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Master thesis

Master of Science

Adverse pregnancy and birth outcomes in women exposed to glucagon-like peptide-1 receptor agonists – A nationwide register-based study

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Abstract

Prescription and use of glucagon-like peptide-1 receptor agonist (GLP-1RA) medicines for type 2 diabetes (T2D) and weight management have been rising notably in Denmark in recent years, including among women of fertile age.

To date, limited information about the safety of GLP-1RA in pregnancy is available. Animal studies have shown reproductive toxicity, and women are therefore advised to stop treatment if they plan to become pregnant or in the case a pregnancy occurs. Despite clinical recommendations, some women may still become pregnant during treatment. To be able to counsel these women, we investigated the association between periconceptional GLP-1RA use and potential risks of adverse pregnancy and birth outcomes.

Nationwide Danish health registry data was utilized to investigate the risks of miscarriage, major congenital malformations (MCM) and small for gestational age (SGA) among pregnancies exposed to GLP-1RA during pregnancy versus no exposure to GLP-1RA during pregnancy. Exposure was defined as prescription between 3 months prior pregnancy and an outcome-specific end date. Confounding was adjusted for by propensity score inverse probability of treatment weighting. Prevalence odds ratios (OR) of MCM and SGA were estimated by log-binomial regression and the hazard ratio (HR) of miscarriage by cox proportional hazards modelling.

A total of 1 195 415 pregnancies were eligible for the study of which 900 733 (74.3%) ended as live or still births, 170 331 (14.3%) as terminations, and 124 351 (10.4%) as miscarriage. Of all eligible pregnancies, 1087 (0.09%) had been exposed to GLP-1RA.

No statistically significant association was found between GLP-1RA exposure and risk of MCM and SGA (adjusted prevalence OR for MCM, 1.36; 95% CI, 0.88-2.16; adjusted prevalence OR for SGA, 0.86, 95% CI, 0.55-1.34. Although the estimated HR of miscarriage was statistically significant (adjusted HR, 1.24; 95% CI, 1.05 -1.47), pre-specified sensitivity analyses did not support this finding, suggesting possible unmeasured confounding of the association.

In conclusion, the findings of this study did not suggest an increased risk of adverse pregnancy and birth outcomes related to GLP-1RA exposure during pregnancy. More research is needed before a pregnancy or birth related risk can be reassuringly excluded.

Layman's summary

Prescription and use of glucagon-like peptide-1 receptor agonist (GLP-1RA) medicines for type 2 diabetes (T2D) and weight management have been rising notably in Denmark in recent years, including among women in the childbearing age.

To date, limited information about the safety of GLP-1RA in pregnancy is available. Animal studies have shown harmful effects to foetuses, and women are therefore advised to stop treatment if they plan to become pregnant or in the case a pregnancy occurs. Despite these recommendations, some women may still become pregnant during treatment. To be able to counsel these women appropriately, we used existing Danish nationwide health registry data to investigate the possible link between the use of GLP-1RA in pregnancy and adverse pregnancy and birth related outcomes, including severe malformations of the child, small birthweight of the child, and the risk of miscarriage.

Technically, we assigned a summary score (a propensity score) to each pregnancy based on a range of available characteristics, which summarised the likelihood of being treated with GLP-1RA medicines. This information was utilised to control the influence of each individual pregnancy in the analysis in order to achieve comparability between the pregnancies exposed to GLP-1RA and pregnancies not exposed (inverse probability of treatment weighting, IPTW).

A total of 1 195 415 pregnancies were available for the study of which 900 733 (74.3%) ended as live or still births, 170 331 (14.3%) as induced pregnancy terminations, and 124 351 (10.4%) as miscarriage. Of all the pregnancies, 1087 (0.09%) had been of women exposed to GLP-1RA.

We found no increased risk of neither severe malformations, nor of small birthweight, nor of miscarriage among the pregnancies exposed to GLP-1RA, but the results also indicated problems with comparability and precision which warrants caution in the interpretation. Pregnancy risks by GLP-1RA exposure cannot therefore be excluded on basis of this study alone, and more studies are needed before a final conclusion eventually can be drawn regarding the safety of GLP-1 RA in pregnancy.

Introduction

Obesity and overweight are among the major health challenges in the Western world (1). Glucagon-like peptide-1 receptor agonist (GLP-1RA) drugs were originally developed for the treatment of type 2 diabetes (T2D) (2). Weight-loss was observed during GLP1-RA treatment as a side effect (3), which led to further drug development specifically for use among overweight and obese persons (2).

Exenatide was the first drug in the class of GLP-1RA to be approved for the treatment of T2D in the EU in 2006 (4), and other drugs in the class have since followed: liraglutide in 2009 (5), lixisenatide in 2013 (6), dulaglutide in 2014 (7), and semaglutide in 2018 (8). Two of the substances approved in the T2D indication were later approved for use in the obesity and overweight indication; i.e. liraglutide in 2015 (9) and semaglutide in 2022 (10).

The utilisation of GLP-1RA for T2D and weight management is increasing dramatically worldwide (11,12). In Denmark, between 2018 and 2024, the prevalence of users in the general population increased 7-fold, i.e. from 5.5 per 1000 adults to 36.3 per 1000 adults (13,14). Notably, this increase was most pronounced among women in the fertile age. For instance, among women aged 18-24 years, the prevalence went from 0.3 per 1000 in 2018 to 11.3 per 1000 in 2023, i.e. a 38-fold increase. Among women aged 25-44 years, the prevalence went from 2.4 per 1000 in 2018 to 43.3 per 1000 in 2023, i.e. an 18-fold increase (14).

Despite warnings on use during pregnancy, considering the growing population of women in long-term treatment with GLP-1RA, some may inadvertently become pregnant during the course of their treatment.

<u>Existing knowledge on safety of GLP-1RA during pregnancy</u>

The knowledge on the safety of GLP-1RA during pregnancy in humans is limited (4–10). For all GLP-1RA currently approved, pre-clinical animal studies have shown reproductive toxicity, possibly due to the anorexigenic maternal effect (4–10). For semaglutide and lixisenatide, few malformations were in addition noticed in the animal's offspring without an identifiable biological mechanism (6,8). During their initial marketing approvals, it was concluded that a causal relation between these observations and the exposure could not be ruled out (6,8), and for this reason it is recommended that women should use contraception during treatment, and they should discontinue treatment if planning to become pregnant, or in case of pregnancy (15–21).

The European Medicines Agency (EMA) did not request post-authorisation safety studies in pregnancy for any of the GLP-1RA (4–10) in relation to the approval procedures, whereas the American Food and Drug Administration (FDA) issued two post market requirements for the product Wegovy with regard to use in

pregnancy. The first FDA requirement was for the marketing authorisation holder (MAH) to conduct a prospective product-specific registry study to collect information based on voluntary consent from pregnant women exposed at any time during pregnancy, to be compared to an unexposed reference population. The estimated study completion date is 30-12-2032 (NCT05872022, same as EUPAS104613). The second FDA requirement was for the MAH to conduct a retrospective study using administrative insurance claims data, but the details on the study design and statistical analysis plan are not publicly available. The estimated study completion date is 15-08-2027 (NCT05503927).

In addition, an investigator-initiated observational multicentre study plans to utilize data from "Participating centres of the European Network of Teratogen Information Services (ENTIS)". The anticipated study size is 200, and a final study report is expected due on 30-06-2023 (EUPAS50643).

In late 2023, the first observational study to examine the safety of GLP-1RA during pregnancy was published (22). The authors investigated the risk of major congenital malformations (MCM) during periconceptional use of second-line non-insulin antidiabetic medications, including GLP-1RA, compared to periconceptional insulin use in pregnant women with T2D. The study utilised data from 4 Nordic countries (Denmark not included) in addition to the US and Israel, including a total of 3 514 865 pregnancies of which 938 were exposed to GLP-1RA. This study found no indications of a large increased risk of MCM when GLP-1RA use was compared to insulin use (relative risk of 0.95 (95% CI: 0.72-1.26).

Due to an unmet and growing need for data on the possible association between periconceptional or pregnancy exposure to GLP-1RA and adverse pregnancy and birth outcomes, a well-conducted observational study is required.

The aim of the present study was to investigate the association between periconceptional or pregnancy exposure to GLP-1RA and the risks of adverse pregnancy and birth outcomes in an observational study using Danish nationwide and prospectively collected healthcare data. The results of the present study may be used to support informed counselling of women who may become pregnant while using GLP-1RA.

Methods

Data sources

The study utilised existing secondary data from five Danish nationwide registries:

- the Danish Civil Registration System (CRS)
- the Danish National Patient Register (NPR)
- the Danish National Prescription Registry (DNPR)

- the Danish Medical Birth Register (MBR)
- the Clinical Laboratory Information Register (CLIR)

The CRS provides a unique personal identifier assigned to every legal resident of Denmark at birth or immigration since 1968 and enables linkage between all registries at an individual level (28).

The NPR stores data on all in-hospital encounters since 1995, including the date of the encounter and primary and secondary diagnoses recorded according to ICD-10. Virtually all in-hospital medical care in Denmark, including encounters at outpatient specialist clinics, is provided by the public hospitals (25).

The DNPR provides data on all prescription medications dispensed in the community pharmacies since 1995 (26).

The MBR provides maternal, pregnancy, and childbirth-related characteristics including the date of delivery, gestational age at birth, status of a birth (live vs stillbirth), maternal age at delivery, smoking status at 1st prenatal visit on all deliveries ending in a live or stillbirth in Denmark since 1997. Maternal BMI is recorded in MBR since 2004 (27).

The CLIR provides information about biochemical and immunological analyses performed at the major clinical biochemistry and clinical immunology laboratories in Denmark since 2008 (28); however a complete national coverage was first fully established in Q3 2015 with regard to clinical biochemical analyses (28).

The national abortion registry (ABR) was not used since it was only updated until 2019 at time of data access.

Study population

The study population consisted of pregnancies registered with an abortion outcome (spontaneous or induced) in NPR between 10 May 2007 (i.e. 2 weeks after first GLP-1RA launch in Denmark on 26 April 2007) and 31 December 2023 or with a birth outcome (live or still) in MBR between 04 October 2007 (i.e. 23 weeks after launch date of 26 April 2007) and 18 February 2024. The same woman was allowed to enter the study population several times if she had more than one recorded pregnancy during the study period. The unit of analysis was the single pregnancy.

For each individual pregnancy, the first day of the last menstrual period (LMP) was calculated as date of birth minus gestational age in days. LMP was used as start of follow up for the longitudinal outcome analysis of miscarriage.

For each outcome analysis, a study population was defined based on exposure time periods. Analysis of MCM and SGA was performed on pregnancies registered with a birth outcome, whereas analysis of miscarriage was based on all pregnancies. For multifoetal pregnancies, a single pregnancy observation was randomly selected.

Pregnancies were moreover excluded if:

- the woman was not a resident of Denmark 12 months prior to LMP,
- information on gestational age was missing,
- the foetus or neonate was registered with birth defects resulting from a known cause according to EUROCAT definitions (ICD-10: P350, P351, P354, P358, P371, Q8680, Q90-Q93, Q96-Q99) (22,29).
- the woman had filled a prescription of a known teratogenic drug during pregnancy (Appendix Table 1).

GLP-1RA exposure definition

The exposure was defined as at least one redeemed prescription of a medicinal product from the class of GLP-1RA (ATC code: A10BJ, refer to Appendix table 2) within the exposure time window of interest. Redeeming a prescription does not infer that the medicine is taken, but this is used as an underlying assumption in this study. The start of the exposure time window was defined as 3 months before the LMP date, because the largest package sizes of GLP-1RA medicines provide for three months of treatment (Appendix Table 2) and the longest elimination half-life within the class is 1 week for semaglutide (21).

The exposure time windows were defined as follows:

- Miscarriage outcome: [LMP -90 days; LMP +154 days]
- MCM outcome: [LMP -90 days; LMP +97 days] (30)
- SGA outcome: [LMP -90 days; LMP +pregnancy end]

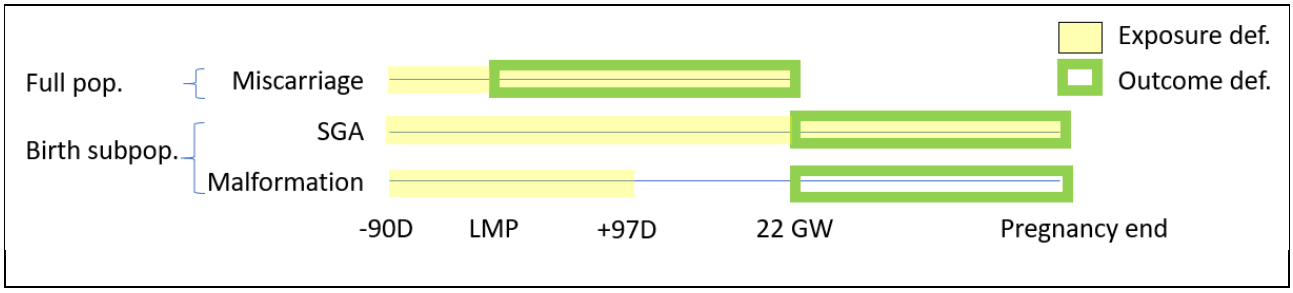
Outcomes

MCM was measured as a composite outcome and defined according to the EUROCAT classification system (29) with adaptation to the Danish registries (31). Refer to Appendix 1, Table 1.3 for the ICD-10 codes. Analysis of subgroups of malformations was not feasible in this study due to a low number of outcome events. The granted data access did not allow for a complete year of neonatal follow-up after birth via the NPR. Hence, malformation data was available only via the information provided in MBR, using the same cut-off date as for the entire dataset.

Miscarriage was defined as pregnancies ending in foetal death before the end of gestational week 22, according to ICD-10 classification codes DO021 and DO03.

SGA was defined as a birth weight below the lowest 10th percentile of the gestational age specific and sex specific birth weight. The birthweight distribution was calculated on basis of the actual dataset.

Figure 1. An illustration of the three subpopulations under study, each characterised by their distinct exposure and outcome definitions.



Abbreviations: LMP, last menstrual period; GW, gestational weeks; SGA, small for gestational age.

Baseline maternal/pregnancy characteristics and potential confounders

A look-back period of 365 days prior to the LMP date was used to establish pre-pregnancy comorbidities using the mother's diagnostic history and drug prescription history. For opioid prescription history, the look back period was limited to 90 days, and for anti-infectives and NSAIDs to 30 days since the LMP date (Appendix 1, Table 1).

Three subpopulations were defined for the individual outcome analyses in accordance with Figure 1. Within each subpopulation a propensity score (PS) was calculated for each pregnancy observation. Briefly, a PS is an estimate of the likelihood of exposure for each individual, given a set of known risk factors for the outcome. (32). A PS can be utilized to achieve balance of measured confounding variables between the exposed and unexposed pregnancies.

Covariates were selected based on empirical knowledge about risk factors associated with adverse pregnancy and birth outcomes from the literature (31,33–38). For covariates entered in the PS model, imputation by was done by the mode value (39).

Statistical analysis

A PS was calculated within each outcome-specific study population. The dataset had a multilevel data structure consisting of three levels: mothers, pregnancies and foetuses, and the PS was therefore estimated

by multilevel generalised linear logistic regression using the R package lme4 (40) to estimate the probability of GLP-1RA exposure taking into account the risk factors for the outcome. Since each data structure level had a high number of clusters relative to the total number observations and only few observations per cluster, multilevel data analysis was computationally intensive. To avoid issues with model convergence, only a single random intercept was included at the maternal level to address sibling interrelatedness. Interrelatedness within multifoetal pregnancies was instead addressed by randomly selecting only a single observation per pregnancy. A seed number was specified to ensure reproducibility of the random selection. Additionally, within the glmer function, nAGQ was set to 0, and calculation derivatives were set to false inside glmerControl to reduce computational time.

Since the PS distribution was extremely right skewed for the exposed and unexposed populations, the *a priori* decision to trim by 1st and 99th percentiles caused a reduction in the exposed population by over 90%. For this reason, it was decided to carry out common range trimming instead to exclude non-overlapping regions of the PS distribution (41). The excluded observations were investigated to check for possible explanations or outliers. The PS was re-estimated within the trimmed population as recommended by Stürmer et al. (42).

In accordance with the aetiologic research question, the interest of this study was to estimate the average treatment effect among the treated (ATT). Hence, weighting was done by standardised mortality ratio weighting (SMRW) (43) by assigning a constant weight of 1 to all pregnancies categorised as exposed, and a weight of the PS-odds (i.e., PS/(1-PS)) to all unexposed pregnancies (41,44,45). By applying these weights, the baseline characteristics of the exposed remained unchanged, while a pseudopopulation was constructed from the weighted unexposed pregnancies so that its baseline characteristics resembled those of the exposed.

The distribution of weights was checked. Since maximum weights were below 10 (41), no further stabilization of weights was applied.

Covariate balance was considered sufficient when absolute standardized mean differences (SMD) between exposed and unexposed were below 10%. SMD for continuous and dichotomous variables was calculated as defined by (46). If sufficient balance was not initially achieved, transformation or recategorization of variables was applied. This step was only carried out for the main analysis, with the sensitivity analyses reusing the categories from the main analysis.

Miscarriage was modelled in a time-to-event framework with gestational age in days as the underlying time unit. Data were left-truncated until 6 weeks of gestation due to inconsistent reporting of miscarriage in

very early pregnancy. Time-varying exposure or covariates were not adjusted for. Unadjusted and adjusted hazard ratios with corresponding 95% confidence intervals (CIs) were computed using Cox proportional hazards regression. The proportional hazards assumption was checked by testing the relationship between Schoenfeld residuals and time, and by visual inspection of Schoenfeld residuals against time, using the function cox.zph() in the R package "survival" (47).

For the outcomes MCM and SGA, unadjusted and adjusted prevalence proportions were calculated as odds ratios with corresponding 95% Wald CIs using log-binomial regression.

All analyses were conducted using Rstudio version 4.3.3 (48) and the following R packages: tidyverse, lubridate, magrittr, here, cobalt, WeightIt, lme4, broom, gtsummary, survival, survminer, gridExtra, naniar, flextable, tableone.

Expected study size and precision estimates were calculated prior to the study from the information available on GLP-1RA exposed pregnancies until 2022 and national trends in general use of GLP-1RA (49,50).

Sensitivity analyses

To address the robustness of the study results, the following prespecified sensitivity analyses were performed:

Sensitivity analysis 1: Stratification by T2D status

The study population was stratified according to presence of T2D at baseline. GLP-1RA users whom would not be fulfilling the T2D criterium at baseline would presumably be users in the overweight indication.

T2D was defined as (1) at least one prescription of a glucose-lowering medication (ATC code: A10B) except GLP-1RA (ATC code: A10BJ) in the year before conception; or (2) a diagnosis of T2D (icd-10 code: E11) in the year of conception; or (3) at least one prescription of a GLP-1RA (ATC code: A10BJ) in the year before conception AND at least one HbA1c measurement above 48.0 mmol/mol within a year before conception. This definition was a simplified adaptation of the criteria applied by the Danish Diabetes Register (51,52).

Sensitivity analysis 2: The pregnancy comparator subgroup of GLP-1RA stoppers

Substantial heterogeneity could be expected in the main analysis *a priori*. To address the risk of unmeasured confounding by indication, a comparator subgroup of prior users of GLP-1RA was identified within the main comparator group. Specifically, this group was defined as unexposed pregnancies of women who had filled a GLP-1RA prescription between 365 days and 125 days prior LMP. The threshold of

125 days prior LMP was defined as a prescription lasting for 90 days + 35 days wash-out. This group is onwards called “stoppers.”

Sensitivity analysis 3: Impact of defining exposure start based on days’ prescription

In the main analysis, the beginning of the exposure window aligns with the number of days’ supply in a single GLP-1RA prescription based on the assumption that the medicine is taken as prescribed (53). To investigate the effect of misclassification of the GLP-1RA exposure definition, a sensitivity analysis was performed which narrowed the exposure window to begin at the date of LMP.

Sensitivity analysis 4: Impact of not adjusting for BMI and smoking

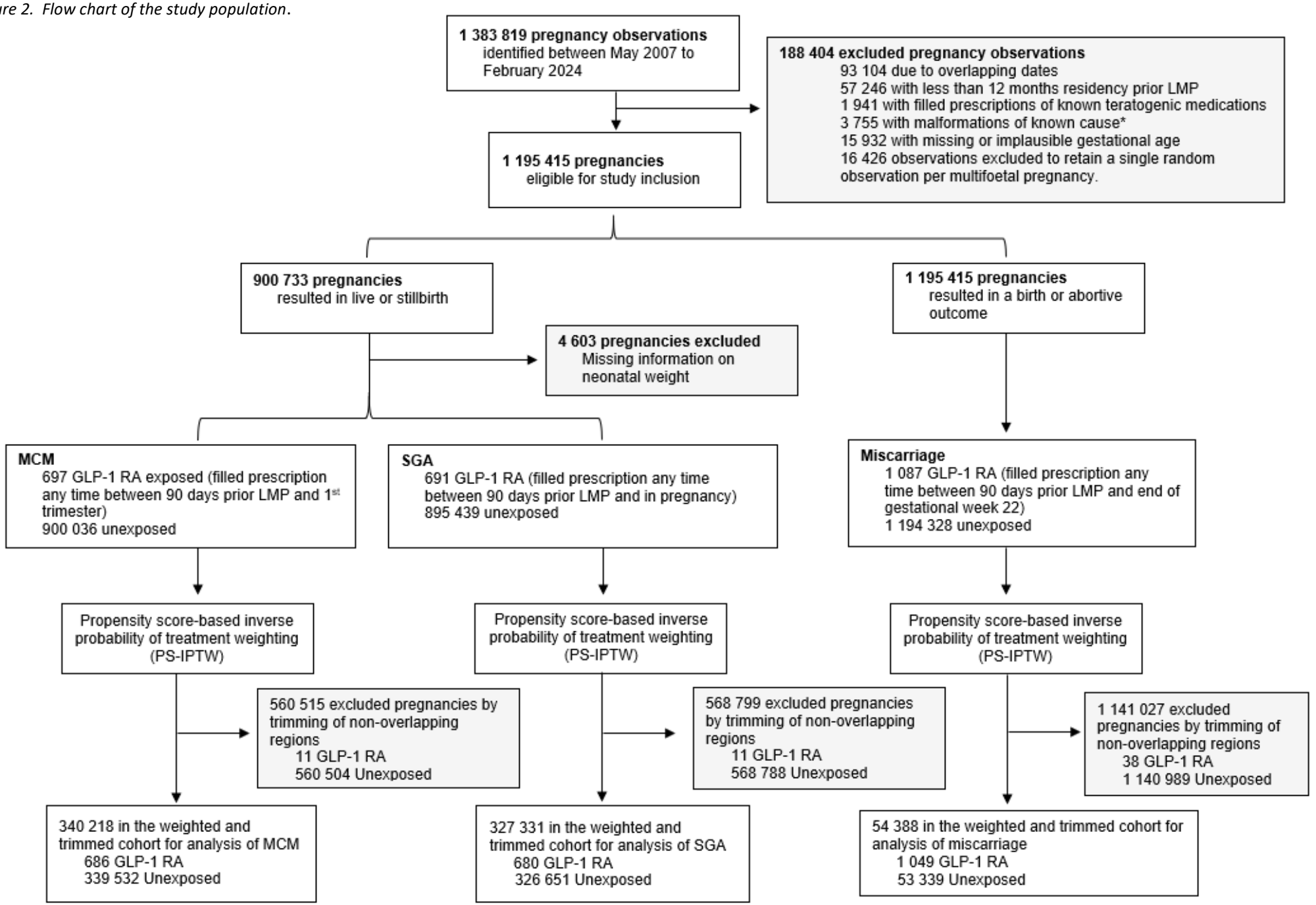
Two potentially important confounding variables, i.e. BMI and smoking, were available only within the birth subpopulation (i.e. the population from the MBR). Consequentially, in the miscarriage outcome analysis which utilises the full pregnancy population, adjustment for these variables could not be performed. To investigate the impact, the PS-IPTW analysis of the MCM outcome was repeated with these variables excluded from the PS model.

