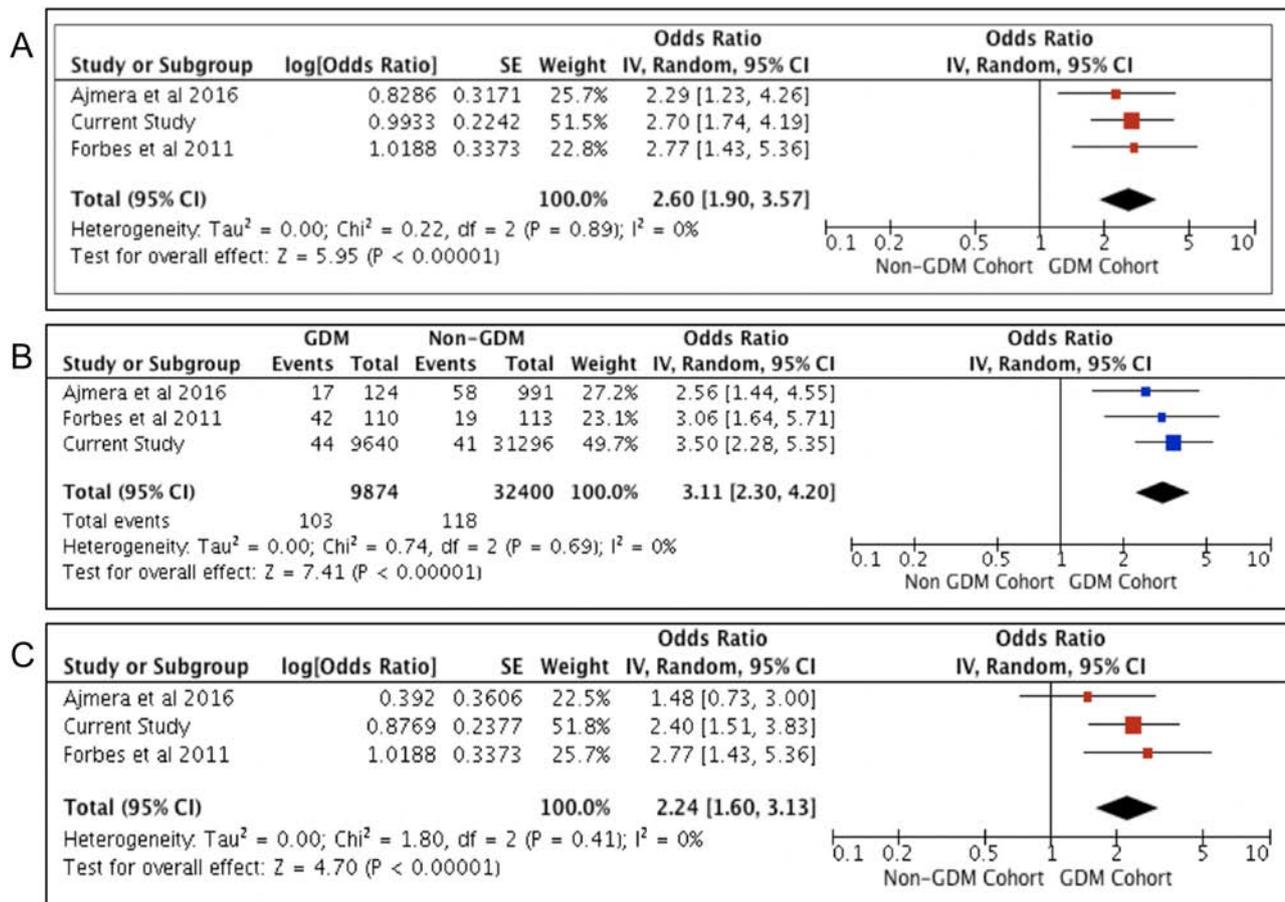
Fig. 2. The risk of developing NAFLD following a diagnosis of GDM.

that the development of GDM itself might be an indication of poor underlying metabolic health and this might subsequently contribute to the manifestation of the aforementioned metabolic disorders including NAFLD following GDM. These factors might play an important role in explaining the observed increased risk of NAFLD in women with GDM vs women without GDM. In contrast to a previous study,[19] GDM conferred an increased risk of NAFLD independent of the development of type 2 diabetes during follow up in this study. Nonetheless, the fact that obesity, PCOS and hypothyroidism were independent predictors of NAFLD in women with GDM supports the role of insulin resistance, hyperlipidaemia and inflammation in developing NAFLD.