Results

Characteristics of study populations

A study population flowchart is provided in Figure 2. During the study period, 1 195 415 pregnancies were eligible for the study of which 900 733 (74.3%) ended as live or still births, 170 331 (14.3%) as terminations, and 124 351 (10.4%) as miscarriage. Of all eligible pregnancies, 1087 (0.09%) had been exposed to GLP-1RA, and 17 523 (1.5%) were multifoetal pregnancies.

Figure 2. Flow chart of the study population.



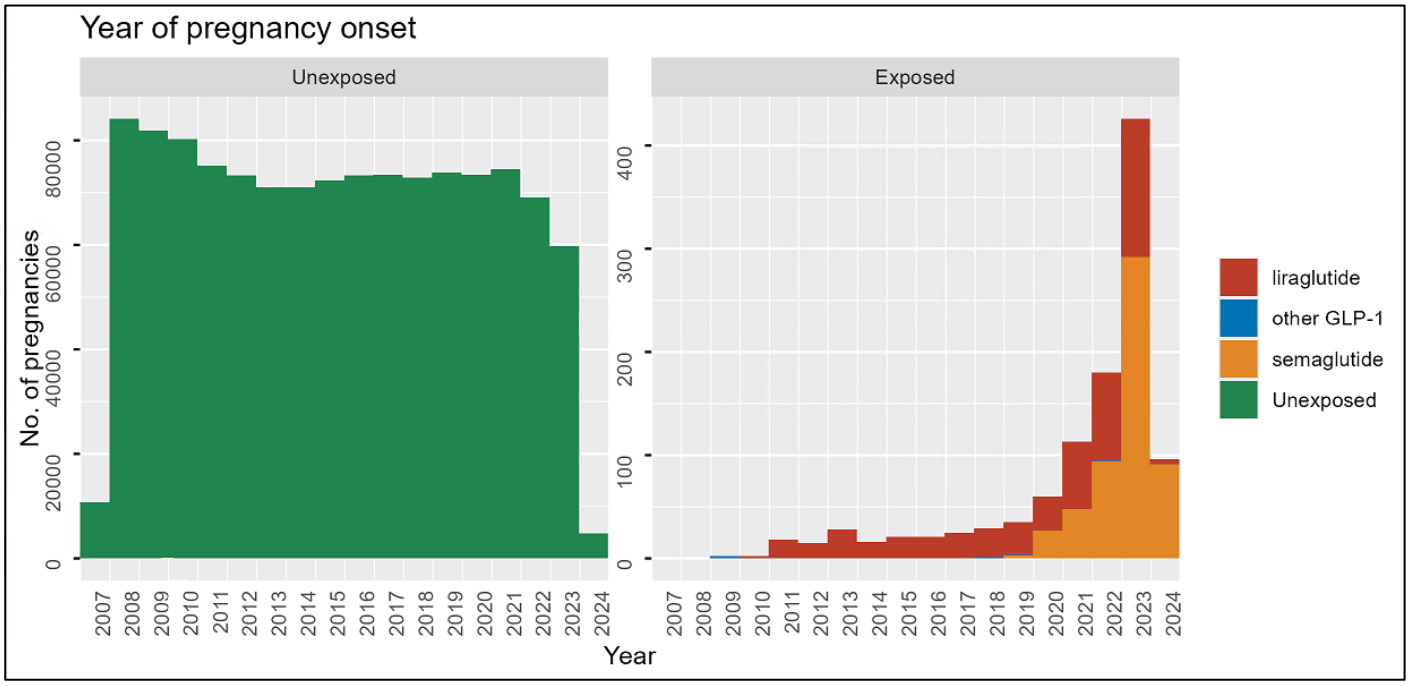
The baseline characteristics in the crude populations before trimming and weighting are provided in Appendix 3, Table 1.

Baseline imbalances between exposed and unexposed pregnancies were especially pronounced for the characteristics outlined below:

- year of pregnancy onset (see Figure 3 below),
- age,
- BMI,
- HbA1c measurements in the year before pregnancy,
- prescriptions in the year before pregnancy of:
    - insulins,
    - glucose-lowering drugs (GLP-1RA excluded),
    - antihypertensive drugs,
    - lipid-modifying drugs.
- Diagnosis code registered in the year before pregnancy:
    - T2D
    - obesity.

As reflected in Figure 3, semaglutide and liraglutide together made up almost 100% of the total exposure. Other GLP-1RAs were very rarely used. The number of exposed pregnancies has been increasing markedly in Denmark over the course of the study period. I.e., from 2018 to 2024, an approximate 14-fold increase in number of exposed pregnancies occurred.

Figure 3. Number of eligible pregnancies per year from 2007-2024 by exposure status, defined as a filled prescription at any time between 90 days prior LMP and in pregnancy.



Propensity score estimation, balance assessment and diagnostics

Few variables contained missing values ranging from 0.0% to 2.2% (Appendix 2, table 2.1). The continuous variables pregnancy year, age at pregnancy onset and BMI, were entered in the PS model as categorical variables. No particular outliers or unexpected observations were identified among the excluded observations in the non-overlap regions. Sufficient balance (SMD <10%) was achieved for all covariates following trimming and weighting.

Figures of the propensity score distributions and covariate balance in the crude populations vs. after trimming and weighting are provided in Appendix 3, section 3.3. The propensity score distributions were extremely different between exposed and unexposed both before and after trimming primarily due to the extreme difference in number of observations in each population, and the resulting lower range of the overlap distribution was always very close to zero. The stoppers vs. users analysis (sensitivity analysis 2) was however exceptionally different, both due to better balance at baseline, and also due to the more comparable number of observations between groups.

Estimation of effect

Table 2 presents the estimated treatment effects for each outcome.

An outcome of major congenital malformation was observed in 7.3% of pregnancies exposed to GLP-1RA vs. in 5.4% in the pseudopopulation used as reference population. This difference was not statistically significant (adjusted prevalence OR, 1.36; 95% CI, 0.88-2.16).

The outcome small for gestational age was observed in 6.0% of pregnancies exposed to GLP-1RA vs. in 6.9% in the adjusted reference population. The difference was not statistically significant (adjusted prevalence OR, 0.86, 95% CI, 0.55-1.34).

Among GLP-1RA exposed pregnancies, 17.1% ended in miscarriage vs. 14.0% in the adjusted reference population. The difference was statistically significant (HR of 1.24, 95% CI, 1.05-1.47).

Table 2. The association between maternal GLP-1RA exposure and the risk of major congenital malformations, miscarriage or small for gestational age. Data are presented as odds ratios (OR) or hazard ratios (HRs) and 95% confidence interval (CI).

	Crude analysis			**Adjusted analysis**		
	No. with outcome/total No. (%)			No. with outcome/total No. (%)		
Out-come	GLP-1RA	Unexposed	Measure of association (95% CI) - unadjusted	GLP-1RA	Pseudo-population, unexposed	Measure of association (95% CI) - adjusted
MCM	51/697 (7.3)	43728/900036 (4.9)	Prevalence OR 1.55 (1.15-2.03)	50/686 (7.3)	18293/339532 (5.4)	Prevalence OR 1.38 (0.88-2.16)
SGA	42/691 (6.1)	81496/895439 (9.1)	Prevalence OR 0.65 (0.47-0.87)	41/680 (6.0)	22635/326651 (6.9)	Prevalence OR 0.86 (0.55-1.34)
Mis-carriage	191/1087 (17.6)	124160/1194328 (10.3)	HR 1.73 (1.48-2.02)	179/1049 (17.1)	7464/53339 (14.0)	HR 1.24 (1.05-1.47)

Multilevel log binomial regression (MCM and SGA) and multilevel cox proportional hazards regression (miscarriage) were adjusted by PS-IPTW. The unexposed pseudopopulation represents the weighted distribution in the unexposed population after each unexposed pregnancy has been weighted according to its unique propensity score value. SGA is defined as birth weight is below the 10th percentile for gestational age and sex.
Abbreviations: HR, hazards ratio; MCM, major congenital malformation; OR, odds ratio; PS-IPTW, propensity score inverse probability of treatment weighting; SGA, small for gestational age.

Sensitivity analyses

The outcomes of the sensitivity analyses are presented in Table 3. Baseline characteristics before and after adjustment, as well as the supporting tables of PS distribution and covariate balance, are provided within Appendixes 4-7.

The percentage of terminations differed between GLP-1RA exposed pregnancies (18.2%) and unexposed pregnancies (14.2%) in the crude population (Table 3, sensitivity analysis 0). This imbalance was more pronounced following the PS-IPTW adjustment which reduced the estimated proportion of terminations to 12.6% among unexposed (Table 3). The difference was statistically significant (HR, 1.49; 95% CI, 1.27-1.75).

When stratifying the pregnancy population according to T2D status (sensitivity analysis 1), the T2D subgroup constituted 1.0% of all pregnancies. The baseline characteristics were more balanced between exposed and unexposed in the T2D subgroup compared to the non-T2D subgroup (refer to Appendix 4). The effect estimates in the T2D subgroup (Table 3) were consistently lower for all outcomes than in the main analysis (Table 2), whereas the effect estimates in the non-T2D subgroup (Table 3) were consistently higher than in the main analysis. Hence, in the T2D subgroup, no outcome effect estimates achieved statistical significance, whereas in the non-T2D subgroup, miscarriage reached statistical significance (HR, 1.34; 95% CI, 1.11-1.60).

When the unexposed comparator population was reduced to include only pregnancies of previous GLP-1RA users who filled their last prescription between 365 and 125 days before a pregnancy occurred, their baseline characteristics resembled the exposed more closely (sensitivity analysis 2, refer to Appendix 5). Before adjustment, imbalance was mainly pronounced with regard to the frequency of prescription of drugs related to *in vitro* fertilisation in the look back period, suggesting higher frequency of infertility treatment among previous GLP-1RA users within the year before pregnancy than GLP-1RA exposed. In this sensitivity analysis, no difference would be found between exposed and unexposed for any of the measured outcomes, neither before, nor after the PS-IPTW adjustment.

Exclusion of prescriptions filled before the start of first trimester from the exposure definition (sensitivity analysis 3) gave overall consistent results compared with the main analysis, except from widened confidence intervals for all outcome analyses, resulting from the reduced number of exposed pregnancies (Table 3).

Leaving out the two covariates smoking and BMI from the PS model for the outcome MCM (sensitivity analysis 4) did not change the effect estimate importantly (in main analysis: OR, 1.38 (95% CI, 0.88-2.16), vs. in sensitive analysis 4: OR, 1.34 (95% CI, 0.87-2.11). Although smoking and BMI was not adjusted for, the remaining covariates still improved the baseline imbalance of smoking and BMI (Appendix 7).

Table 3. Sensitivity analyses. Data are presented as odds ratios (OR) or hazard ratios (HRs) and 95% confidence interval (CI).

	Crude analysis			**Adjusted analysis**		
Outcome	No. with outcome/total No. (%)		Measure of association (95% CI) - unadjusted	No. with outcome/total No. (%)		Measure of association (95% CI) - adjusted
	GLP-1RA	Unexposed		GLP-1RA	Pseudopopulation, unexposed	
Pregnancy population from main analysis						
Termination	198/1087 (18.2)	170133/1194328 (14.2)	HR 1.26 (1.08-1.47)	195/1049 (18.6)	6731/53339 (12.6)	HR 1.49 (1.27-1.75)
Subset of pregnancies of mothers with T2D[a]						

MCM	11/170 (6.5)	593/10264 (5.8)	OR 1.12 (0.57-1.99)	11/168 (6.5)	503/7351 (6.8)	OR 0.95 (0.40-2.28)
SGA[b]	8/170 (4.7)	916/10199 (9.0)	OR 0.50 (0.23-0.96)	8/168 (4.8)	722/7315 (9.9)	OR 0.46 (0.18-1.06)
Miscarriage	45/237 (19.0)	1434/12265 (11.7)	HR 1.76 (1.29-2.42)	41/227 (18.1)	1540/9234 (16.7)	HR 1.05 (0.73-1.52)
Subset of pregnancies of mothers without T2D[a]						
MCM	40/527 (7.6)	43135/889772 (4.8)	OR 1.61 (1.15-2.20)	39/512 (7.6)	23363/462753 (5.0)	OR 1.50 (0.90-2.53)
SGA[b]	34/521 (6.5)	80580/885240 (9.1)	OR 0.70 (0.48-0.97)	34/505 (6.7)	35707/456811 (7.8)	OR 1.02 (0.62-1.68)
Miscarriage	146/850 (17.2)	122726/1182063 (10.4)	HR 1.71 (1.43-2.04)	141/839 (16.8)	34612/268498 (12.9)	HR 1.34 (1.11-1.60)
Pregnancies of GLP-1RA exposed vs. GLP-1RA stoppers[c]						
MCM	51/697 (7.3)	29/357 (8.1)	OR 0.89 (0.56-1.45)	50/689 (7.3)	29/352 (8.2)	OR 1.00 (0.66-1.51)
SGA[b]	42/691 (6.1)	20/354 (5.6)	OR 1.08 (0.63-1.91)	42/683 (6.1)	20/349 (5.7)	OR 1.08 (0.69-1.72)
Miscarriage	191/1087 (17.6)	98/520 (18.8)	HR 0.98 (0.76-1.28)	185/1059 (17.5)	94/513 (18.3)	HR 0.97 (0.73-1.29)
Expoure definition changed to begin at date of LMP instead of LMP -90 days						
MCM	27/357 (7.6)	43752/900376 (4.9)	OR 1.60 (1.06-2.32)	27/334 (8.1)	4959/86952 (5.7)	OR 1.45 (0.79-2.73)
SGA[b]	17/362 (4.7)	81521/895768 (9.1)	OR 0.49 (0.29-0.77)	17/348 (4.9)	5326/80163 (6.6)	OR 0.72 (0.37-1.38)
Miscarriage	95/598 (15.9)	124256/1194817 (10.4)	HR 1.71 (1.39-2.12)	87/580 (15.0)	10945/77675 (14.1)	HR 1.18 (0.94-1.48)
Main MCM outcome analysis repeated without BMI and smoking variables						
MCM	51/697 (7.3)	43728/900036 (4.9)	OR 1.55 (1.15-2.03)	50/676 (7.4)	12505/222937 (5.6)	OR 1.34 (0.87-2.11)

[a]Type 2 diabetes (T2D) was defined as (1) at least one prescription of a glucose-lowering medication (ATC code: A10B) except GLP-1 RA (ATC code: A10BJ) in the year before conception; or (2) a diagnosis of type 2 diabetes (icd-10 code: E11) in the year of conception; or (3) at least one prescription of a GLP-1 RA (ATC code: A10BJ) in the year before conception AND at least one HbA1c measurement above 48 mmol/mol within a year before conception (51,52).
[b]Birth weight is below the 10th percentile for gestational age and sex.
[c]GLP-1RA stoppers were defined as a subgroup among the unexposed who had prior use of GLP-1RA between 365 and 125 days before the day of last menstrual period (LMP).

Discussion

The recent years' rise in the use of GLP-1RA among women in Denmark is mirrored by a proportional increase in the number GLP-1RA exposed pregnancies. Due to the limited knowledge about safety of GLP-1RA in pregnancy, this nationwide study was designed to investigate possible pregnancy and birth related risks associated with GLP-1RA exposure in pregnancy.

The results of this study did not suggest an increased risk of pregnancy and birth related adverse outcomes associated with GLP-1RA exposure during pregnancy, although the uncertainties in the estimates should be considered. A true effect cannot be precluded from this study alone and more research is therefore needed.

For the MCM outcome, the result is overall consistent with a previous study (22) which among women with T2D reported an adjusted relative risk for MCM of 0.95, 95% CI, 0.72-1.26 when compared to insulin users. The effect estimate by Cesta et al. compares well with the subgroup analysis of T2D users in sensitivity analysis 1, which showed an OR of 0.95 (95% CI, 0.40-2.28). Although reassuring, further studies are still needed to exclude the possibility of an association with MCM due to the width of the confidence limits. However, a large true effect of GLP1-RA exposure on the risk of MCM seems less likely on the grounds of these results.

Among overweight and obese women, SGA is usually not a concern due to the positive association between birth weight and maternal BMI (54). However, since SGA is a relevant marker of prenatal adverse effects (55), SGA was a relevant outcome to investigate in the context of this study, although the study did not suggest an increased risk.

To our knowledge, the association between GLP-1RA pregnancy exposure and miscarriage has not been previously investigated in observational studies. Reduced litter size in rat studies was among the preclinical safety findings during drug development, possibly directly associated with the anorexigenic effect of GLP-1RA, and a similar effect could be hypothesised in humans. Although a statistically significant association was achieved for the outcome of miscarriage in the main analysis, further sensitivity analyses indicated a lack of robustness of this result.

Strengths and limitations

This study is one of the earliest to investigate safety of GLP-1RA exposure in pregnancy using nationwide registry data, thus contributing significantly to existing knowledge. However, several limitations should be noted.

Observational research of drug exposures in pregnancy is inherently methodologically challenging, since several assumptions about the studied population and multiple design and analysis choices are usually required (56). Moreover, confounding by indication is a major concern, since T2D (57,58) and high BMI (59) are risk factors for adverse pregnancy and birth outcomes.

A limitation to this study was the inability to apply the standard active comparator new user (ACNU) design. The heterogeneity in the approved indications made it difficult to define a relevant subgroup or a relevant comparator population. An unrestricted pregnancy cohort was instead applied. Inevitably, this resulted in major baseline heterogeneity between exposure and comparator populations, which made the study particularly vulnerable to bias by unmeasured confounding. To accommodate this, the high quality of the Danish nationwide registers was utilised to create a detailed propensity score model from a comprehensive

set of potential risk factors for the outcomes, by which balanced baseline characteristics could be achieved. However, the inconsistency in results between the pre-planned sensitivity analyses and the main analysis suggested that the PS model was unable to account for all confounding present in the unrestricted cohorts.

For instance, when comparing pregnancies of mothers with T2D vs. no T2D (sensitivity analysis 1), the stratum specific effect estimates for all three studied outcomes were different from each other and placed on each side of the original effect estimates from the main analysis. Usually, a pattern like this would suggest effect modification by the stratifying variable, i.e. by indication. Since higher doses are generally recommended for the substances approved in the obesity/overweight indication (20,21) compared with the T2D indication (16,19) a dose-response relationship between GLP-1RA and risk of miscarriage could be the putative underlying explanation. However, acknowledging the different degrees of heterogeneity between subgroups, another explanation might be that unmeasured confounding and residual confounding was more pronounced within the more heterogenous and less well-defined population constituted by non-T2D pregnancies.

Moreover, the putative association between GLP-1RA exposure and miscarriage could not be confirmed when the GLP-1RA exposed pregnancies were compared to pregnancies of previous GLP-1RA users (sensitivity analysis 2). This analysis is particularly noteworthy due to the improved clinical equipoise at baseline than in the main analysis, which reduces the likelihood for unmeasured and residual confounding.

Pregnancy terminations occurred more frequently among GLP-1RA exposed pregnancies than unexposed, possibly reflecting a greater proportion of unplanned pregnancies among GLP-1RA users who may have become unintentionally pregnant. This observation violates the cox-PH model assumption of non-informative censoring. The resulting bias could theoretically lead towards an underestimated effect estimate of miscarriage, since a pregnancy termination would technically prevent a pregnancy from developing into a potential miscarriage.

Taken together, these sensitivity analyses revealed problems with the validity of the unrestricted study design.

The study excluded pregnancies exposed to known teratogenic substances and pregnancies with malformations of known cause to improve precision of the results. Although the number of excluded cases was negligible (0.2% for teratogenic exposure and 0.3% for malformations of known cause) (60), these exclusion criteria may limit the generalisability of the results to the general pregnancy population. Other factors limited the generalisability of the results further, i.e. the exclusion of non-overlapping regions of the PS distribution, and the application of weights defined by the ATT estimand. Indeed, the research question

was not focused on representativeness but on causal inference, and generalisability was therefore not of concern (61).

Some confounders could introduce bias when adjusted for in the PS model. For instance, high gravidity (i.e. captured by the variable parity) and recurrent risk of an outcome (captured by the variables: prior risk of MCM, miscarriage or SGA) are associated with increased risk of adverse outcomes, but conversely, past pregnancy experience may affect the desire for a new pregnancy (55,62,63). To counteract these potential biases, hierarchical multilevel modelling was applied at the maternal level (55,63).

Smoking and BMI characteristics were not available for the miscarriage outcome analysis, however a sensitivity analysis showed only little impact if excluding them from the PS model for the MCM outcome, possibly reflecting shared common causal pathways with some of the other included covariates.

Laboratory measurements of HbA1c were included as a proxy for diabetes, and high correlation with GLP-1RA use was indeed evident from this study. The adjustment for HbA1c measurements as a potential confounder could however be controversial, since the causal arrow points in both directions. I.e., as soon as GLP-1RA therapy is considered, the patient could be more likely to get an HbA1c measurement prior to starting therapy, and the HbA1c value could likewise impact on the final treatment decision. GLP-1RA treatment may also cause patients to have regular HbA1c measurements. Chronological and geographical completeness of the laboratory register was also not accounted for in this study.

Wald estimation was used to compute the confidence intervals for the effect estimates, but other more robust approaches exist, for example estimation by bootstrapping. Bootstrapping was not pursued within this study since it was computationally intensive.

The incomplete 1-year follow up of MCM after birth is a source of potential of information bias for the births occurring in the year before the end of the study period in case some MCM diagnoses have been registered later than at time of birth. The impact of this decision was not further investigated, but since proportionately more GLP-1RA exposed neonates were born towards the end of the study period, the possible bias could possibly underestimate the effect estimate.

Lastly, this study has important limitations by time constraints. A coding error caused all pregnancies before 2019 with “smoking unknown” to be wrongly assigned to the smoker’s category, which needs to be corrected before further dissemination of these results, and in addition, the R code should be reviewed by a second reviewer to eliminate the likelihood of similar coding errors. The impact of the error in the smoking variable was considered as minor, since it only applied to pregnancies before 2019 and since a

sensitivity analysis confirmed that dropping smoking and BMI variables did not change the effect estimate of the MCM outcome.

Pre-planned sensitivity analyses not pursued

A sensitivity analysis had originally been specified to stratify the study population by date of first approval of the obesity indication (i.e. 23-03-2015), but due to only few exposed pregnancies before 2015, this analysis was not feasible. Moreover, it had been planned to compare the subgroup of stoppers with the remaining comparator group. This analysis was carried out, but on further reflection it was difficult to interpret meaningfully in context of the research question, and the results are therefore not further pursued in this report.

Future research directions

Further studies are needed before a pregnancy and birth related risk related by GLP-1RA exposure can be possibly excluded. Over time, more pregnancy information will be accrued within registries, and it will be important to utilise this growing amount of data to improve the precision of estimates. Over time, alternative treatments with comparable effectiveness may also become available in the weight management indication to enable conduct of ACNU designs, which means that some of the design challenges in this study can be solved over time.

Pack sizes and medication strengths were not considered in this study, but could be considered for future studies in order to investigate a possible dose-response relationship between GLP-1RA and risk of adverse pregnancy and birth outcomes. Future studies should also consider pregnancy termination as a competing risk to miscarriage.

Conclusion

The results of this study on Danish nationwide data did not suggest an increased risk from GLP-1RA exposure on the pregnancy and birth related outcomes MCM, SGA and miscarriage. Although these results are essentially reassuring for a growing population at risk, the imprecise estimates and the important study limitations warrant further research before the possibility of adverse pregnancy and birth effects can be fully excluded.

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Appendices

Table of contents

Appendix 1. Definitions

Table 1.1 Definition and data sources of the variables included in the study

Variable	Definition	Data source
Maternal/pregnancy characteristics at pregnancy onset		
Year of pregnancy	<2016, 2016-2019, 2020-2023	The Danish national Patient Registry (NPR)
Age at pregnancy onset	<20, 20-24, 25-29, 30-34, >35	The Danish Civil Registration System (CRS)
Smoking	yes/no. Yes: SKS codes DUT10-11 and 20-29; RGAB10-11 and 20-29. No: DUT00 and RGAB00. Status unknown: DUT99[4] and RGAB99 and "." or "NA".	The Danish Medical Birth Register (MBR)
BMI, kg/m2	<20, 20-25, 25-30, >35	MBR
Blood glucose, mmol/L	NPU02192, NPU02195	The Clinical Laboratory Information Register (CLIR)
HbA1c, mmol/mol	NPU2730	CLIR
Parity	Derived from the MFR parity variable -1, from 1997 onwards. Women without previous births in MFR were assigned with the value 0.	MBR
Prior MCM	Derived from the data available from 1997 and onwards	MBR
Prior SGA	Derived from the data available from 1997 and onwards	MBR
Prior miscarriage	Derived from the data available from 1997 and onwards	MBR
Married	Defined as married when C_CIVSTD: G or P.	CRS
Maternal place of birth	Denmark, Europe, outside Europe	CRS
Region of residence	Capital Region of Denmark, Region Zealand, Southern Denmark, Central Denmark Region, North Denmark	NPR
Season of conception	Winter, spring, summer, autumn	NPR
Maternal drug use and co-morbidity		
Prescription of drugs within 1 year of pregnancy onset	***ATC-codes***	
Antiobesity preparations	A08A	Danish National Prescription Registry (DNPR)
Insulins and analogues	A10A	DNPR
Antidiabetics	A10B (excluding A10BJ)	DNPR
Antihypertensives	C02, C03, C07, C08, C09	DNPR
Lipid-modifying drugs	C10	DNPR
Drugs used in IVF treatment	G03G, G03DA, G03XA, H01AA, H01CA, H01CC, LA02AE	DNPR
Glucocorticoids	H02AB, H02B	DNPR
Drugs for underactive thyroid	H03AA	DNPR
Systemic antiinfective drugs[1]	J01-J05	DNPR
NSAIDs[1]	M01A, excluding M01AX	DNPR
Opioids[1]	N02A	DNPR
Antimigraine drugs	N02C	DNPR
Antiepileptics	N03	DNPR
Antipsychotics	N05A	DNPR
Anxiolytics	N05B	DNPR
Hypnotics	N05C	DNPR
Antidepressants	N06A, N06C	DNPR
Psychostimulants	N06B	DNPR
Drugs for obstructive airway diseases	R03	DNPR
No. of unique drugs prescribed	Derived from the drug classes listed above	DNPR

Variable	Definition	Data source
Comorbidities		
Diagnosis within 1 year of pregnancy onset	**ICD-10 codes**	
Thyroid disorders	E00-E07	NPR
Diabetes Type 1	E109, E109A	NPR
Diabetes Type 2	E11	NPR
PCOS	E282, N970	NPR
Obesity	E66, E68	NPR
Alcohol abuse	F10	
Drug abuse	F11-F19	
Mood [affective] disorders	F30-F39	NPR
Neurotic, stress-related and somatoform disorders	F40-F48	NPR
Behavioural syndromes associated with physiological disturbances and physical factors	F50-F59	NPR
Hypertension	I10-I15	NPR
Ischaemic heart diseases	I21-I25	NPR
Asthma	J45	NPR
No. of hospital admissions	In LPR2: C_PATTYPE: 0. In LPR3: PROCEDUREKODE: AAF1, AAF11, AAF12, AAF14, AAF16	NPR
No. of outpatient visits	In LPR2: C_PATTYPE: 2 but not with C_INDM: 1. In LPR3: PROCEDUREKODE: AAF3, AAF3	NPR
Outcomes and related variables		
(For MCM, see separate table)		MFR
SGA	Birth weight below the 10-percentile of sex- and completed gestational week-specific mean (calculated from the dataset). SGA was set to missing when values for birth weight were missing.	MFR
Miscarriage	O021, O03	NPR
Termination	O04, O05, O06	NPR
Exclusion criteria		
Teratogenic substances (from Cesta et al., 2023)		
Warfarin[2]	B01AA03	DNPR
Antineoplastic drugs[2]	L01DA	DNPR
	L01AB01	DNPR
	L01AA02	DNPR
	M04AC01	DNPR
	L01AA01	DNPR
	L01DB01	DNPR
	L01BB02	DNPR
	L01BA01	DNPR
	L04AX03	DNPR
	L01CA01	DNPR
	L01CA02	DNPR
Lithium[2]	N05AN01	DNPR
Topical or systemic retinoids, including isotretinoin[2]	D10BA01	DNPR
	D10AD54	DNPR
	D10BA04	DNPR
	D05BB	DNPR

Variable	Definition	Data source
	D11AH04	DNPR
Misoprostol[3]	A02BB01	DNPR
	G02AD06	DNPR
	M01AE56	DNPR
	M01AB55	DNPR
Thalidomide[2]	L04AX02	DNPR
Valproic acid[2]	N03AG01	DNPR
Other		
Any pregnancy of a woman who has an invalid personal identifier (an invalid CRS number)		CRS
Any pregnancy of a woman who was not a resident of Denmark 12 months prior to LMP.		CRS
Any pregnancy with missing information on gestational age.		NPR/MBR

[1]For antiinfectives and NSAIDS, a look-back period of 30 days was used. For opioids, a look back period of 90 days was used.

[2]Prescription filled between LMP date to pregnancy end date, both dates inclusive.

[3]In Denmark, misoprostol is approved for induction of labour and termination of pregnancy. To ensure that pregnancies were only excluded when prescriptions for misoprostol were timely unrelated to the pregnancy end date, the exposure definition for misoprostol was adjusted to prescriptions filled between LMP date to 7 days prior the pregnancy end date, both dates inclusive.

[4]Note that an error was discovered in the coding of the smoking variable: DUT99 was erroneously classified as smoking, in the study. Since DUT codes were in use until 2019, the error impacts only on the data before 2019. This error needs to be corrected at first coming opportunity.

Table 1.2 Overview of EU-approved GLP-1RA medicines.

MA date	Date of with-drawal	Product name	INN	ATC code	Formulation	Pack sizes[1]	Recommended posology	MAH	Indication
20-11-2006	NA	Byetta	exenatide	A10BJ01	Prefilled pens that provide either 5 or 10 micrograms of exenatide in each dose. For s.c. injection.	1 and 3 pens	5-10 mg s.c. twice daily	AstraZeneca	Diabetes Mellitus, Type 2
30-06-2009	NA	Victoza	liraglutide	A10BJ02	pre-filled pens (6 mg/ml). One pre-filled pen contains 18 mg liraglutide in 3 ml, hence contains 30 doses of 0.6 mg, 15 doses of 1.2 mg or 10 doses of 1.8 mg.	1, 2, 3, 5 and 10 pens.	0.6-1.8 mg s.c. once daily	Novo Nordisk A/S	Diabetes Mellitus, Type 2
17-06-2011	NA	Bydureon	exenatide	A10BJ01	2 mg powder and solvent for prolonged-release suspension for s.c. injection	1 pack of 4 single-dose kits and 3 packs of 4 single-dose kits	2mg s.c. once weekly	AstraZeneca	Diabetes Mellitus, Type 2
01-02-2013	NA	Lyxumia	lixisenatide	A10BJ03	Prefilled pens (10-20 mcg solutions)	10 mcg solutions: 1 pen. 20 mcg solution: 1, 2, and 6 pens.	10-20 mcg s.c. once daily	Sanofi Winthrop Industrie	Diabetes Mellitus, Type 2
21-03-2014	29-10-2018[2]	Eperzan	albiglutide	A10BJ04	30 mg or 50 mg powder and solvent for solution for s.c. injection	Packs of 4 pens, and multipacks containing 3 packs with 4 pens in each.	30-50 mg once weekly	GlaxoSmithKline Trading Services Limited	Diabetes Mellitus, Type 2
21-11-2014	NA	Trulicity	dulaglutide	A10BJ05	prefilled pens (solutions: 0.75 mg, 1.5 mg, 3 mg, 4.5 mg)	Pack sizes of 2, 4 or multipacks of 12 (3 packs of 4) pre-filled pens.	0.75-4.5 mg s.c. once weekly.	Eli Lily	Diabetes Mellitus, Type 2
23-03-2015	NA	Saxenda	liraglutide	A10BJ02	Pre-filled pens, contains 18 mg liraglutide in 3 ml.	1, 3, and 5 pens.	0.6-3.0 mg s.c. once daily	Novo Nordisk A/S	Obesity and overweight
08-02-2018	NA	Ozempic	semaglutide	A10BJ06	Prefilled pens (0.25-2 mg solutions)	1 and 3 pens.	0.25-1 mg s.c. once weekly	Novo Nordisk A/S	Diabetes Mellitus
03-04-2020	NA	Rybelsus	semaglutide	A10BJ06	Tablets (3, 7 and 14 mg)	Pack sizes of 10, 30, 60, 90 and 100 tablets.	3-14 mg p.o. once daily	Novo Nordisk A/S	Diabetes Mellitus, Type 2
06-01-2022	NA	Wegovy	semaglutide	A10BJ06	Prefilled pens (0.25-2.4 mg solutions), 4 doses per pen	1 pen: all solutions. 3 pens: 2.5 mg solution.	0.25-2.4 mg s.c. once weekly	Novo Nordisk A/S	Obesity and overweight

Abbreviations: ATC: anatomical therapeutic classification, INN: international non-proprietary name, MA date: marketing authorisation date, MAH: marketing authorisation holder, NA: not applicable.

[1]*Approved pack sizes according to the product information. Not all pack sizes may have been available in Denmark.*

[2]*Note that Eperzan is no longer authorised in the EU.*

Table 1.3. Definition of major congenital malformations

		Definitions		Exceptions	
	Type of malformation	**ICD-10 codes**	**Additional DK-specific codes[1]**	**ICD-10 codes**	**Additional DK-specific codes[1]**
1	Nervous system anomalies	Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07, Q8703		Q0461, Q0780, Q0782	Q078G
2	**Eye anomalies**	Q10-Q15		Q101-Q103, Q105, Q135	
3	**Ear, face and neck anomalies**	Q16, Q17, Q18		Q170-Q175, Q179, Q180- Q182, Q184- Q187, Q1880, Q189	
4	**Congenital Heart Defects**	Q20-Q26		Q2111, Q246, Q2541, Q261. *If GA <37 weeks:* Q250, Q256.	Q211C, Q354E
5	Respiratory anomalies	Q300, Q32-Q34		Q320, Q322, Q3300, Q331, Q336	
6	Oro-facial clefts	Q35-Q37		Q357. *If occurring with Q042:* Q35-Q37	
7	Gastro-intestinal anomalies	Q38-Q45, Q790		Q381, Q382, Q3850, Q400, Q401, Q4021, Q430, Q4320, Q4381, Q4382, Q444, Q4583. *If occurring with Q792-Q793:* Q411-Q418, Q433	Q458B, Q385B
8	**Abdominal wall defects**	Q792, Q793, Q795			
9	Congenital anomalies of kidney and urinary tract (CAKUT)	Q60-Q64, Q794		Q610, Q627, Q633. *If occurring with Q627 or Q00 or Q01 or Q05:* Q620-Q623	
10	Genital anomalies	Q50-Q52, Q54- Q56		Q523, Q525, Q527, Q5520, Q5521, Q501, Q502, Q505, Q544	Q552F, Q552B
11	Limb anomalies	Q65-Q74		Q653-Q656, Q662-Q669, Q670-Q678, Q680, Q6810, Q6821, Q683- Q685, Q7400, Q658, Q659, Q661. *If occurring with Q00 or Q01 or Q05:* Q660, Q650-Q652.	Q682A, Q740G
12	**Other anomalies / syndromes**:				
	Craniosynostosis	Q750			
	Congenital constriction bands / amniotic band sequence resulting in major malformations	Q7980	Q798S	Q code of major malformation must be present for Q7980.	Q code of major malformation must be present for Q798S
	Situs inversus	Q893			
	Conjoined twins	Q894			
	VATER/VACTERL association	Q8726			
	Pierre-Robin sequence	Q8708	Q870G		
	Caudal regression sequence	Q8980			
	Sirenomelia	Q8724	Q872G		

		Definitions		Exceptions	
	Type of malformation	**ICD-10 codes**	**Additional DK-specific codes[1]**	**ICD-10 codes**	**Additional DK-specific codes[1]**
	Septo-optic dysplasia	Q044			
	Vascular disruption anomalies	Q0435, Q411, Q412, Q418, Q710, Q712, Q7180, Q720, Q722, Q7280, Q730, Q793, Q7980, Q7982, Q8706		Q code of major malformation must be present for Q7980.	Q code of major malformation must be present for Q798S
	Laterality anomalies	Q206, Q240, Q3381, Q890, Q893			
X	Teratogenic syndromes resulting in major malformations	Q86, P350, P351, P354, P358, P371			
	Valproate syndrome	Q8680			
	Chromosomal anomalies	Q90-Q93, Q96-Q99			Q936
	Genetic disorders (genetic syndromes, hereditary skin disorders, skeletal dysplasias)	D821, Q4471, Q6190, Q7402, Q7484, Q751, Q754, Q7581, Q77, Q780- Q789, Q796, Q800-Q824, Q8282, Q8283, Q850, Q851, Q8581, Q87, Q8934	Q447B, Q619A, Q740B, Q936		Q870D, Q870F, Q870G, Q870I, Q872E, Q872G
	Any MCM	Any of the subgroups 1-12, excluding those in subgroup X.			

Major malformations according to EUROCAT 1.5 classification system (1). Information on major malformations was obtained from the Medical Birth Registry. We excluded pregnancies with malformations of known causes (subgroup X).

(1) EUROCAT. Guide 1.5. Chapters 3.2 and 3.3. https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/eurocat/Guide_1.5_Chapter_3.2.pdf and https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/eurocat/Guide_1.5_Chapter_3.3.pdf

[1]Broe, A., Damkier, P., Pottegård, A., Hallas, J., Bliddal, M., 2020. Congenital Malformations in Denmark: Considerations for the Use of Danish Health Care Registries. CLEP Volume 12, 1371–1380. https://doi.org/10.2147/CLEP.S278596

Appendix 2. Missing values

Table 2.1. The missing values (n, %) for the untrimmed, unweighted cohorts

	Major congenital malformations/SGA[1]			Miscarriage		
	No. (%) of pregnancies			No. (%) of pregnancies		
	Total, N = 900 733	Unexposed, N = 900 036	GLP-1 RA users, N = 697	Total, N = 1 195 415	Unexposed, N = 1 194 328	GLP-1 RA users, N = 1 087
Covariates						
Maternal age	0	0	0	<5 (0.0)	<5 (0.0)	0
Smoking	7 465 (0.8)	7 450 (0.8)	15 (2.2)	NA	NA	NA
BMI	20 169 (2.2)	20 160 (2.2)	9 (1.3)	NA	NA	NA
Civil status (married/defacto)	20 (0.0)	20 (0.0)	0	32 (0.0)	32 (0.0)	0
Place of birth	0	0	0	<5 (0.0)	<5 (0.0)	0
Outcome variables						
Birthweight of child[2]	4 603 (0.5)	4 596 (0.5)	7 (1.0)	NA	NA	NA

Abbreviations: BMI, body mass index; NA, not applicable.
[1]Note that the SGA population had a single extra exposed pregnancy compared to the MCA population (i.e. N = 698 and N = 900 035 exposed and unexposed pregnancies, respectively) but the missing values of the two populations were otherwise identical and have been merged for the sake of overview.
[2]Pregnancies with missing or implausible birthweight was excluded from the SGA outcome analysis.

Appendix 3. Main analysis

3.1. Baseline population characteristics

Appendix table 1. Baseline characteristics before trimming and IPTW, main analysis.

	Major congenital malformations[a]			Small for gestational age (SGA)[a]			Miscarriage/spontaneous abortion		
	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference
	Unexposed, N = 900 036	GLP-1 RA users, N = 697		Unexposed, N = 895 439	GLP-1 users, N = 691		Unexposed, N = 1 194 328	GLP-1 RA users, N = 1 087	
Maternal/pregnancy characteristics									
Year of pregnancy onset[b]									
<2016	482269 (53.6)	69 (9.9)	-1.063	479041 (53.5)	69 (10)	-1.057	659638 (55.2)	109 (10)	-1.100
2016-2019	229984 (25.6)	108 (15.5)	-0.251	229327 (25.6)	107 (15.5)	-0.253	293223 (24.6)	138 (12.7)	-0.308
2020-2023	187783 (20.9)	520 (74.6)	1.276	187071 (20.9)	515 (74.5)	1.273	241467 (20.2)	840 (77.3)	1.390
Multipregnancy	17177 (1.9)	14 (2.0)	0.007	16939 (1.9)	14 (2)	0.010	17509 (1.5)	14 (1.3)	-0.015
Age at pregnancy onset, years									
<20	13548 (1.5)	0 (0)	-0.175	13446 (1.5)	0 (0)	-0.175	Redacted	<5	Redacted
20-24	108364 (12)	46 (6.6)	-0.188	107793 (12)	46 (6.7)	-0.186	163996 (13.7)	85 (7.8)	-0.192
25-29	317134 (35.2)	195 (28)	-0.157	315711 (35.3)	192 (27.8)	-0.161	384866 (32.2)	264 (24.3)	-0.177
30-34	306510 (34.1)	258 (37)	0.062	304983 (34.1)	255 (36.9)	0.059	374540 (31.4)	400 (36.8)	0.115
≥35	154480 (17.2)	198 (28.4)	0.270	153506 (17.1)	198 (28.7)	0.277	227908 (19.1)	336 (30.9)	0.276
Smoking	102128 (11.3)	95 (13.6)	0.069	101459 (11.3)	94 (13.6)	0.069	Missing	Missing	Missing
BMI (kg/m^2)									
<20	112004 (12.4)	0 (0)	-0.533	111424 (12.4)	0 (0)	-0.533	Missing	Missing	Missing
20-25	459661 (51.1)	40 (5.7)	-1.163	457260 (51.1)	39 (5.6)	-1.167	Missing	Missing	Missing
25-30	203295 (22.6)	130 (18.7)	-0.097	202334 (22.6)	127 (18.4)	-0.105	Missing	Missing	Missing
30-35	80230 (8.9)	230 (33)	0.619	79800 (8.9)	227 (32.9)	0.616	Missing	Missing	Missing
>35	44846 (5)	297 (42.6)	0.985	44621 (5)	298 (43.1)	0.997	Missing	Missing	Missing
Parity at pregnancy onset[c]									
0	410926 (45.7)	294 (42.2)	-0.070	408656 (45.6)	293 (42.4)	-0.065	546947 (45.8)	429 (39.5)	-0.128
1	338390 (37.6)	261 (37.4)	-0.003	336873 (37.6)	255 (36.9)	-0.015	413719 (34.6)	370 (34)	-0.013
2	114851 (12.8)	96 (13.8)	0.030	114258 (12.8)	97 (14)	0.038	170598 (14.3)	198 (18.2)	0.107
≥3	35869 (4)	46 (6.6)	0.117	35652 (4)	46 (6.7)	0.119	63064 (5.3)	90 (8.3)	0.120
Prior registered miscarriages									
None	776416 (86.3)	567 (81.3)	-0.134	772507 (86.3)	564 (81.6)	-0.127	1030400 (86.3)	865 (79.6)	-0.179
1	103012 (11.4)	100 (14.3)	0.087	102431 (11.4)	97 (14)	0.078	134877 (11.3)	171 (15.7)	0.130
≥2	20608 (2.3)	30 (4.3)	0.113	20501 (2.3)	30 (4.3)	0.115	29051 (2.4)	51 (4.7)	0.122
Previous SGA outcome[d]	55257 (6.1)	32 (4.6)	-0.069	54953 (6.1)	32 (4.6)	-0.067	77421 (6.5)	54 (5)	-0.065
Previous MCM outcome[d]	27452 (3.1)	40 (5.7)	0.131	27320 (3.1)	40 (5.8)	0.133	36710 (3.1)	64 (5.9)	0.136
Married/registered partnership	370151 (41.1)	302 (43.3)	0.045	368306 (41.1)	299 (43.3)	0.043	458066 (38.4)	440 (40.5)	0.043
Maternal place of birth									