There are currently no established screening strategies in women with GDM to identify NAFLD. Developing such strategies is beyond the scope of the current study but we have identified age, obesity and a previous diagnosis of PCOS or hypothyroidism as independent risk factors of incident NAFLD. Hence, women with GDM who have any of these risk factors are particularly at increased risk of NAFLD development and clinicians should have low threshold for examining for NAFLD in these cohorts.

The findings of this study need to be interpreted in light of its limitations. The diagnosis of GDM in our study is based on primary care physicians recording GDM as a READ code in the patient record. We acknowledge that GDM diagnoses might be under-recorded in primary care; however, our estimates in our previous analysis for cardiovascular risk in the GDM cohort[9] suggested there were no systematic differences. The criteria for diagnosing GDM might vary between centres and would

have changed during the course of the study as we included women with GDM over a long period of time (1990 to 2016). GDM screening strategy in the UK is based on screening high risk individuals, hence some patients in the control group might have had undiagnosed GDM. To account for this, we used a 1:4 matching ratio to reduce the impact of undiagnosed GDM and our results were consistent with the 2 previous studies published in literature. Our study also had shorter follow-up period in comparison to previous studies.[19,20] Our study is based on routine clinical diagnosis in contrast to the previous two studies that used systematic screening for NAFLD, and consequently this study could potentially have underestimated the risk of NAFLD development. A significant limitation of the meta-analysis is the heterogeneity in adjusting for confounders across the included studies.

This is the largest study to-date that has examined the impact of GDM on development of incident NAFLD. It is also the first population-based study, representative of the UK population in a primary care setting that has examined incident NAFLD in women with GDM. Finally, this study adjusted for a large number of potential confounders.

In conclusion, women with GDM are at an increased risk of developing NAFLD compared to women without GDM independent of subsequent diagnosis of type 2 diabetes. It was also observed that the development of NAFLD occurred earlier in women with GDM compared to women without GDM. Age, obesity and history of PCOS or hypothyroidism were newly identified as independent predictors of the development of NAFLD within the GDM cohort. Clinicians need to be aware

of the increased risk of NAFLD in women with GDM and have a lower threshold to investigate for NAFLD, particularly in women with GDM and obesity, PCOS or hypothyroidism. Further studies to develop appropriate screening and preventative strategies in this cohort are needed.

Author contributions

A.L. contributed to concept and design, literature extraction, writing the first draft manuscript, reviewing and editing the manuscript. T.T. contributed to concept, study design, literature extraction, statistical analysis, writing the first draft manuscript, reviewing and editing the manuscript. A.S. contributed to data extraction, statistical analysis, writing the first draft summary tables and manuscript revision. G.V. contributed to critical review of the methodology and liaison between the two departments. N.T. contributed to conceptualization and manuscript revision. K.T. contributed to conceptualization and manuscript revision. B.D. contributed to conceptualization and draft manuscript evaluation. P.S. contributed to conception of the GDM cohort, interpretation of the data and revising the draft manuscript. D.S. contributed to conceptualization and revising the draft manuscript. G.M. contributed to conceptualization, critical review for intellectual content, liaison between the two departments and funding of the investigator (A.L.) A.A.T. contributed to concept and design, draft manuscript evaluation and critical review for intellectual content. K.N. conceived the idea, contributed to design, analysis and revising the draft manuscript. K.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version prior to submission.

Prior presentation

Parts of this work were presented at the 20th European Congress of Endocrinology, Barcelona Spain, 19–22 May 2018. The population-based cohort study has been presented in the 54th EASD Annual Meeting, Berlin, 1–5 October 2018.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2019.06.006.

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