Denmark	753883 (83.8)	600 (86.1)	0.065	750086 (83.8)	597 (86.4)	0.074	999590 (83.7)	919 (84.5)	0.023
Europe	69670 (7.7)	30 (4.3)	-0.145	69299 (7.7)	30 (4.3)	-0.143	90052 (7.5)	57 (5.2)	-0.094
Outside of Europe	76483 (8.5)	67 (9.6)	0.039	76054 (8.5)	64 (9.3)	0.027	104686 (8.8)	111 (10.2)	0.049
Region of residence									
The Capital Region	269847 (30)	262 (37.6)	0.161	268236 (30)	257 (37.2)	0.154	355692 (29.8)	371 (34.1)	0.093
Central Denmark	215060 (23.9)	146 (20.9)	-0.071	214206 (23.9)	146 (21.1)	-0.067	284535 (23.8)	236 (21.7)	-0.05
Northern Denmark	101225 (11.2)	66 (9.5)	-0.058	100620 (11.2)	66 (9.6)	-0.055	135727 (11.4)	120 (11)	-0.01
Region Zealand	113052 (12.6)	101 (14.5)	0.056	112422 (12.6)	99 (14.3)	0.052	153890 (12.9)	176 (16.2)	0.094
Southern Denmark	200852 (22.3)	122 (17.5)	-0.121	199955 (22.3)	123 (17.8)	-0.113	264484 (22.1)	184 (16.9)	-0.132
Season of conception									
Winter	222156 (24.7)	201 (28.8)	0.094	221176 (24.7)	200 (28.9)	0.096	293289 (24.6)	265 (24.4)	-0.004
Spring	215367 (23.9)	210 (30.1)	0.140	214043 (23.9)	205 (29.7)	0.13	286915 (24)	306 (28.2)	0.094
Summer	221711 (24.6)	115 (16.5)	-0.202	220469 (24.6)	115 (16.6)	-0.198	296958 (24.9)	246 (22.6)	-0.052
Autumn	240802 (26.8)	171 (24.5)	-0.051	239751 (26.8)	171 (24.7)	-0.046	317166 (26.6)	270 (24.8)	-0.039
Plasma glucose ≥11.0 mmol/L									
Yes	157 (0)	10 (1.4)	0.168	156 (0)	10 (1.4)	0.168	246 (0)	14 (1.3)	0.158
No	26896 (3)	38 (5.5)	0.123	26758 (3)	38 (5.5)	0.125	36729 (3.1)	55 (5.1)	0.101
Not measured	872983 (97)	649 (93.1)	-0.180	868525 (97)	643 (93.1)	-0.182	1157353 (96.9)	1018 (93.7)	-0.154
HbA1c ≥48.0 mmol/mol									
Yes	2876 (0.3)	151 (21.7)	0.726	2854 (0.3)	151 (21.9)	0.73	3941 (0.3)	213 (19.6)	0.679
No	112539 (12.5)	350 (50.2)	0.890	112069 (12.5)	345 (49.9)	0.882	146980 (12.3)	556 (51.1)	0.918
Not measured	784621 (87.2)	196 (28.1)	-1.459	780516 (87.2)	195 (28.2)	-1.487	1043407 (87.4)	318 (29.3)	-1.459
No. of hospital admissions within 1 year of pregnancy onset									
None	774880 (86.1)	646 (92.7)	0.215	771008 (86.1)	641 (92.8)	0.218	1016340 (85.1)	1007 (92.6)	0.242
1	99216 (11)	36 (5.2)	-0.216	98643 (11)	36 (5.2)	-0.214	139175 (11.7)	56 (5.2)	-0.236
≥2	25940 (2.9)	15 (2.2)	-0.047	25788 (2.9)	14 (2)	-0.055	38813 (3.2)	24 (2.2)	-0.064
No. of outpatient visits within 1 year of pregnancy onset									
None	611442 (67.9)	489 (70.2)	0.048	608424 (67.9)	486 (70.3)	0.052	801148 (67.1)	766 (70.5)	0.073
1	156480 (17.4)	87 (12.5)	-0.138	155643 (17.4)	87 (12.6)	-0.135	210241 (17.6)	134 (12.3)	-0.148
2	71562 (8)	43 (6.2)	-0.070	71140 (7.9)	42 (6.1)	-0.073	97800 (8.2)	67 (6.2)	-0.079
≥3	60552 (6.7)	78 (11.2)	0.157	60232 (6.7)	76 (11)	0.151	85139 (7.1)	120 (11)	0.136
Prescription of drugs within 1 year of pregnancy onset									
Antiobesity preparations	2196 (0.2)	10 (1.4)	0.131	2176 (0.2)	10 (1.4)	0.132	3185 (0.3)	20 (1.8)	0.155
Insulins and analogues	2286 (0.3)	59 (8.5)	0.411	2258 (0.3)	59 (8.5)	0.413	3131 (0.3)	79 (7.3)	0.374
Antidiabetics, excl. GLP-1 RA	9935 (1.1)	142 (20.4)	0.655	9873 (1.1)	142 (20.5)	0.659	11768 (1)	200 (18.4)	0.616
Antihypertensives	13194 (1.5)	50 (7.2)	0.284	13109 (1.5)	50 (7.2)	0.286	18675 (1.6)	86 (7.9)	0.302
Lipid-modifying drugs	2034 (0.2)	41 (5.9)	0.333	2021 (0.2)	41 (5.9)	0.335	2929 (0.2)	74 (6.8)	0.362
Drugs used in IVF treatment	67237 (7.5)	72 (10.3)	0.101	66826 (7.5)	72 (10.4)	0.104	79139 (6.6)	89 (8.2)	0.060
Glucocorticoids	15107 (1.7)	24 (3.4)	0.112	15031 (1.7)	24 (3.5)	0.113	20121 (1.7)	37 (3.4)	0.109
Drugs for underactive thyroid	12825 (1.4)	24 (3.4)	0.131	12742 (1.4)	24 (3.5)	0.133	16143 (1.4)	42 (3.9)	0.158
Antimigraine drugs	18192 (2)	30 (4.3)	0.131	18102 (2)	30 (4.3)	0.132	23834 (2)	57 (5.2)	0.175

Antiepileptics	5144 (0.6)	9 (1.3)	0.075	5105 (0.6)	9 (1.3)	0.076	7805 (0.7)	20 (1.8)	0.107
Antipsychotics	6707 (0.7)	12 (1.7)	0.089	6666 (0.7)	12 (1.7)	0.09	12001 (1)	28 (2.6)	0.119
Anxiolytics	7162 (0.8)	7 (1.0)	0.022	7127 (0.8)	7 (1)	0.023	11166 (0.9)	16 (1.5)	0.049
Hypnotics	11835 (1.3)	27 (3.9)	0.161	11761 (1.3)	27 (3.9)	0.163	18314 (1.5)	39 (3.6)	0.130
Antidepressants	37362 (4.2)	72 (10.3)	0.240	37175 (4.2)	72 (10.4)	0.243	57067 (4.8)	124 (11.4)	0.245
Psychostimulants	4115 (0.5)	6 (0.9)	0.050	4097 (0.5)	6 (0.9)	0.051	7343 (0.6)	15 (1.4)	0.077
Drugs for obstructive airway diseases	32086 (3.6)	39 (5.6)	0.097	31900 (3.6)	39 (5.6)	0.099	43198 (3.6)	62 (5.7)	0.099
Antiinfectives	42055 (4.7)	43 (6.2)	0.066	41849 (4.7)	43 (6.2)	0.068	58920 (4.9)	70 (6.4)	0.065
NSAIDs	12293 (1.4)	25 (3.6)	0.143	12237 (1.4)	24 (3.5)	0.137	16989 (1.4)	45 (4.1)	0.166
Opioids	9317 (1)	18 (2.6)	0.116	9278 (1)	18 (2.6)	0.118	13825 (1.2)	28 (2.6)	0.105
No. of drugs prescribed									
None	667511 (74.2)	317 (45.5)	-0.612	664195 (74.2)	312 (45.2)	-0.619	881073 (73.8)	506 (46.6)	-0.579
1-2 drugs	217752 (24.2)	296 (42.5)	0.395	216564 (24.2)	295 (42.7)	0.4	291333 (24.4)	442 (40.7)	0.353
3-4 drugs	13631 (1.5)	73 (10.5)	0.384	13546 (1.5)	73 (10.6)	0.387	20065 (1.7)	115 (10.6)	0.378
≥5 drugs	1142 (0.1)	11 (1.6)	0.158	1134 (0.1)	11 (1.6)	0.159	1857 (0.2)	24 (2.2)	0.191
Diagnosis within 1 year of pregnancy onset									
Diabetes Type 1	1237 (0.1)	21 (3.0)	0.232	1225 (0.1)	21 (3)	0.234	1722 (0.1)	25 (2.3)	0.197
Diabetes Type 2	568 (0.1)	67 (9.6)	0.457	564 (0.1)	67 (9.7)	0.459	831 (0.1)	88 (8.1)	0.414
PCOS	5078 (0.6)	26 (3.7)	0.220	5055 (0.6)	26 (3.8)	0.221	6066 (0.5)	31 (2.9)	0.183
Obesity	16945 (1.9)	89 (12.8)	0.427	16861 (1.9)	89 (12.9)	0.43	23196 (1.9)	123 (11.3)	0.384
Thyroid disorders	8204 (0.9)	15 (2.2)	0.101	8159 (0.9)	15 (2.2)	0.102	10356 (0.9)	21 (1.9)	0.091
Mood [affective] disorders	2143 (0.2)	10 (1.4)	0.132	2128 (0.2)	10 (1.4)	0.133	3518 (0.3)	17 (1.6)	0.133
Neurotic, stress-related and somatoform disorders	3625 (0.4)	15 (2.2)	0.156	3611 (0.4)	15 (2.2)	0.157	6126 (0.5)	27 (2.5)	0.163
Asthma	3966 (0.4)	8 (1.1)	0.080	3939 (0.4)	8 (1.2)	0.081	5486 (0.5)	13 (1.2)	0.081
Drug abuse	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Alcohol abuse	886 (0.1)	0 (0.0)	-0.044	881 (0.1)	0 (0)	-0.044	2032 (0.2)	0 (0.0)	-0.058
Behavioural syndromes associated with physiological disturbances and physical factors	Redacted	<5	Redacted	Redacted	<5	Redacted	1374 (0.1)	5 (0.5)	0.064
Hypertension	Redacted	<5	Redacted	Redacted	<5	Redacted	1743 (0.1)	5 (0.5)	0.057
Ischaemic heart diseases	73 (0)	0 (0.0)	-0.013	73 (0)	0 (0)	-0.013	Redacted	<5	Redacted

[a]For all outcomes, the start of the exposure period was set to 90 days prior LMP. For MCA, the exposure period ended after the first trimester of pregnancy. For SGA, the GLP-RA exposure period continued until end of pregnancy. For miscarriage, the GLP-1 RA exposure period ended after 22 weeks.
[c]Number of prior births, excluding the present pregnancy.

[e]All ATC/ICD10 codes and other definitions are provided in Appendix 1.
Abbreviations: BMI, body mass index; IVF, *in vitro* fertilisation; GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGA, small for gestational age; NA, not available; NSAID, Non-Steroidal Anti-Inflammatory Drug; PCOS, polycystic Ovary Syndrome.
Counts <5 are not shown for data protection purposes and information in adjacent columns have been redacted to ensure that the precise counts cannot be inferred.

3.2. Adjusted baseline characteristics after trimming and weighting

Appendix Table 2. Baseline characteristics after trimming and IPTW, main analysis

	Major congenital malformations[a]			Small for gestational age (SGA)[a]			Miscarriage/spontaneous abortion		
	No. (%) of pregnancies[b]		Standardised mean difference (%)	No. (%) of pregnancies[b]		Standardised mean difference (%)	No. (%) of pregnancies[b]		Standardised mean difference (%)
	Pseudopopulation, unexposed, N = 339 532	GLP-1 users, N = 686		Pseudopopulation, unexposed, N = 327 331	GLP-1 users, N = 680		Pseudopopulation, unexposed, N = 53 339	GLP-1 users, N = 1 049	
Maternal/pregnancy characteristics									
Year of pregnancy onset[b]									
<2016	33335 (9.8)	69 (10.1)	0.006	32379 (9.9)	69 (10)	0.006	5529 (10.4)	105 (10)	-0.015
2016-2019	51282 (15.1)	107 (15.6)	0.012	49263 (15.1)	107 (15.5)	0.013	6745 (12.6)	129 (12.3)	-0.013
2020-2023	254915 (75.1)	510 (74.3)	-0.016	245009 (75)	515 (74.5)	-0.016	41065 (77)	815 (77.7)	0.021
Multipregnancy	6331 (1.9)	14 (2)	0.013	6146 (1.9)	14 (2)	0.013	700 (1.3)	14 (1.3)	0.002
Age at pregnancy onset, years									
<20	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Redacted	<5	Redacted
20-24	22730 (6.7)	46 (6.7)	0.000	22060 (6.8)	46 (6.7)	0	4345 (8.1)	84 (8)	-0.005
25-29	96030 (28.3)	194 (28.3)	0.000	91779 (28.1)	192 (27.8)	0	12922 (24.2)	254 (24.2)	0.000
30-34	122409 (36.1)	252 (36.7)	0.014	117369 (35.9)	255 (36.9)	0.014	19527 (36.6)	386 (36.8)	0.004
≥35	98362 (29)	194 (28.3)	-0.016	95444 (29.2)	198 (28.7)	-0.016	16441 (30.8)	323 (30.8)	-0.001
Smoking	46233 (13.6)	94 (13.7)	0.003	44368 (13.6)	94 (13.6)	0.003	Missing	Missing	Missing
BMI (kg/m^2)									
<20	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Missing	Missing	Missing
20-25	21135 (6.2)	40 (5.8)	-0.011	20013 (6.1)	39 (5.6)	-0.011	Missing	Missing	Missing
25-30	66058 (19.5)	129 (18.8)	-0.015	62642 (19.2)	127 (18.4)	-0.015	Missing	Missing	Missing
30-35	112905 (33.3)	227 (33.1)	-0.004	108166 (33.1)	227 (32.9)	-0.004	Missing	Missing	Missing
>35	139435 (41.1)	290 (42.3)	0.029	135830 (41.6)	298 (43.1)	0.028	Missing	Missing	Missing
Parity at pregnancy onset[c]									
0	142388 (41.9)	288 (42)	0.001	137747 (42.2)	293 (42.4)	0.001	20710 (38.8)	408 (38.9)	0.001
1	128093 (37.7)	258 (37.6)	-0.002	121379 (37.2)	255 (36.9)	-0.002	18229 (34.2)	359 (34.2)	0.001
2	46109 (13.6)	95 (13.8)	0.008	45264 (13.9)	97 (14)	0.007	9937 (18.6)	195 (18.6)	-0.001
≥3	22942 (6.8)	45 (6.6)	-0.008	22261 (6.8)	46 (6.7)	-0.008	4463 (8.4)	87 (8.3)	-0.003
Prior registered miscarriages									
None	278221 (81.9)	560 (81.6)	-0.008	268649 (82.2)	564 (81.6)	-0.009	42679 (80)	840 (80.1)	0.002
1	47806 (14.1)	98 (14.3)	0.006	44900 (13.7)	97 (14)	0.007	8226 (15.4)	161 (15.3)	-0.002
≥2	13505 (4)	28 (4.1)	0.006	13101 (4)	30 (4.3)	0.006	2434 (4.6)	48 (4.6)	0.001
Previous SGA outcome[d]	16287 (4.8)	32 (4.7)	-0.006	15831 (4.8)	32 (4.6)	-0.006	2743 (5.1)	54 (5.1)	0.000
Previous MCM outcome[d]	18588 (5.5)	39 (5.7)	0.01	18036 (5.5)	40 (5.8)	0.01	3090 (5.8)	61 (5.8)	0.001
Married/registered partnership	147314 (43.4)	297 (43.3)	-0.002	141531 (43.3)	299 (43.3)	-0.002	21783 (40.8)	428 (40.8)	-0.001
Maternal place of birth									
Denmark	292587 (86.2)	592 (86.3)	0.004	282635 (86.5)	597 (86.4)	0.003	44969 (84.3)	888 (84.7)	0.01
Europe	14003 (4.1)	29 (4.2)	0.005	13592 (4.2)	30 (4.3)	0.005	2789 (5.2)	54 (5.1)	-0.004

Outside of Europe	32942 (9.7)	65 (9.5)	-0.008	30424 (9.3)	64 (9.3)	-0.007	5581 (10.5)	107 (10.2)	-0.009
Region of residence									
The Capital Region	128420 (37.8)	259 (37.8)	-0.001	122229 (37.4)	257 (37.2)	-0.001	18449 (34.6)	362 (34.5)	-0.002
Central Denmark	69006 (20.3)	143 (20.8)	0.013	67019 (20.5)	146 (21.1)	0.012	11598 (21.7)	229 (21.8)	0.002
Northern Denmark	29801 (8.8)	63 (9.2)	0.014	28923 (8.9)	66 (9.6)	0.014	5649 (10.6)	110 (10.5)	-0.003
Region Zealand	51653 (15.2)	101 (14.7)	-0.014	49050 (15)	99 (14.3)	-0.013	8688 (16.3)	171 (16.3)	0.000
Southern Denmark	60653 (17.9)	120 (17.5)	-0.01	59431 (18.2)	123 (17.8)	-0.01	8956 (16.8)	177 (16.9)	0.002
Season of conception									
Winter	95756 (28.2)	197 (28.7)	0.011	92461 (28.3)	200 (28.9)	0.012	13209 (24.8)	260 (24.8)	0.000
Spring	102112 (30.1)	206 (30)	-0.001	96701 (29.6)	205 (29.7)	-0.001	15116 (28.3)	297 (28.3)	-0.001
Summer	58706 (17.3)	113 (16.5)	-0.021	56948 (17.4)	115 (16.6)	-0.021	11861 (22.2)	234 (22.3)	0.002
Autumn	82958 (24.4)	170 (24.8)	0.008	80541 (24.7)	171 (24.7)	0.008	13153 (24.7)	258 (24.6)	-0.002
Plasma glucose ≥11.0 mmol/L									
Yes	3954 (1.2)	8 (1.2)	0.000	3839 (1.2)	10 (1.4)	0.000	652 (1.2)	12 (1.1)	-0.01
No	18395 (5.4)	37 (5.4)	-0.001	17867 (5.5)	38 (5.5)	-0.001	2718 (5.1)	53 (5.1)	-0.002
Not measured	317183 (93.4)	641 (93.4)	0.001	304945 (93.4)	643 (93.1)	0.001	49969 (93.7)	984 (93.8)	0.005
HbA1c ≥48.0 mmol/mol									
Yes	64531 (19)	140 (20.4)	0.048	62549 (19.1)	151 (21.9)	0.049	9513 (17.8)	184 (17.5)	-0.01
No	172650 (50.8)	350 (51)	0.004	165228 (50.6)	345 (49.9)	0.003	27718 (52)	548 (52.2)	0.006
Not measured	102351 (30.1)	196 (28.6)	-0.035	98874 (30.3)	195 (28.2)	-0.036	16108 (30.2)	317 (30.2)	0.001
No. of hospital admissions within 1 year of pregnancy onset									
None	316312 (93.2)	635 (92.6)	-0.021	304591 (93.2)	641 (92.8)	-0.021	49345 (92.5)	972 (92.7)	0.007
1	16774 (4.9)	36 (5.2)	0.012	16268 (5)	36 (5.2)	0.013	2771 (5.2)	54 (5.1)	-0.003
≥2	6446 (1.9)	15 (2.2)	0.019	5792 (1.8)	14 (2)	0.019	1223 (2.3)	23 (2.2)	-0.009
No. of outpatient visits within 1 year of pregnancy onset									
None	239617 (70.6)	483 (70.4)	-0.004	231248 (70.8)	486 (70.3)	-0.005	37722 (70.7)	746 (71.1)	0.009
1	42272 (12.4)	86 (12.5)	0.003	41056 (12.6)	87 (12.6)	0.002	6573 (12.3)	129 (12.3)	-0.001
2	21880 (6.4)	43 (6.3)	-0.007	20740 (6.3)	42 (6.1)	-0.007	3324 (6.2)	64 (6.1)	-0.006
≥3	35764 (10.5)	74 (10.8)	0.009	33607 (10.3)	76 (11)	0.011	5720 (10.7)	110 (10.5)	-0.008
Prescription of drugs within 1 year of pregnancy onset									
Antiobesity preparations	5050 (1.5)	10 (1.5)	-0.003	4902 (1.5)	10 (1.4)	-0.003	1010 (1.9)	18 (1.7)	-0.017
Insulins and analogues	28447 (8.4)	52 (7.6)	-0.041	27560 (8.4)	59 (8.5)	-0.041	3350 (6.3)	65 (6.2)	-0.004
Antidiabetics, excl. GLP-1 RA	65515 (19.3)	134 (19.5)	0.008	63526 (19.4)	142 (20.5)	0.009	9235 (17.3)	178 (17)	-0.011
Antihypertensives	21246 (6.3)	46 (6.7)	0.022	20611 (6.3)	50 (7.2)	0.022	3825 (7.2)	75 (7.1)	-0.001
Lipid-modifying drugs	18701 (5.5)	37 (5.4)	-0.007	18100 (5.5)	41 (5.9)	-0.006	3351 (6.3)	64 (6.1)	-0.01
Drugs used in IVF treatment	36952 (10.9)	70 (10.2)	-0.023	35909 (11)	72 (10.4)	-0.024	4416 (8.3)	86 (8.2)	-0.003
Glucocorticoids	11988 (3.5)	24 (3.5)	-0.002	11632 (3.6)	24 (3.5)	-0.002	1792 (3.4)	35 (3.3)	-0.001
Drugs for underactive thyroid	11553 (3.4)	22 (3.2)	-0.013	11213 (3.4)	24 (3.5)	-0.013	2064 (3.9)	40 (3.8)	-0.003
Antimigraine drugs	14277 (4.2)	29 (4.2)	0.001	13873 (4.2)	30 (4.3)	0.001	2690 (5)	53 (5.1)	0.000
Antiepileptics	4657 (1.4)	9 (1.3)	-0.006	4526 (1.4)	9 (1.3)	-0.006	897 (1.7)	18 (1.7)	0.003
Antipsychotics	6166 (1.8)	12 (1.7)	-0.006	5988 (1.8)	12 (1.7)	-0.006	1399 (2.6)	28 (2.7)	0.003

Anxiolytics	3143 (0.9)	6 (0.9)	-0.006	3058 (0.9)	7 (1)	-0.006	799 (1.5)	15 (1.4)	-0.006
Hypnotics	12315 (3.6)	27 (3.9)	0.019	11958 (3.7)	27 (3.9)	0.019	1892 (3.5)	37 (3.5)	-0.001
Antidepressants	33838 (10)	69 (10.1)	0.003	32883 (10.1)	72 (10.4)	0.003	5851 (11)	115 (11)	0.000
Psychostimulants	2927 (0.9)	6 (0.9)	0.001	2838 (0.9)	6 (0.9)	0.002	579 (1.1)	12 (1.1)	0.005
Drugs for obstructive airway diseases	18580 (5.5)	38 (5.5)	0.003	18043 (5.5)	39 (5.6)	0.003	3006 (5.6)	59 (5.6)	-0.001
Opioids	18834 (5.5)	43 (6.3)	0.031	18287 (5.6)	43 (6.2)	0.031	3444 (6.5)	68 (6.5)	0.001
Antiviral drugs	12077 (3.6)	23 (3.4)	-0.013	11145 (3.4)	24 (3.5)	-0.011	2121 (4)	42 (4)	0.001
NSAIDs	7768 (2.3)	18 (2.6)	0.024	7545 (2.3)	18 (2.6)	0.024	1436 (2.7)	27 (2.6)	-0.008
No. of drugs prescribed									
None	159198 (46.9)	316 (46.1)	-0.017	152186 (46.6)	312 (45.2)	-0.018	25351 (47.5)	502 (47.9)	0.007
1-2 drugs	140117 (41.3)	291 (42.4)	0.024	135454 (41.5)	295 (42.7)	0.025	21658 (40.6)	425 (40.5)	-0.002
3-4 drugs	35938 (10.6)	71 (10.3)	-0.01	34857 (10.7)	73 (10.6)	-0.01	5328 (10)	103 (9.8)	-0.006
≥5 drugs	4278 (1.3)	8 (1.2)	-0.011	4154 (1.3)	11 (1.6)	-0.011	1002 (1.9)	19 (1.8)	-0.006
Diagnosis within 1 year of pregnancy onset[e]									
Diabetes Type 1	10016 (2.9)	20 (2.9)	-0.003	9710 (3)	21 (3)	-0.003	1167 (2.2)	23 (2.2)	0.000
Diabetes Type 2	28718 (8.5)	57 (8.3)	-0.008	27841 (8.5)	67 (9.7)	-0.007	3452 (6.5)	65 (6.2)	-0.015
PCOS	13656 (4)	26 (3.8)	-0.015	13303 (4.1)	26 (3.8)	-0.016	1442 (2.7)	28 (2.7)	-0.002
Obesity	40961 (12.1)	85 (12.4)	0.012	39800 (12.2)	89 (12.9)	0.011	5828 (10.9)	112 (10.7)	-0.009
Thyroid disorders	6435 (1.9)	14 (2)	0.011	6244 (1.9)	15 (2.2)	0.011	997 (1.9)	19 (1.8)	-0.004
Mood [affective] disorders	5817 (1.7)	10 (1.5)	-0.027	5655 (1.7)	10 (1.4)	-0.027	851 (1.6)	17 (1.6)	0.002
Neurotic, stress-related and somatoform disorders	7339 (2.2)	15 (2.2)	0.002	7112 (2.2)	15 (2.2)	0.002	1379 (2.6)	27 (2.6)	-0.001
Asthma	3240 (1)	7 (1)	0.007	3147 (1)	8 (1.2)	0.007	605 (1.1)	12 (1.1)	0.001
Drug abuse	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Alcohol abuse	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0
Behavioural syndromes associated with physiological disturbances and physical factors	Redacted	<5	Redacted	Redacted	<5	Redacted	253 (0.5)	5 (0.5)	0
Hypertension	Redacted	<5	Redacted	Redacted	<5	Redacted	287 (0.5)	5 (0.5)	-0.011
Ischaemic heart diseases	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Redacted	<5	Redacted

[a]For all outcomes, the start of the exposure period was set to 90 days prior LMP. For MCA, the exposure period ended after the first trimester of pregnancy. For SGA, the GLP-RA exposure period continued until end of pregnancy. For miscarriage, the GLP-1 RA exposure period ended after 22 weeks.

[b]Represents pseudopopulations constructed from the weighted unexposed pregnancies.

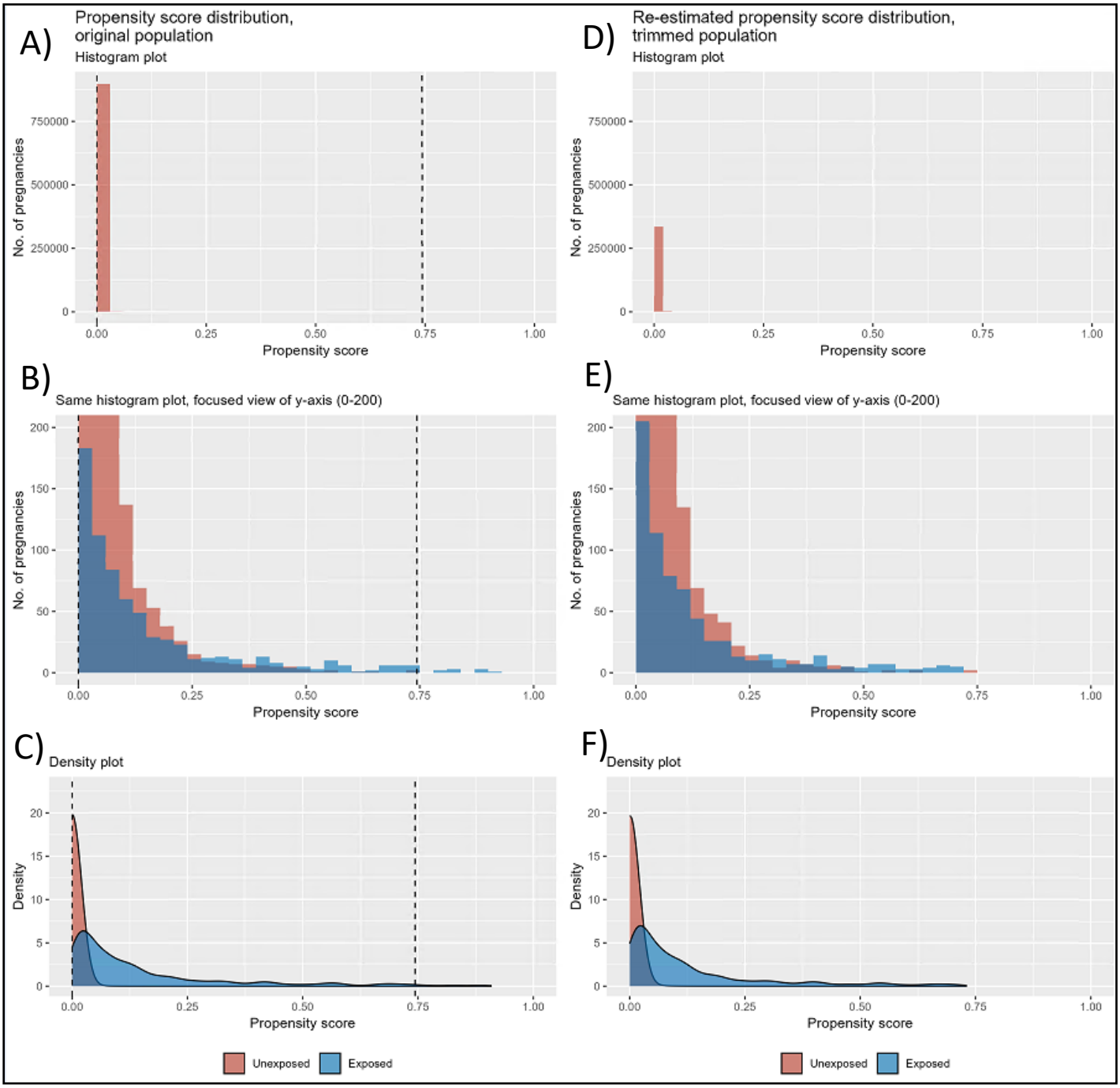
[c]Number of prior births excluding the present pregnancy.

[e]All ATC/ICD10 codes and other definitions are provided in Appendix 1.

Abbreviations: BMI, body mass index; IVF, *in vitro* fertilisation; GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGA, small for gestational age; NA, not available; NSAID, Non-Steroidal Anti-Inflammatory Drug; PCOS, polycystic Ovary Syndrome.
Counts <5 are not shown for data protection purposes and information in adjacent columns have been redacted to ensure that the precise counts cannot be inferred.

3.3. Supporting figures

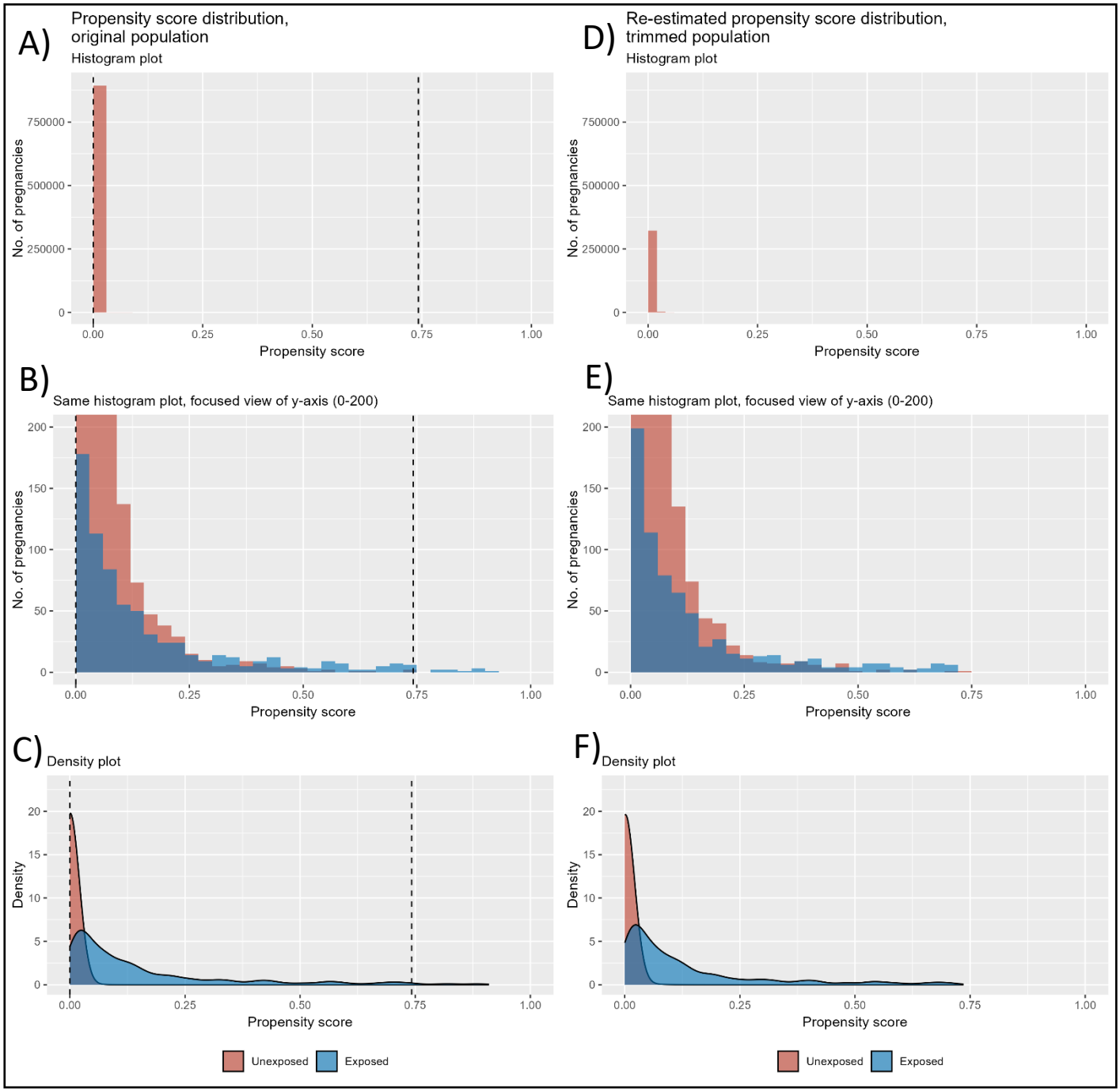
Appendix Figure 1. Main analysis, MCM population, propensity score distribution



The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

Appendix figure 2. Main analysis, MCM population, covariate balance

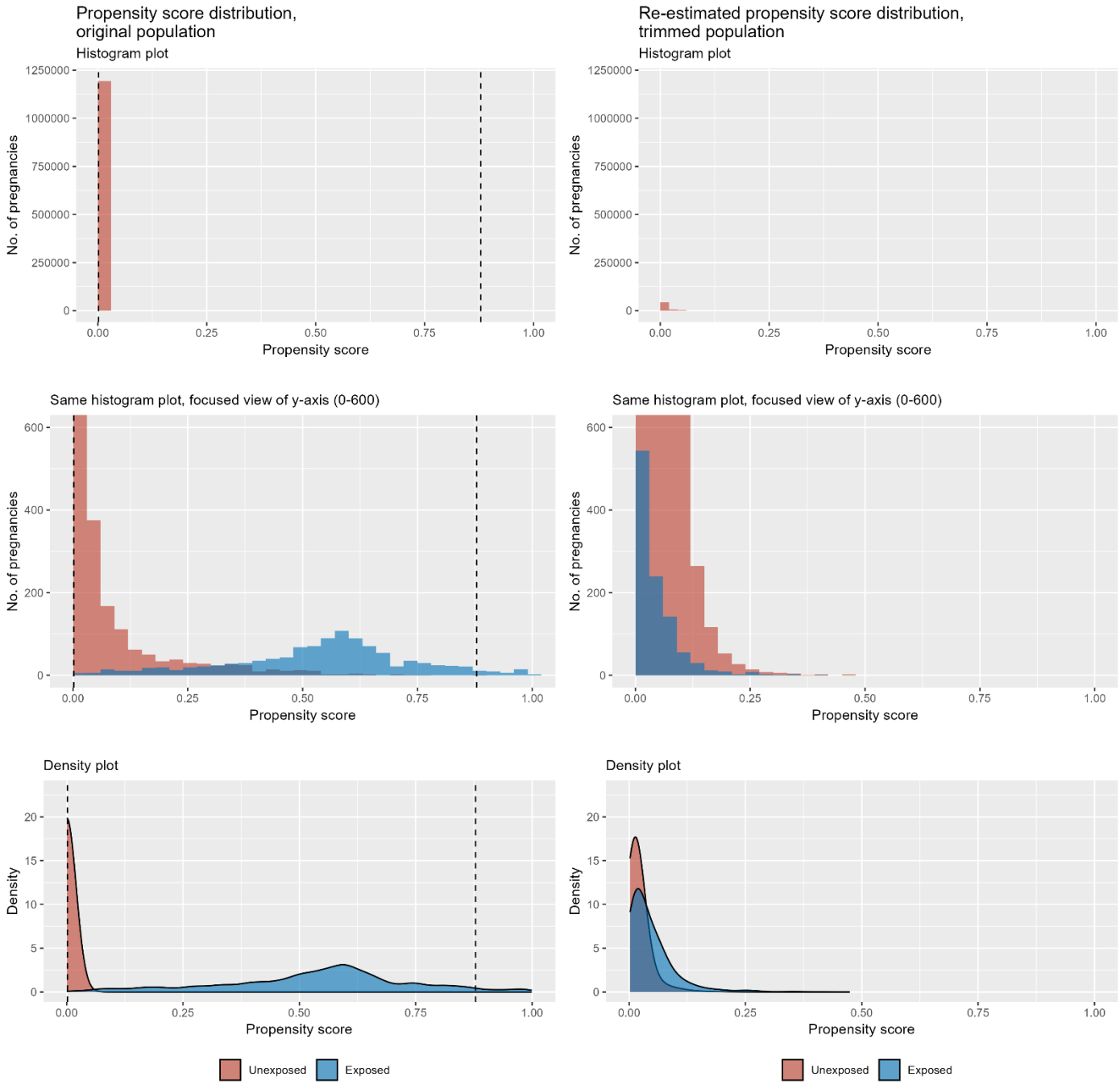
Appendix figure 3. Main analysis, SGA population, PS distribution.



The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

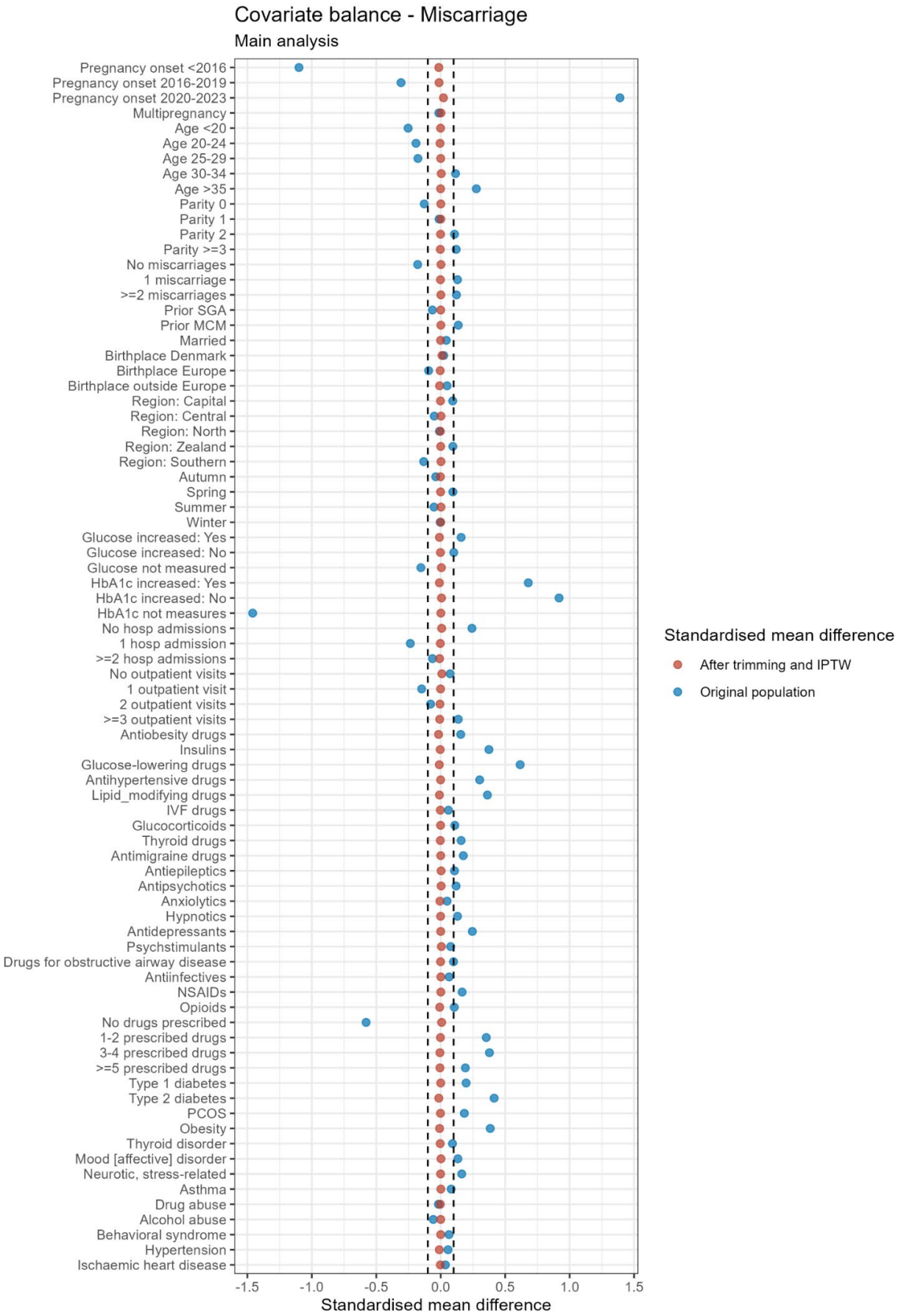
Appendix figure 4. Main analysis, SGA population, covariate balance.

Appendix figure 5. Main analysis, miscarriage population, PS distribution.



The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

Appendix figure 6. Main analysis, miscarriage population, covariate balance



Appendix 4. Sensitivity analysis 1. Pregnancies of women stratified according to their T2D status

4.1. The subpopulation with type 2 diabetes, sensitivity analysis 1a

4.1.1. Baseline characteristics, sensitivity analysis 1a

Appendix Table 3. Subgroup analysis of pregnancies of women **with** type 2 diabetes: Baseline characteristics before trimming and IPTW.

	Major congenital malformations[a]			Small for gestational age (SGA)[a]			Miscarriage/spontaneous abortion		
	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference
	Unexposed, N = 10 264	GLP-1 RA users, N = 170		Unexposed, N = 10 199	GLP-1 RA users, N = 170		Unexposed, N = 12 265	GLP-1 RA users, N = 237	
Maternal/pregnancy characteristics									
Year of pregnancy onset[b]									
<2016	6327 (61.6)	41 (24.1)	-0.819	6275 (61.5)	41 (24.1)	-0.817	7577 (61.8)	66 (27.8)	-0.726
2016-2019	2182 (21.3)	50 (29.4)	0.188	2176 (21.3)	50 (29.4)	0.186	2581 (21)	60 (25.3)	0.101
2020-2023	1755 (17.1)	79 (46.5)	0.665	1748 (17.1)	79 (46.5)	0.664	2107 (17.2)	111 (46.8)	0.67
Multipregnancy	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Age at pregnancy onset, years									
<20	45 (0.4)	0 (0)	-0.094	45 (0.4)	0 (0)	-0.094	66 (0.5)	0 (0)	-0.104
20-24	1106 (10.8)	12 (7.1)	-0.131	1096 (10.7)	12 (7.1)	-0.13	1334 (10.9)	17 (7.2)	-0.13
25-29	4299 (41.9)	55 (32.4)	-0.198	4275 (41.9)	55 (32.4)	-0.199	4855 (39.6)	68 (28.7)	-0.231
30-34	3263 (31.8)	58 (34.1)	0.05	3248 (31.8)	58 (34.1)	0.048	3854 (31.4)	78 (32.9)	0.032
≥35	1551 (15.1)	45 (26.5)	0.283	1535 (15.1)	45 (26.5)	0.284	2156 (17.6)	74 (31.2)	0.322
Smoking	1143 (11.1)	27 (15.9)	0.139	1133 (11.1)	27 (15.9)	0.14	Missing	Missing	Missing
BMI (kg/m^2)									
<20	734 (7.2)	0 (0)	-0.392	730 (7.2)	0 (0)	-0.393	Missing	Missing	Missing
20-25	3277 (31.9)	8 (4.7)	-0.752	3253 (31.9)	8 (4.7)	-0.751	Missing	Missing	Missing
25-30	2604 (25.4)	27 (15.9)	-0.236	2592 (25.4)	27 (15.9)	-0.237	Missing	Missing	Missing
30-35	2054 (20)	50 (29.4)	0.219	2036 (20)	50 (29.4)	0.22	Missing	Missing	Missing
>35	1595 (15.5)	85 (50.0)	0.789	1588 (15.6)	85 (50)	0.788	Missing	Missing	Missing
Parity at pregnancy onset[c]									
0	6936 (67.6)	106 (62.4)	-0.11	6894 (67.6)	106 (62.4)	-0.11	8080 (65.9)	144 (60.8)	-0.106
1	2443 (23.8)	44 (25.9)	0.048	2426 (23.8)	44 (25.9)	0.049	2899 (23.6)	58 (24.5)	0.02
2	616 (6)	13 (7.6)	0.065	611 (6)	13 (7.6)	0.066	853 (7)	22 (9.3)	0.085
≥3	269 (2.6)	7 (4.1)	0.083	268 (2.6)	7 (4.1)	0.083	433 (3.5)	13 (5.5)	0.094
Prior registered miscarriages									
None	9347 (91.1)	153 (90)	-0.036	9287 (91.1)	153 (90)	-0.036	11069 (90.2)	210 (88.6)	-0.053
1	777 (7.6)	13 (7.6)	0.003	772 (7.6)	13 (7.6)	0.003	990 (8.1)	20 (8.4)	0.013
≥2	Redacted	<5	Redacted	Redacted	<5	Redacted	206 (1.7)	7 (3)	0.085
Previous SGA outcome[d]	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Previous MCM outcome[d]	163 (1.6)	7 (4.1)	0.152	161 (1.6)	7 (4.1)	0.153	214 (1.7)	9 (3.8)	0.125
Married/registered partnership	4635 (45.2)	80 (47.1)	0.038	4605 (45.2)	80 (47.1)	0.038	5529 (45.1)	106 (44.7)	-0.007
Maternal place of birth									

Denmark	8660 (84.4)	141 (82.9)	-0.039	8603 (84.4)	141 (82.9)	-0.038	10220 (83.3)	197 (83.1)	-0.005
Europe	590 (5.7)	10 (5.9)	0.006	588 (5.8)	10 (5.9)	0.005	719 (5.9)	14 (5.9)	0.002
Outside of Europe	1014 (9.9)	19 (11.2)	0.042	1008 (9.9)	19 (11.2)	0.042	1326 (10.8)	26 (11)	0.005
Region of residence									
The Capital Region	3012 (29.3)	67 (39.4)	0.213	3002 (29.4)	67 (39.4)	0.211	3642 (29.7)	83 (35)	0.114
Central Denmark	2487 (24.2)	37 (21.8)	-0.059	2471 (24.2)	37 (21.8)	-0.059	2981 (24.3)	52 (21.9)	-0.056
Northern Denmark	929 (9.1)	16 (9.4)	0.012	922 (9)	16 (9.4)	0.013	1129 (9.2)	24 (10.1)	0.031
Region Zealand	1331 (13)	17 (10)	-0.093	1317 (12.9)	17 (10)	-0.092	1578 (12.9)	33 (13.9)	0.031
Southern Denmark	2505 (24.4)	33 (19.4)	-0.121	2487 (24.4)	33 (19.4)	-0.12	2935 (23.9)	45 (19)	-0.121
Season of conception									
Winter	2479 (24.2)	40 (23.5)	-0.015	2468 (24.2)	40 (23.5)	-0.016	2971 (24.2)	48 (20.3)	-0.096
Spring	2676 (26.1)	47 (27.6)	0.036	2660 (26.1)	47 (27.6)	0.035	3157 (25.7)	64 (27)	0.029
Summer	2288 (22.3)	30 (17.6)	-0.116	2267 (22.2)	30 (17.6)	-0.115	2778 (22.6)	54 (22.8)	0.003
Autumn	2821 (27.5)	53 (31.2)	0.081	2804 (27.5)	53 (31.2)	0.081	3359 (27.4)	71 (30)	0.057
Plasma glucose ≥11.0 mmol/L									
Yes	46 (0.4)	8 (4.7)	0.271	45 (0.4)	8 (4.7)	0.272	64 (0.5)	9 (3.8)	0.227
No	724 (7.1)	12 (7.1)	0	722 (7.1)	12 (7.1)	-0.001	837 (6.8)	14 (5.9)	-0.038
Not measured	9494 (92.5)	150 (88.2)	-0.145	9432 (92.5)	150 (88.2)	-0.144	11364 (92.7)	214 (90.3)	-0.085
HbA1c ≥48.0 mmol/mol									
Yes	578 (5.6)	87 (51.2)	1.17	574 (5.6)	87 (51.2)	1.17	815 (6.6)	121 (51.1)	1.125
No	2917 (28.4)	55 (32.4)	0.086	2903 (28.5)	55 (32.4)	0.085	3418 (27.9)	72 (30.4)	0.055
Not measured	6769 (65.9)	28 (16.5)	-1.163	6722 (65.9)	28 (16.5)	-1.162	8032 (65.5)	44 (18.6)	-1.08
No. of hospital admissions within 1 year of pregnancy onset									
None	8927 (87)	146 (85.9)	-0.032	8874 (87)	146 (85.9)	-0.033	10566 (86.1)	198 (83.5)	-0.073
1	1021 (9.9)	16 (9.4)	-0.018	1012 (9.9)	16 (9.4)	-0.017	1256 (10.2)	28 (11.8)	0.05
≥2	316 (3.1)	8 (4.7)	0.084	313 (3.1)	8 (4.7)	0.085	443 (3.6)	11 (4.6)	0.052
No. of outpatient visits within 1 year of pregnancy onset									
None	5509 (53.7)	96 (56.5)	0.056	5476 (53.7)	96 (56.5)	0.056	6506 (53)	135 (57)	0.079
1	2419 (23.6)	32 (18.8)	-0.116	2409 (23.6)	32 (18.8)	-0.118	2875 (23.4)	43 (18.1)	-0.131
2	1186 (11.6)	14 (8.2)	-0.111	1178 (11.6)	14 (8.2)	-0.111	1430 (11.7)	21 (8.9)	-0.092
≥3	1150 (11.2)	28 (16.5)	0.153	1136 (11.1)	28 (16.5)	0.155	1454 (11.9)	38 (16)	0.121
Prescription of drugs within 1 year of pregnancy onset									
Antiobesity preparations	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Insulins and analogues	340 (3.3)	39 (22.9)	0.607	338 (3.3)	39 (22.9)	0.607	480 (3.9)	54 (22.8)	0.578
Antidiabetics, excl. GLP-1 RA	9935 (96.8)	142 (83.5)	-0.457	9873 (96.8)	142 (83.5)	-0.457	11768 (95.9)	200 (84.4)	-0.396
Antihypertensives	505 (4.9)	31 (18.2)	0.425	502 (4.9)	31 (18.2)	0.425	679 (5.5)	51 (21.5)	0.481
Lipid-modifying drugs	282 (2.7)	30 (17.6)	0.508	281 (2.8)	30 (17.6)	0.508	447 (3.6)	54 (22.8)	0.589
Drugs used in IVF treatment	4958 (48.3)	24 (14.1)	-0.794	4927 (48.3)	24 (14.1)	-0.794	5619 (45.8)	32 (13.5)	-0.756
Glucocorticoids	317 (3.1)	6 (3.5)	0.025	315 (3.1)	6 (3.5)	0.025	380 (3.1)	7 (3)	-0.008
Drugs for underactive thyroid	385 (3.8)	6 (3.5)	-0.012	380 (3.7)	6 (3.5)	-0.011	477 (3.9)	12 (5.1)	0.057
Antimigraine drugs	314 (3.1)	11 (6.5)	0.161	313 (3.1)	11 (6.5)	0.16	372 (3)	18 (7.6)	0.204
Antiepileptics	Redacted	<5	Redacted	Redacted	<5	Redacted	136 (1.1)	6 (2.5)	0.107
Antipsychotics	Redacted	<5	Redacted	Redacted	<5	Redacted	203 (1.7)	7 (3)	0.087
Anxiolytics	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted

Hypnotics	194 (1.9)	9 (5.3)	0.184	193 (1.9)	9 (5.3)	0.184	260 (2.1)	14 (5.9)	0.194
Antidepressants	693 (6.8)	28 (16.5)	0.307	689 (6.8)	28 (16.5)	0.307	900 (7.3)	40 (16.9)	0.296
Psychostimulants	Redacted	<5	Redacted	Redacted	<5	Redacted	79 (0.6)	8 (3.4)	0.196
Drugs for obstructive airway diseases	620 (6)	14 (8.2)	0.085	613 (6)	14 (8.2)	0.087	754 (6.1)	18 (7.6)	0.057
Antiinfectives	598 (5.8)	12 (7.1)	0.05	594 (5.8)	12 (7.1)	0.05	747 (6.1)	20 (8.4)	0.091
NSAIDs	218 (2.1)	8 (4.7)	0.143	217 (2.1)	8 (4.7)	0.142	275 (2.2)	12 (5.1)	0.151
Opioids	Redacted	<5	Redacted	Redacted	<5	Redacted	230 (1.9)	8 (3.4)	0.094
No. of drugs prescribed									
None	131 (1.3)	9 (5.3)	0.227	130 (1.3)	9 (5.3)	0.227	195 (1.6)	9 (3.8)	0.137
1-2 drugs	7984 (77.8)	100 (58.8)	-0.416	7936 (77.8)	100 (58.8)	-0.417	9390 (76.6)	137 (57.8)	-0.408
3-4 drugs	1950 (19)	52 (30.6)	0.271	1935 (19)	52 (30.6)	0.272	2408 (19.6)	71 (30)	0.241
≥5 drugs	199 (1.9)	9 (5.3)	0.18	198 (1.9)	9 (5.3)	0.18	272 (2.2)	20 (8.4)	0.28
Diagnosis within 1 year of pregnancy onset									
Diabetes Type 1	120 (1.2)	8 (4.7)	0.211	119 (1.2)	8 (4.7)	0.211	166 (1.4)	10 (4.2)	0.175
Diabetes Type 2	568 (5.5)	67 (39.4)	0.888	564 (5.5)	67 (39.4)	0.888	831 (6.8)	88 (37.1)	0.788
PCOS	1236 (12)	15 (8.8)	-0.105	1230 (12.1)	15 (8.8)	-0.106	1466 (12)	18 (7.6)	-0.147
Obesity	633 (6.2)	30 (17.6)	0.36	629 (6.2)	30 (17.6)	0.36	806 (6.6)	38 (16)	0.302
Thyroid disorders	Redacted	<5	Redacted	Redacted	<5	Redacted	191 (1.6)	6 (2.5)	0.069
Mood [affective] disorders	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Neurotic, stress-related and somatoform disorders	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Asthma	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Drug abuse	38 (0.4)	0 (0)	-0.086	38 (0.4)	0 (0)	-0.086	52 (0.4)	0 (0)	-0.092
Alcohol abuse	11 (0.1)	0 (0)	-0.046	11 (0.1)	0 (0)	-0.046	16 (0.1)	0 (0)	-0.051
Behavioural syndromes associated with physiological disturbances and physical factors	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Hypertension	64 (0.6)	0 (0)	-0.112	64 (0.6)	0 (0)	-0.112	Redacted	<5	Redacted
Ischaemic heart diseases	<5	0 (0)	Redacted	<5	0 (0)	Redacted	Redacted	<5	Redacted

4.1.2. Adjusted characteristics after trimming and weighting, sensitivity analysis 1a

Appendix Table 4. Subgroup analysis of pregnancies of women **with** type 2 diabetes: Baseline characteristics after trimming and IPTW.

	Major congenital malformations[a]			Small for gestational age (SGA)[a]			Miscarriage/spontaneous abortion		
	No. (%) of pregnancies		Standardised mean difference (%)	No. (%) of pregnancies		Standardised mean difference (%)	No. (%) of pregnancies		Standardised mean difference (%)
	Pseudopopulation, unexposed, N = 7 351	GLP-1 RA users, N = 168		Pseudopopulation, unexposed, N = 7 315	GLP-1 RA users, N = 168		Pseudopopulation, unexposed, N = 9 234	GLP-1 RA users, N = 227	
Maternal/pregnancy characteristics									
Year of pregnancy onset[b]									
<2016	1724 (23.4)	40 (23.8)	0.008	1713 (23.4)	41 (24.1)	0.008	2680 (29)	64 (28.2)	-0.018
2016-2019	2137 (29.1)	49 (29.2)	0.002	2126 (29.1)	50 (29.4)	0.002	2325 (25.2)	58 (25.6)	0.009
2020-2023	3491 (47.5)	79 (47)	-0.01	3475 (47.5)	79 (46.5)	-0.011	4228 (45.8)	105 (46.3)	0.01

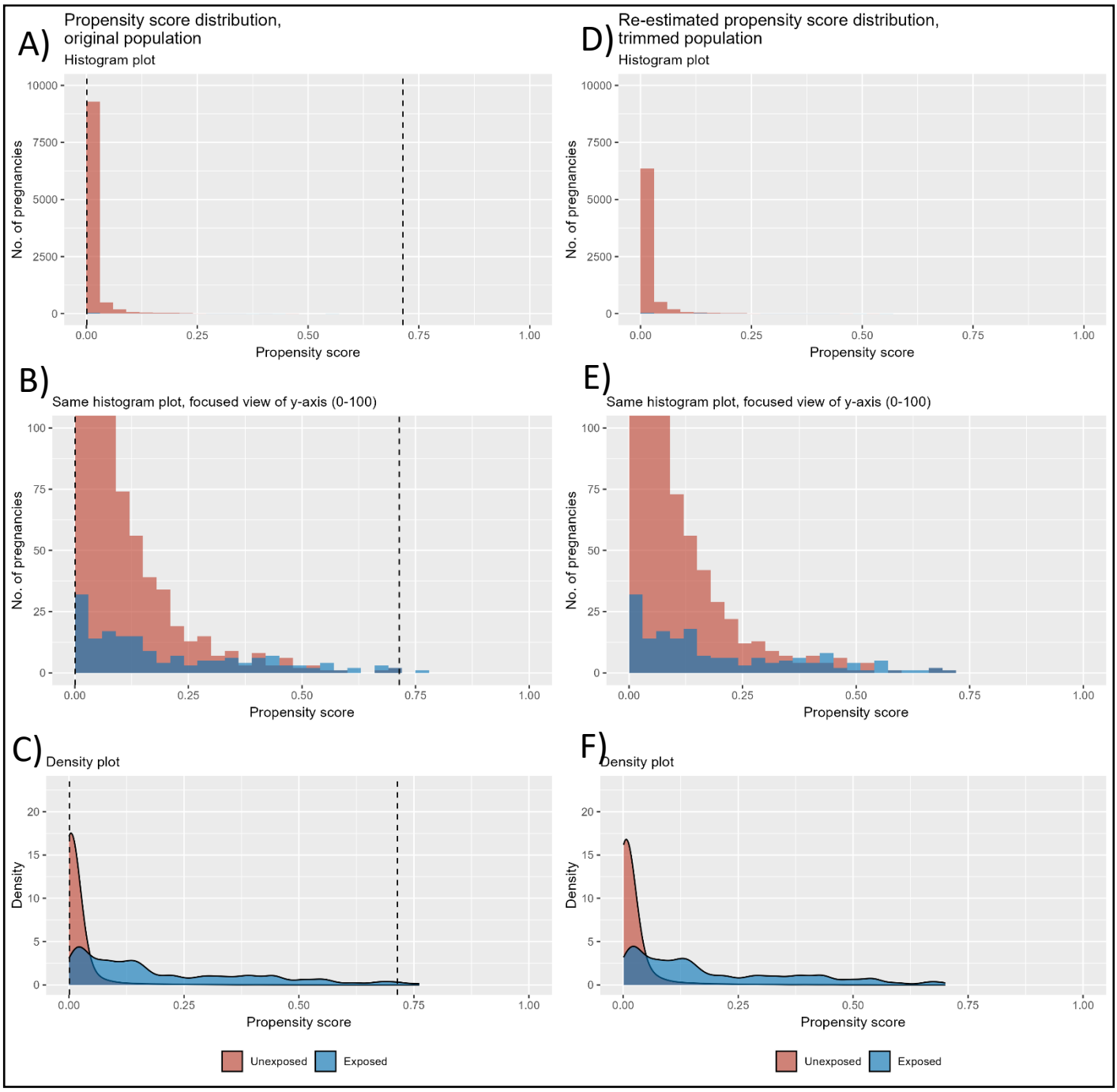
Multipregnancy	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Age at pregnancy onset, years									
<20	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0
20-24	496 (6.7)	12 (7.1)	0.014	493 (6.7)	12 (7.1)	0.014	733 (7.9)	17 (7.5)	-0.016
25-29	2300 (31.3)	54 (32.1)	0.018	2290 (31.3)	55 (32.4)	0.017	2739 (29.7)	67 (29.5)	-0.003
30-34	2406 (32.7)	57 (33.9)	0.025	2394 (32.7)	58 (34.1)	0.026	2866 (31)	75 (33)	0.043
≥35	2149 (29.2)	45 (26.8)	-0.06	2138 (29.2)	45 (26.5)	-0.06	2897 (31.4)	68 (30)	-0.033
Smoking	1179 (16)	27 (16.1)	0.001	1173 (16)	27 (15.9)	0.001	Missing	Missing	Missing
BMI (kg/m^2)									
<20	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Missing	Missing	Missing
20-25	344 (4.7)	8 (4.8)	0.003	341 (4.7)	8 (4.7)	0.003	Missing	Missing	Missing
25-30	1125 (15.3)	27 (16.1)	0.018	1120 (15.3)	27 (15.9)	0.018	Missing	Missing	Missing
30-35	2175 (29.6)	49 (29.2)	-0.009	2165 (29.6)	50 (29.4)	-0.009	Missing	Missing	Missing
>35	3707 (50.4)	84 (50)	-0.01	3689 (50.4)	85 (50)	-0.009	Missing	Missing	Missing
Parity at pregnancy onset[c]									
0	4547 (61.9)	104 (61.9)	0.001	4526 (61.9)	106 (62.4)	0.001	5565 (60.3)	136 (59.9)	-0.007
1	1943 (26.4)	44 (26.2)	-0.006	1933 (26.4)	44 (25.9)	-0.006	2223 (24.1)	56 (24.7)	0.014
2	536 (7.3)	13 (7.7)	0.017	533 (7.3)	13 (7.6)	0.018	896 (9.7)	22 (9.7)	0
≥3	324 (4.4)	7 (4.2)	-0.013	322 (4.4)	7 (4.1)	-0.013	550 (6)	13 (5.7)	-0.011
Prior registered miscarriages									
None	6642 (90.4)	152 (90.5)	0.004	6610 (90.4)	153 (90)	0.004	8232 (89.2)	201 (88.5)	-0.02
1	553 (7.5)	12 (7.1)	-0.015	551 (7.5)	13 (7.6)	-0.015	720 (7.8)	19 (8.4)	0.021
≥2	Redacted	<5	Redacted	Redacted	<5	Redacted	282 (3.1)	7 (3.1)	0.002
Previous SGA outcome[d]	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Previous MCM outcome[d]	347 (4.7)	7 (4.2)	-0.032	345 (4.7)	7 (4.1)	-0.032	357 (3.9)	9 (4)	0.006
Married/registered partnership	3492 (47.5)	78 (46.4)	-0.022	3475 (47.5)	80 (47.1)	-0.022	4159 (45)	103 (45.4)	0.007
Maternal place of birth									
Denmark	6100 (83)	139 (82.7)	-0.006	6069 (83)	141 (82.9)	-0.006	7604 (82.3)	187 (82.4)	0.001
Europe	390 (5.3)	10 (6)	0.028	388 (5.3)	10 (5.9)	0.028	540 (5.9)	14 (6.2)	0.013
Outside of Europe	861 (11.7)	19 (11.3)	-0.013	858 (11.7)	19 (11.2)	-0.014	1089 (11.8)	26 (11.5)	-0.011
Region of residence									
The Capital Region	2910 (39.6)	66 (39.3)	-0.006	2897 (39.6)	67 (39.4)	-0.007	3350 (36.3)	82 (36.1)	-0.003
Central Denmark	1543 (21)	36 (21.4)	0.01	1534 (21)	37 (21.8)	0.011	1866 (20.2)	46 (20.3)	0.001
Northern Denmark	651 (8.9)	16 (9.5)	0.023	648 (8.9)	16 (9.4)	0.023	934 (10.1)	24 (10.6)	0.015
Region Zealand	781 (10.6)	17 (10.1)	-0.016	776 (10.6)	17 (10)	-0.016	1339 (14.5)	32 (14.1)	-0.012
Southern Denmark	1467 (20)	33 (19.6)	-0.008	1460 (20)	33 (19.4)	-0.008	1745 (18.9)	43 (18.9)	0.001
Season of conception									
Winter	1529 (20.8)	40 (23.8)	0.07	1520 (20.8)	40 (23.5)	0.071	1780 (19.3)	46 (20.3)	0.024
Spring	2088 (28.4)	47 (28)	-0.01	2079 (28.4)	47 (27.6)	-0.01	2607 (28.2)	63 (27.8)	-0.011
Summer	1372 (18.7)	28 (16.7)	-0.051	1365 (18.7)	30 (17.6)	-0.051	2060 (22.3)	49 (21.6)	-0.017
Autumn	2362 (32.1)	53 (31.5)	-0.013	2351 (32.1)	53 (31.2)	-0.013	2787 (30.2)	69 (30.4)	0.005
Plasma glucose ≥11.0 mmol/L									
Yes	295 (4)	7 (4.2)	0.01	294 (4)	8 (4.7)	0.01	321 (3.5)	9 (4)	0.033
No	518 (7)	12 (7.1)	0.004	516 (7.1)	12 (7.1)	0.003	583 (6.3)	14 (6.2)	-0.006

Not measured	6538 (88.9)	149 (88.7)	-0.008	6505 (88.9)	150 (88.2)	-0.008	8330 (90.2)	204 (89.9)	-0.012
HbA1c ≥48.0 mmol/mol									
Yes	3759 (51.1)	85 (50.6)	-0.014	3743 (51.2)	87 (51.2)	-0.014	4351 (47.1)	111 (48.9)	0.044
No	2343 (31.9)	55 (32.7)	0.018	2331 (31.9)	55 (32.4)	0.019	2981 (32.3)	72 (31.7)	-0.012
Not measured	1248 (17)	28 (16.7)	-0.007	1242 (17)	28 (16.5)	-0.007	1903 (20.6)	44 (19.4)	-0.027
No. of hospital admissions within 1 year of pregnancy onset									
None	6380 (86.8)	144 (85.7)	-0.031	6349 (86.8)	146 (85.9)	-0.032	7712 (83.5)	190 (83.7)	0.005
1	641 (8.7)	16 (9.5)	0.028	637 (8.7)	16 (9.4)	0.028	1091 (11.8)	27 (11.9)	0.002
≥2	331 (4.5)	8 (4.8)	0.013	329 (4.5)	8 (4.7)	0.013	431 (4.7)	10 (4.4)	-0.013
No. of outpatient visits within 1 year of pregnancy onset									
None	4101 (55.8)	95 (56.5)	0.015	4080 (55.8)	96 (56.5)	0.016	5189 (56.2)	129 (56.8)	0.013
1	1427 (19.4)	32 (19)	-0.009	1419 (19.4)	32 (18.8)	-0.009	1727 (18.7)	42 (18.5)	-0.005
2	667 (9.1)	14 (8.3)	-0.025	664 (9.1)	14 (8.2)	-0.025	903 (9.8)	21 (9.3)	-0.018
≥3	1157 (15.7)	27 (16.1)	0.01	1153 (15.8)	28 (16.5)	0.009	1415 (15.3)	35 (15.4)	0.003
Prescription of drugs within 1 year of pregnancy onset									
Antiobesity preparations	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Insulins and analogues	1850 (25.2)	38 (22.6)	-0.078	1843 (25.2)	39 (22.9)	-0.079	1903 (20.6)	47 (20.7)	0.003
Antidiabetics, excl. GLP-1 RA	6091 (82.9)	140 (83.3)	0.016	6061 (82.9)	142 (83.5)	0.016	7871 (85.2)	191 (84.1)	-0.037
Antihypertensives	1285 (17.5)	29 (17.3)	-0.007	1280 (17.5)	31 (18.2)	-0.007	1735 (18.8)	43 (18.9)	0.005
Lipid-modifying drugs	1206 (16.4)	28 (16.7)	0.009	1201 (16.4)	30 (17.6)	0.008	1897 (20.5)	46 (20.3)	-0.009
Drugs used in IVF treatment	1089 (14.8)	24 (14.3)	-0.012	1083 (14.8)	24 (14.1)	-0.012	1383 (15)	32 (14.1)	-0.021
Glucocorticoids	256 (3.5)	6 (3.6)	0.005	255 (3.5)	6 (3.5)	0.005	266 (2.9)	6 (2.6)	-0.015
Drugs for underactive thyroid	228 (3.1)	6 (3.6)	0.025	228 (3.1)	6 (3.5)	0.025	469 (5.1)	10 (4.4)	-0.034
Antimigraine drugs	458 (6.2)	11 (6.5)	0.014	455 (6.2)	11 (6.5)	0.015	637 (6.9)	16 (7)	0.007
Antiepileptics	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	0
Antipsychotics	Redacted	<5	Redacted	Redacted	<5	Redacted	258 (2.8)	6 (2.6)	-0.01
Anxiolytics	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Hypnotics	344 (4.7)	8 (4.8)	0.004	343 (4.7)	9 (5.3)	0.004	415 (4.5)	10 (4.4)	-0.005
Antidepressants	1206 (16.4)	28 (16.7)	0.008	1201 (16.4)	28 (16.5)	0.008	1427 (15.4)	36 (15.9)	0.012
Psychostimulants	Redacted	<5	Redacted	Redacted	<5	Redacted	188 (2)	5 (2.2)	0.014
Drugs for obstructive airway diseases	554 (7.5)	14 (8.3)	0.03	551 (7.5)	14 (8.2)	0.031	651 (7.1)	16 (7)	0
Antiinfectives	414 (5.6)	12 (7.1)	0.061	411 (5.6)	12 (7.1)	0.061	643 (7)	16 (7)	0.003
NSAIDs	347 (4.7)	8 (4.8)	0.002	345 (4.7)	8 (4.7)	0.002	390 (4.2)	10 (4.4)	0.01
Opioids	Redacted	<5	Redacted	Redacted	<5	Redacted	297 (3.2)	7 (3.1)	-0.008
No. of drugs prescribed									
None	391 (5.3)	9 (5.4)	0.002	388 (5.3)	9 (5.3)	0.003	355 (3.8)	9 (4)	0.007
1-2 drugs	4387 (59.7)	100 (59.5)	-0.003	4364 (59.7)	100 (58.8)	-0.003	5559 (60.2)	137 (60.4)	0.003
3-4 drugs	2172 (29.5)	50 (29.8)	0.005	2162 (29.6)	52 (30.6)	0.005	2739 (29.7)	68 (30)	0.007
≥5 drugs	402 (5.5)	9 (5.4)	-0.006	401 (5.5)	9 (5.3)	-0.006	582 (6.3)	13 (5.7)	-0.029
Diagnosis within 1 year of pregnancy onset									

Diabetes Type 1	347 (4.7)	8 (4.8)	0.002	346 (4.7)	8 (4.7)	0.002	388 (4.2)	10 (4.4)	0.012
Diabetes Type 2	2898 (39.4)	65 (38.7)	-0.019	2885 (39.4)	67 (39.4)	-0.019	3081 (33.4)	78 (34.4)	0.025
PCOS	661 (9)	15 (8.9)	-0.002	657 (9)	15 (8.8)	-0.002	742 (8)	18 (7.9)	-0.003
Obesity	1225 (16.7)	30 (17.9)	0.036	1219 (16.7)	30 (17.6)	0.036	1328 (14.4)	34 (15)	0.019
Thyroid disorders	Redacted	<5	Redacted	Redacted	<5	Redacted	220 (2.4)	5 (2.2)	-0.013
Mood [affective] disorders	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Neurotic, stress-related and somatoform disorders	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Asthma	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Drug abuse	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0
Alcohol abuse	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0
Behavioural syndromes associated with physiological disturbances and physical factors	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Hypertension	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Redacted	<5	Redacted
Ischaemic heart diseases	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Redacted	<5	Redacted

4.1.3. Supporting figures of PS distribution and covariate balance for the T2D subpopulation, sensitivity analysis 1a

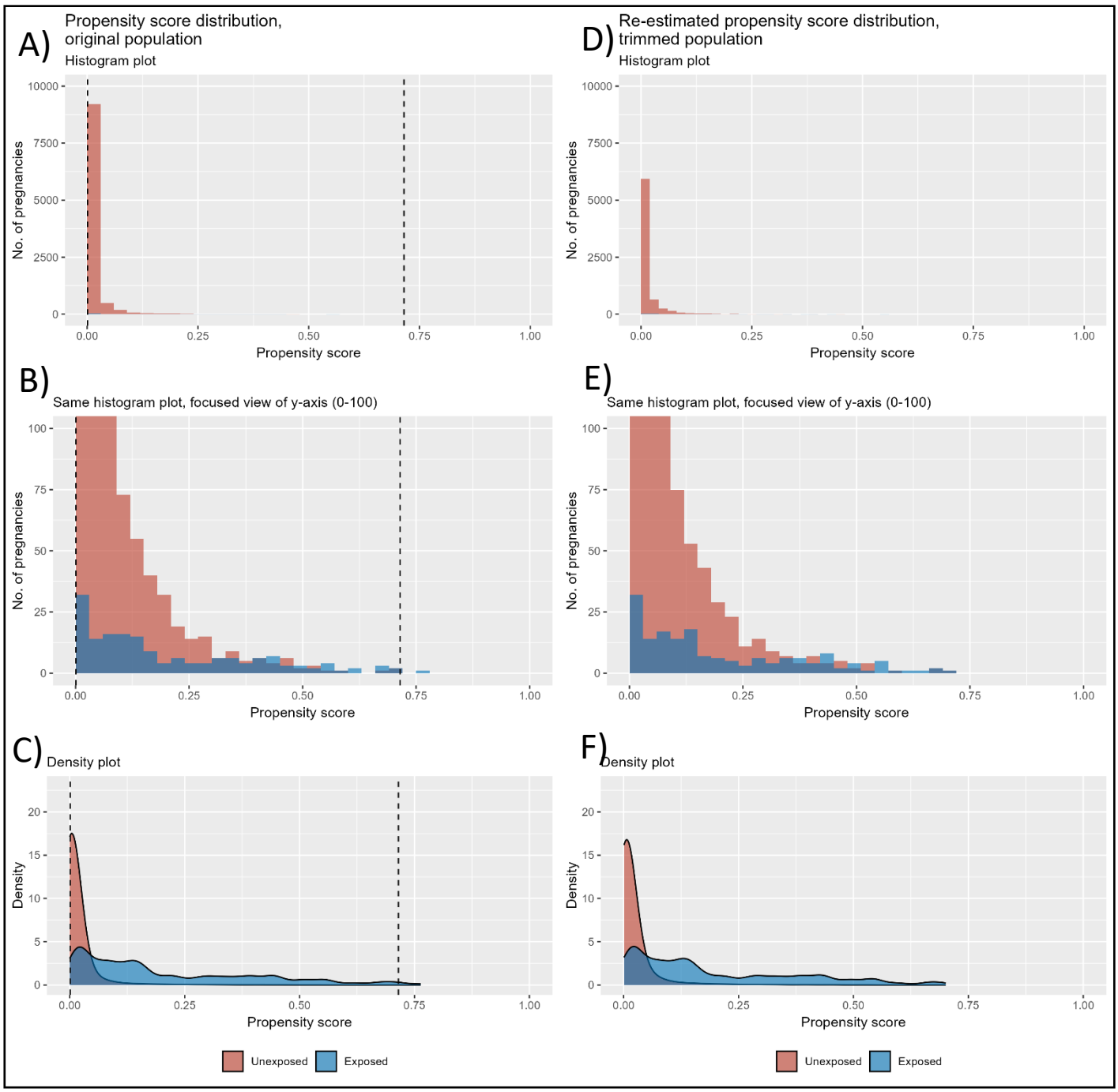
Appendix figure 7. Sensitivity analysis 1a, MCM population, PS distribution



The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

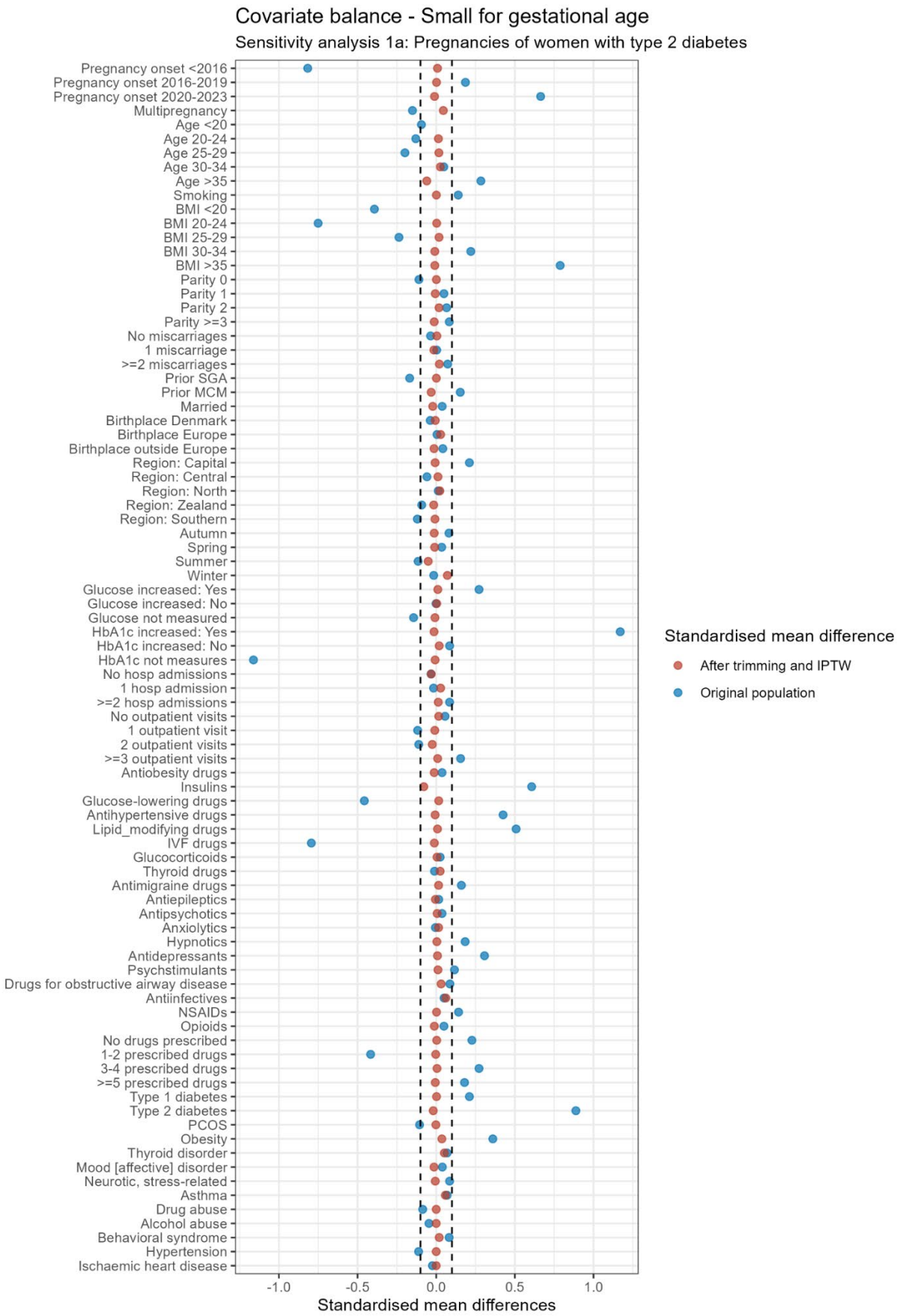
Appendix figure 8. Sensitivity analysis 1a, MCM population, covariate balance

Appendix figure 9. Sensitivity analysis 1a, SGA population, PS distribution

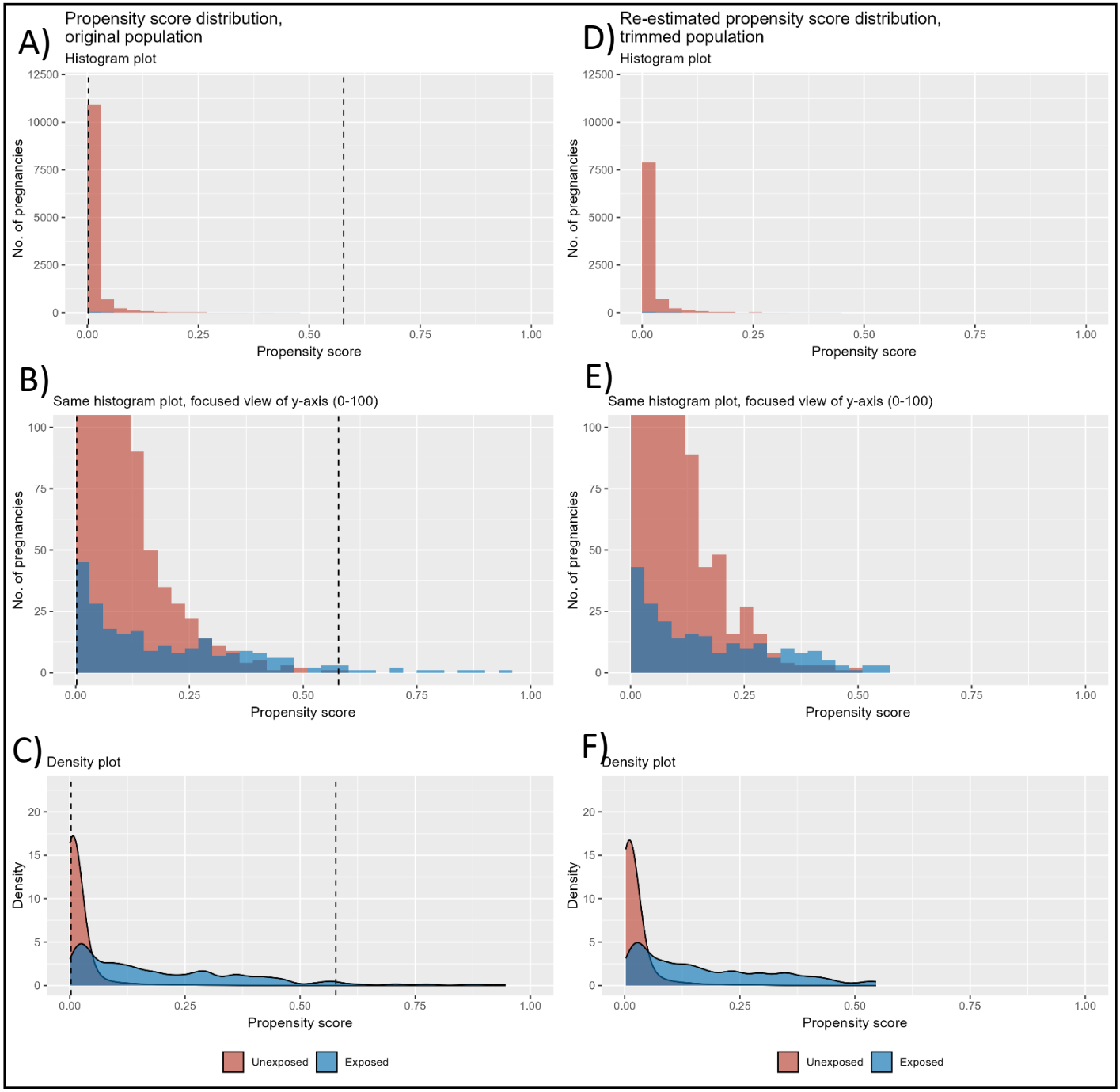


The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

Appendix figure 10. Sensitivity analysis 1a, SGA population, covariate balance

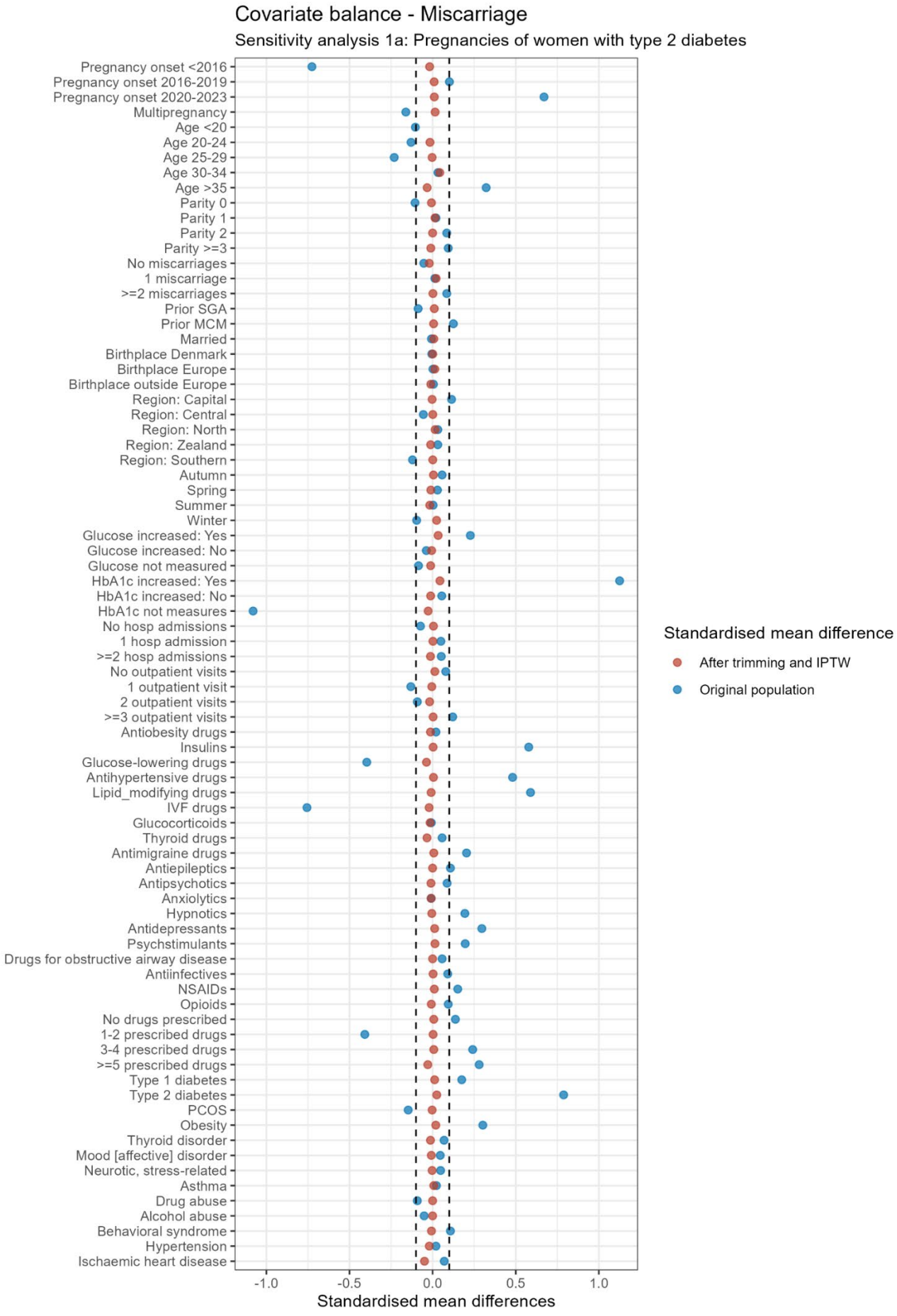


Appendix figure 11. Sensitivity analysis 1a, miscarriage population, PS distribution



The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

Appendix figure 12. Sensitivity analysis 1a, miscarriage population, covariate balance



4.2. The subpopulation without type 2 diabetes, sensitivity analysis 1b

4.2.1. Baseline characteristics, sensitivity analysis 1b

Appendix table 5. Subgroup analysis of pregnancies of women without type 2 diabetes: Baseline characteristics before IPTW.

	Major congenital malformations[a]			Small for gestational age (SGA)[a]			Miscarriage/spontaneous abortion		
	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference
	Unexposed, N = 889 772	GLP-1 RA users, N = 527		Unexposed, N = 885 240	GLP-1 RA users, N = 521		Unexposed, N = 1 182 063	GLP-1 RA users, N = 850	
Maternal/pregnancy characteristics									
Year of pregnancy onset[b]									
<2016	475942 (53.5)	28 (5.3)	-1.246	472766 (53.4)	28 (5.4)	-1.241	652061 (55.2)	43 (5.1)	-1.304
2016-2019	227802 (25.6)	58 (11)	-0.384	227151 (25.7)	57 (10.9)	-0.388	290642 (24.6)	78 (9.2)	-0.42
2020-2023	186028 (20.9)	441 (83.7)	1.616	185323 (20.9)	436 (83.7)	1.615	239360 (20.2)	729 (85.8)	1.74
Multipregnancy	16637 (1.9)	10 (1.9)	0.002	16405 (1.9)	10 (1.9)	0.005	16961 (1.4)	10 (1.2)	-0.023
Age at pregnancy onset, years									
<20	13503 (1.5)	0 (0)	-0.176	13401 (1.5)	0 (0)	-0.175	Redacted	<5	Redacted
20-24	107258 (12.1)	34 (6.5)	-0.194	106697 (12.1)	34 (6.5)	-0.191	162662 (13.8)	68 (8)	-0.186
25-29	312835 (35.2)	140 (26.6)	-0.187	311436 (35.2)	137 (26.3)	-0.193	380011 (32.1)	196 (23.1)	-0.204
30-34	303247 (34.1)	200 (38)	0.081	301735 (34.1)	197 (37.8)	0.078	370686 (31.4)	322 (37.9)	0.137
≥35	152929 (17.2)	153 (29)	0.284	151971 (17.2)	153 (29.4)	0.292	225752 (19.1)	262 (30.8)	0.273
Smoking	100985 (11.3)	68 (12.9)	0.048	100326 (11.3)	67 (12.9)	0.047	Missing	Missing	Missing
BMI (kg/m^2)									
<20	111270 (12.5)	0 (0)	-0.535	110694 (12.5)	0 (0)	-0.535	Missing	Missing	Missing
20-25	456384 (51.3)	32 (6.1)	-1.154	454007 (51.3)	31 (6)	-1.159	Missing	Missing	Missing
25-30	200691 (22.6)	103 (19.5)	-0.074	199742 (22.6)	100 (19.2)	-0.083	Missing	Missing	Missing
30-35	78176 (8.8)	180 (34.2)	0.65	77764 (8.8)	177 (34)	0.646	Missing	Missing	Missing
>35	43251 (4.9)	212 (40.2)	0.934	43033 (4.9)	213 (40.9)	0.949	Missing	Missing	Missing
Parity at pregnancy onset[c]									
0	403990 (45.4)	188 (35.7)	-0.199	401762 (45.4)	187 (35.9)	-0.194	538867 (45.6)	285 (33.5)	-0.248
1	335947 (37.8)	217 (41.2)	0.07	334447 (37.8)	211 (40.5)	0.056	410820 (34.8)	312 (36.7)	0.041
2	114235 (12.8)	83 (15.7)	0.083	113647 (12.8)	84 (16.1)	0.093	169745 (14.4)	176 (20.7)	0.167
≥3	35600 (4)	39 (7.4)	0.147	35384 (4)	39 (7.5)	0.15	62631 (5.3)	77 (9.1)	0.146
Prior registered miscarriages									
None	767069 (86.2)	414 (78.6)	-0.202	763220 (86.2)	411 (78.9)	-0.194	1019331 (86.2)	655 (77.1)	-0.239
1	102235 (11.5)	87 (16.5)	0.145	101659 (11.5)	84 (16.1)	0.135	133887 (11.3)	151 (17.8)	0.183
≥2	20468 (2.3)	26 (4.9)	0.141	20361 (2.3)	26 (5)	0.144	28845 (2.4)	44 (5.2)	0.143
Previous SGA outcome[d]	54976 (6.2)	31 (5.9)	-0.012	54674 (6.2)	31 (6)	-0.009	77052 (6.5)	50 (5.9)	-0.026
Previous MCM outcome[d]	27289 (3.1)	33 (6.3)	0.152	27159 (3.1)	33 (6.3)	0.155	36496 (3.1)	55 (6.5)	0.159
Married/registered partnership	365516 (41.1)	222 (42.1)	0.021	363701 (41.1)	219 (42)	0.019	452537 (38.3)	334 (39.3)	0.021
Maternal place of birth									
Denmark	745223 (83.8)	459 (87.1)	0.095	741483 (83.8)	456 (87.5)	0.107	989370 (83.7)	722 (84.9)	0.034
Europe	69080 (7.8)	20 (3.8)	-0.171	68711 (7.8)	20 (3.8)	-0.168	89333 (7.6)	43 (5.1)	-0.103
Outside of Europe	75469 (8.5)	48 (9.1)	0.022	75046 (8.5)	45 (8.6)	0.006	103360 (8.7)	85 (10)	0.043

Region of residence									
The Capital Region	266835 (30)	195 (37)	0.149	265234 (30)	190 (36.5)	0.138	352050 (29.8)	288 (33.9)	0.088
Central Denmark	212573 (23.9)	109 (20.7)	-0.077	211735 (23.9)	109 (20.9)	-0.072	281554 (23.8)	184 (21.6)	-0.052
Northern Denmark	100296 (11.3)	50 (9.5)	-0.059	99698 (11.3)	50 (9.6)	-0.055	134598 (11.4)	96 (11.3)	-0.003
Region Zealand	111721 (12.6)	84 (15.9)	0.097	111105 (12.6)	82 (15.7)	0.092	152312 (12.9)	143 (16.8)	0.111
Southern Denmark	198347 (22.3)	89 (16.9)	-0.136	197468 (22.3)	90 (17.3)	-0.127	261549 (22.1)	139 (16.4)	-0.147
Season of conception									
Winter	219677 (24.7)	161 (30.6)	0.131	218708 (24.7)	160 (30.7)	0.134	290318 (24.6)	217 (25.5)	0.022
Spring	212691 (23.9)	163 (30.9)	0.158	211383 (23.9)	158 (30.3)	0.145	283758 (24)	242 (28.5)	0.102
Summer	219423 (24.7)	85 (16.1)	-0.213	218202 (24.6)	85 (16.3)	-0.208	294180 (24.9)	192 (22.6)	-0.054
Autumn	237981 (26.7)	118 (22.4)	-0.101	236947 (26.8)	118 (22.6)	-0.096	313807 (26.5)	199 (23.4)	-0.072
Plasma glucose ≥11.0 mmol/L									
Yes	Redacted	<5	Redacted	Redacted	<5	Redacted	182 (0)	5 (0.6)	0.105
No	26172 (2.9)	26 (4.9)	0.103	26036 (2.9)	26 (5)	0.105	35892 (3)	41 (4.8)	0.092
Not measured	863489 (97)	499 (94.7)	-0.119	859093 (97)	493 (94.6)	-0.121	1145989 (96.9)	804 (94.6)	-0.117
HbA1c ≥48.0 mmol/mol									
Yes	2298 (0.3)	64 (12.1)	0.509	2280 (0.3)	64 (12.3)	0.512	3126 (0.3)	92 (10.8)	0.474
No	109622 (12.3)	295 (56)	1.037	109166 (12.3)	290 (55.7)	1.029	143562 (12.1)	484 (56.9)	1.068
Not measured	777852 (87.4)	168 (31.9)	-1.373	773794 (87.4)	167 (32.1)	-1.367	1035375 (87.6)	274 (32.2)	-1.369
No. of hospital admissions within 1 year of pregnancy onset									
None	765953 (86.1)	500 (94.9)	0.303	762134 (86.1)	495 (95)	0.308	1005774 (85.1)	809 (95.2)	0.343
1	98195 (11)	20 (3.8)	-0.279	97631 (11)	20 (3.8)	-0.277	137919 (11.7)	28 (3.3)	-0.322
≥2	25624 (2.9)	7 (1.3)	-0.108	25475 (2.9)	6 (1.2)	-0.123	38370 (3.2)	13 (1.5)	-0.113
No. of outpatient visits within 1 year of pregnancy onset									
None	605933 (68.1)	393 (74.6)	0.144	602948 (68.1)	390 (74.9)	0.15	794642 (67.2)	631 (74.2)	0.155
1	154061 (17.3)	55 (10.4)	-0.2	153234 (17.3)	55 (10.6)	-0.196	207366 (17.5)	91 (10.7)	-0.197
2	70376 (7.9)	29 (5.5)	-0.096	69962 (7.9)	28 (5.4)	-0.102	96370 (8.2)	46 (5.4)	-0.109
≥3	59402 (6.7)	50 (9.5)	0.103	59096 (6.7)	48 (9.2)	0.094	83685 (7.1)	82 (9.6)	0.093
Prescription of drugs within 1 year of pregnancy onset									
Antiobesity preparations	2059 (0.2)	7 (1.3)	0.125	2042 (0.2)	7 (1.3)	0.126	3009 (0.3)	16 (1.9)	0.159
Insulins and analogues	1946 (0.2)	20 (3.8)	0.257	1920 (0.2)	20 (3.8)	0.259	2651 (0.2)	25 (2.9)	0.219
Antidiabetics, excl. GLP-1 RA	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0
Antihypertensives	12689 (1.4)	19 (3.6)	0.139	12607 (1.4)	19 (3.6)	0.142	17996 (1.5)	35 (4.1)	0.157
Lipid-modifying drugs	1752 (0.2)	11 (2.1)	0.179	1740 (0.2)	11 (2.1)	0.18	2482 (0.2)	20 (2.4)	0.191
Drugs used in IVF treatment	62279 (7)	48 (9.1)	0.078	61899 (7)	48 (9.2)	0.081	73520 (6.2)	57 (6.7)	0.02
Glucocorticoids	14790 (1.7)	18 (3.4)	0.112	14716 (1.7)	18 (3.5)	0.114	19741 (1.7)	30 (3.5)	0.117
Drugs for underactive thyroid	12440 (1.4)	18 (3.4)	0.132	12362 (1.4)	18 (3.5)	0.134	15666 (1.3)	30 (3.5)	0.144
Antimigraine drugs	17878 (2)	19 (3.6)	0.097	17789 (2)	19 (3.6)	0.099	23462 (2)	39 (4.6)	0.146
Antiepileptics	5040 (0.6)	7 (1.3)	0.079	5002 (0.6)	7 (1.3)	0.08	7669 (0.6)	14 (1.6)	0.094
Antipsychotics	6572 (0.7)	9 (1.7)	0.088	6532 (0.7)	9 (1.7)	0.09	11798 (1)	21 (2.5)	0.113
Anxiolytics	7036 (0.8)	5 (0.9)	0.017	7002 (0.8)	5 (1)	0.018	10998 (0.9)	13 (1.5)	0.054
Hypnotics	11641 (1.3)	18 (3.4)	0.139	11568 (1.3)	18 (3.5)	0.141	18054 (1.5)	25 (2.9)	0.096

Antidepressants	36669 (4.1)	44 (8.3)	0.176	36486 (4.1)	44 (8.4)	0.179	56167 (4.8)	84 (9.9)	0.198
Psychostimulants	Redacted	<5	Redacted	Redacted	<5	Redacted	7264 (0.6)	7 (0.8)	0.025
Drugs for obstructive airway diseases	31466 (3.5)	25 (4.7)	0.061	31287 (3.5)	25 (4.8)	0.063	42444 (3.6)	44 (5.2)	0.078
Antiinfectives	41457 (4.7)	31 (5.9)	0.055	41255 (4.7)	31 (6)	0.058	58173 (4.9)	50 (5.9)	0.043
NSAIDs	12075 (1.4)	17 (3.2)	0.125	12020 (1.4)	16 (3.1)	0.117	16714 (1.4)	33 (3.9)	0.154
Opioids	9146 (1)	14 (2.7)	0.121	9108 (1)	14 (2.7)	0.123	13595 (1.2)	20 (2.4)	0.092
No. of drugs prescribed									
None	667380 (75)	308 (58.4)	-0.357	664065 (75)	303 (58.2)	-0.363	880878 (74.5)	497 (58.5)	-0.345
1-2 drugs	209768 (23.6)	196 (37.2)	0.299	208628 (23.6)	195 (37.4)	0.305	281943 (23.9)	305 (35.9)	0.265
3-4 drugs	11681 (1.3)	21 (4)	0.167	11611 (1.3)	21 (4)	0.169	17657 (1.5)	44 (5.2)	0.206
≥5 drugs	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Diagnosis within 1 year of pregnancy onset									
Diabetes Type 1	1117 (0.1)	13 (2.5)	0.208	1106 (0.1)	13 (2.5)	0.21	1556 (0.1)	15 (1.8)	0.169
Diabetes Type 2	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0
PCOS	3842 (0.4)	11 (2.1)	0.149	3825 (0.4)	11 (2.1)	0.15	4600 (0.4)	13 (1.5)	0.117
Obesity	16312 (1.8)	59 (11.2)	0.386	16232 (1.8)	59 (11.3)	0.39	22390 (1.9)	85 (10)	0.348
Thyroid disorders	8059 (0.9)	11 (2.1)	0.097	8015 (0.9)	11 (2.1)	0.099	10165 (0.9)	15 (1.8)	0.08
Mood [affective] disorders	2110 (0.2)	9 (1.7)	0.15	2095 (0.2)	9 (1.7)	0.152	3460 (0.3)	15 (1.8)	0.146
Neurotic, stress-related and somatoform disorders	3581 (0.4)	13 (2.5)	0.174	3568 (0.4)	13 (2.5)	0.176	6070 (0.5)	25 (2.9)	0.187
Asthma	3911 (0.4)	6 (1.1)	0.079	3884 (0.4)	6 (1.2)	0.08	5407 (0.5)	11 (1.3)	0.09
Drug abuse	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Alcohol abuse	875 (0.1)	0 (0)	-0.044	870 (0.1)	0 (0)	-0.044	2016 (0.2)	0 (0)	-0.058
Behavioural syndromes associated with physiological disturbances and physical factors	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Hypertension	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Ischaemic heart diseases	70 (0)	0 (0)	-0.013	70 (0)	0 (0)	-0.013	118 (0)	0 (0)	-0.014

4.2.2. Adjusted characteristics, after trimming and weighting, sensitivity analysis 1b

Appendix table 6. Subgroup analysis of pregnancies of women without type 2 diabetes: Baseline characteristics after IPTW.

	Major congenital malformations[a]			Small for gestational age (SGA)[a]			Miscarriage/spontaneous abortion		
	No. (%) of pregnancies			No. (%) of pregnancies			No. (%) of pregnancies		
	Pseudopopulation, unexposed, N = 462 753	GLP-1 RA users, N = 512	Standardised mean difference	Pseudopopulation, unexposed, N = 456 811	GLP-1 RA users, N = 505	Standardised mean difference	Pseudopopulation, unexposed, N = 268 498	GLP-1 RA users, N = 839	Standardised mean difference
Maternal/pregnancy characteristics									
Year of pregnancy onset[b]									
<2016	25869 (5.6)	28 (5.5)	-0.003	25900 (5.7)	28 (5.4)	-0.003	13902 (5.2)	43 (5.1)	-0.003

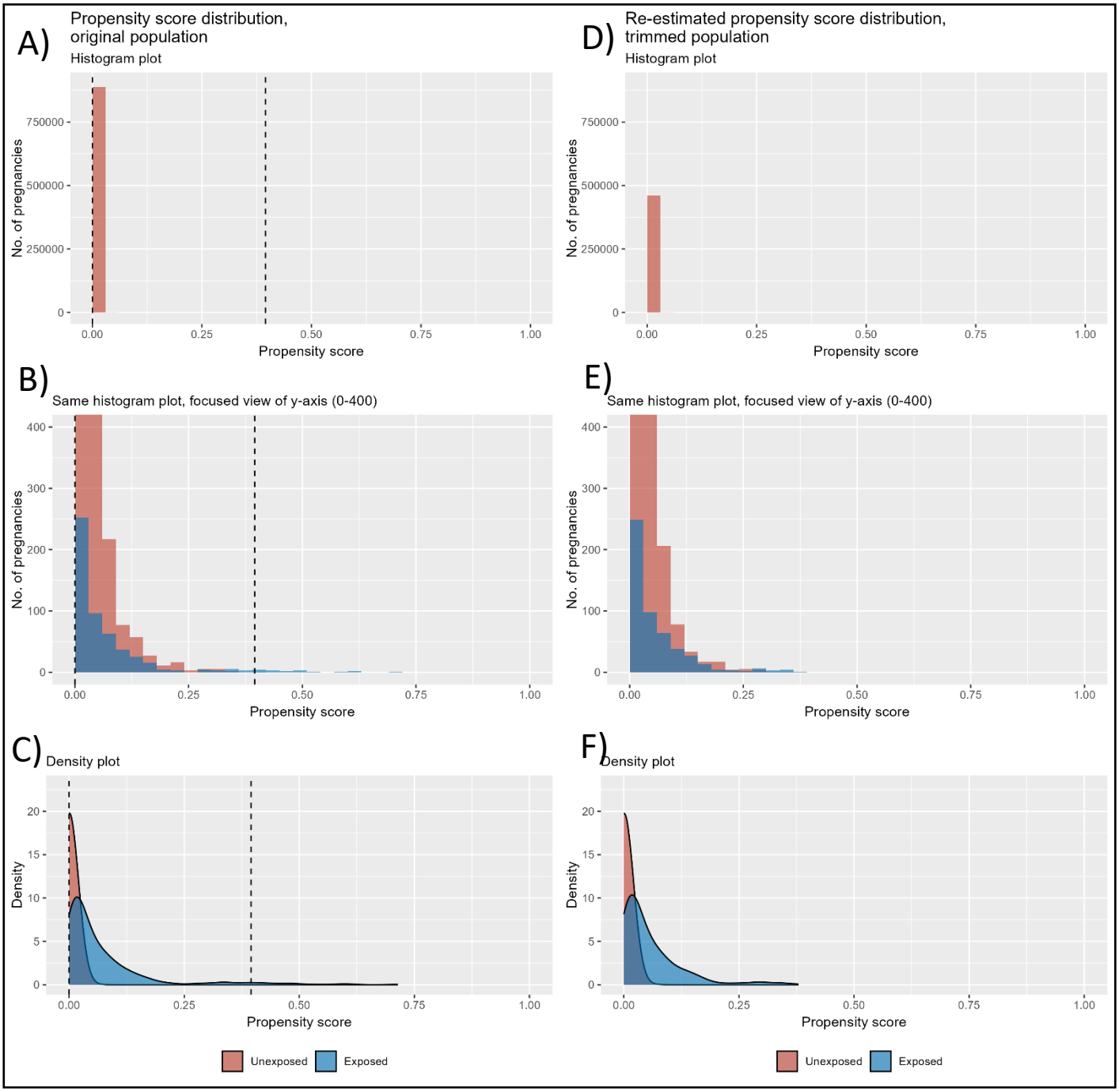
2016-2019	52670 (11.4)	58 (11.3)	-0.001	51763 (11.3)	57 (10.9)	-0.001	24625 (9.2)	76 (9.1)	-0.004
2020-2023	384214 (83)	426 (83.2)	0.004	379148 (83)	436 (83.7)	0.004	229971 (85.7)	720 (85.8)	0.005
Multipregnancy	8406 (1.8)	9 (1.8)	-0.004	8412 (1.8)	10 (1.9)	-0.004	3191 (1.2)	10 (1.2)	0
Age at pregnancy onset, years									
<20	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Redacted	<5	Redacted
20-24	31133 (6.7)	34 (6.6)	-0.003	31155 (6.8)	34 (6.5)	-0.003	21948 (8.2)	68 (8.1)	-0.002
25-29	126214 (27.3)	138 (27)	-0.007	124152 (27.2)	137 (26.3)	-0.005	63654 (23.7)	195 (23.2)	-0.01
30-34	176310 (38.1)	197 (38.5)	0.008	172445 (37.7)	197 (37.8)	0.006	101203 (37.7)	319 (38)	0.007
≥35	129096 (27.9)	143 (27.9)	0.001	129059 (28.3)	153 (29.4)	0.002	81022 (30.2)	255 (30.4)	0.005
Smoking	57542 (12.4)	64 (12.5)	0.002	56687 (12.4)	67 (12.9)	0.002	Missing	Missing	Missing
BMI (kg/m^2)									
<20	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Missing	Missing	Missing
20-25	29797 (6.4)	32 (6.2)	-0.005	28908 (6.3)	31 (6)	-0.005	Missing	Missing	Missing
25-30	95148 (20.6)	103 (20.1)	-0.01	92496 (20.2)	100 (19.2)	-0.01	Missing	Missing	Missing
30-35	157139 (34)	175 (34.2)	0.005	155098 (34)	177 (34)	0.007	Missing	Missing	Missing
>35	180668 (39)	202 (39.5)	0.01	180308 (39.5)	213 (40.9)	0.008	Missing	Missing	Missing
Parity at pregnancy onset[c]									
0	169165 (36.6)	186 (36.3)	-0.005	168328 (36.8)	187 (35.9)	-0.004	91347 (34)	285 (34)	-0.001
1	187982 (40.6)	208 (40.6)	0	183219 (40.1)	211 (40.5)	0.002	98922 (36.8)	308 (36.7)	-0.003
2	71322 (15.4)	80 (15.6)	0.006	71595 (15.7)	84 (16.1)	0.005	54905 (20.4)	173 (20.6)	0.004
≥3	34284 (7.4)	38 (7.4)	0.001	33669 (7.4)	39 (7.5)	-0.002	23324 (8.7)	73 (8.7)	0.001
Prior registered miscarriages									
None	367560 (79.4)	406 (79.3)	-0.003	365039 (79.9)	411 (78.9)	-0.003	208919 (77.8)	648 (77.2)	-0.015
1	75337 (16.3)	84 (16.4)	0.004	71949 (15.8)	84 (16.1)	0.003	46480 (17.3)	148 (17.6)	0.009
≥2	19856 (4.3)	22 (4.3)	0	19823 (4.3)	26 (5)	0.001	13099 (4.9)	43 (5.1)	0.012
Previous SGA outcome[d]	26691 (5.8)	30 (5.9)	0.004	26676 (5.8)	31 (6)	0.004	16084 (6)	50 (6)	-0.001
Previous MCM outcome[d]	25727 (5.6)	29 (5.7)	0.005	25692 (5.6)	33 (6.3)	0.006	15836 (5.9)	50 (6)	0.003
Married/registered partnership	196726 (42.5)	217 (42.4)	-0.003	193420 (42.3)	219 (42)	-0.003	106322 (39.6)	331 (39.5)	-0.003
Maternal place of birth									
Denmark	401924 (86.9)	445 (86.9)	0.002	398761 (87.3)	456 (87.5)	0.001	228316 (85)	713 (85)	-0.001
Europe	17458 (3.8)	19 (3.7)	-0.003	17488 (3.8)	20 (3.8)	-0.003	13843 (5.2)	43 (5.1)	-0.001
Outside of Europe	43370 (9.4)	48 (9.4)	0	40562 (8.9)	45 (8.6)	0.001	26339 (9.8)	83 (9.9)	0.003
Region of residence									
The Capital Region	171750 (37.1)	189 (36.9)	-0.004	167310 (36.6)	190 (36.5)	-0.004	91033 (33.9)	286 (34.1)	0.004
Central Denmark	93912 (20.3)	106 (20.7)	0.01	93278 (20.4)	109 (20.9)	0.009	58128 (21.6)	182 (21.7)	0.001
Northern Denmark	42102 (9.1)	47 (9.2)	0.003	42098 (9.2)	50 (9.6)	0.003	28993 (10.8)	91 (10.8)	0.002
Region Zealand	74971 (16.2)	82 (16)	-0.005	73157 (16)	82 (15.7)	-0.005	45451 (16.9)	141 (16.8)	-0.003
Southern Denmark	80017 (17.3)	88 (17.2)	-0.003	80968 (17.7)	90 (17.3)	-0.003	44894 (16.7)	139 (16.6)	-0.004
Season of conception									
Winter	142112 (30.7)	158 (30.9)	0.003	140597 (30.8)	160 (30.7)	0.003	68540 (25.5)	214 (25.5)	0

Spring	142250 (30.7)	157 (30.7)	-0.002	138345 (30.3)	158 (30.3)	0	76551 (28.5)	240 (28.6)	0.002
Summer	74966 (16.2)	83 (16.2)	0	75006 (16.4)	85 (16.3)	0	61131 (22.8)	191 (22.8)	0
Autumn	103424 (22.3)	114 (22.3)	-0.002	102863 (22.5)	118 (22.6)	-0.003	62277 (23.2)	194 (23.1)	-0.002
Plasma glucose ≥11.0 mmol/L									
Yes	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	0.006
No	23903 (5.2)	26 (5.1)	-0.004	23917 (5.2)	26 (5)	-0.004	13122 (4.9)	40 (4.8)	-0.006
Not measured	437874 (94.6)	485 (94.7)	0.005	431916 (94.6)	493 (94.6)	0.005	254181 (94.7)	795 (94.8)	0.004
HbA1c ≥48.0 mmol/mol									
Yes	43076 (9.3)	49 (9.6)	0.012	42434 (9.3)	64 (12.3)	0.01	23528 (8.8)	83 (9.9)	0.05
No	264534 (57.2)	295 (57.6)	0.01	260038 (56.9)	290 (55.7)	0.011	153829 (57.3)	482 (57.4)	0.003
Not measured	155143 (33.5)	168 (32.8)	-0.016	154338 (33.8)	167 (32.1)	-0.016	91141 (33.9)	274 (32.7)	-0.027
No. of hospital admissions within 1 year of pregnancy onset									
None	439322 (94.9)	486 (94.9)	-0.001	434285 (95.1)	495 (95)	-0.001	255681 (95.2)	799 (95.2)	0
1	17941 (3.9)	20 (3.9)	0.001	17941 (3.9)	20 (3.8)	0.001	8994 (3.3)	28 (3.3)	-0.001
≥2	5490 (1.2)	6 (1.2)	-0.001	4585 (1)	6 (1.2)	-0.001	3823 (1.4)	12 (1.4)	0.001
No. of outpatient visits within 1 year of pregnancy onset									
None	345828 (74.7)	383 (74.8)	0.002	342710 (75)	390 (74.9)	0.001	201365 (75)	627 (74.7)	-0.006
1	49998 (10.8)	55 (10.7)	-0.002	50014 (10.9)	55 (10.6)	-0.002	28105 (10.5)	87 (10.4)	-0.003
2	25647 (5.5)	28 (5.5)	-0.003	24704 (5.4)	28 (5.4)	-0.003	14458 (5.4)	46 (5.5)	0.004
≥3	41280 (8.9)	46 (9)	0.002	39383 (8.6)	48 (9.2)	0.003	24569 (9.2)	79 (9.4)	0.01
Prescription of drugs within 1 year of pregnancy onset									
Antiobesity preparations	6556 (1.4)	7 (1.4)	-0.005	6559 (1.4)	7 (1.3)	-0.005	4760 (1.8)	15 (1.8)	0.001
Insulins and analogues	16556 (3.6)	18 (3.5)	-0.005	16594 (3.6)	20 (3.8)	-0.005	7577 (2.8)	25 (3)	0.012
Antidiabetics, excl. GLP-1 RA	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0
Antihypertensives	17247 (3.7)	19 (3.7)	-0.001	17278 (3.8)	19 (3.6)	-0.001	10515 (3.9)	33 (3.9)	0.001
Lipid-modifying drugs	9199 (2)	10 (2)	-0.003	9197 (2)	11 (2.1)	-0.003	5146 (1.9)	17 (2)	0.01
Drugs used in IVF treatment	42233 (9.1)	46 (9)	-0.005	42245 (9.2)	48 (9.2)	-0.005	18110 (6.7)	56 (6.7)	-0.003
Glucocorticoids	16637 (3.6)	18 (3.5)	-0.005	16647 (3.6)	18 (3.5)	-0.005	9393 (3.5)	30 (3.6)	0.005
Drugs for underactive thyroid	16303 (3.5)	17 (3.3)	-0.013	16349 (3.6)	18 (3.5)	-0.014	9431 (3.5)	30 (3.6)	0.004
Antimigraine drugs	16302 (3.5)	18 (3.5)	0	16334 (3.6)	19 (3.6)	-0.001	12096 (4.5)	39 (4.6)	0.008
Antiepileptics	6371 (1.4)	7 (1.4)	-0.001	6374 (1.4)	7 (1.3)	-0.001	4481 (1.7)	14 (1.7)	0
Antipsychotics	8361 (1.8)	9 (1.8)	-0.004	8364 (1.8)	9 (1.7)	-0.004	6774 (2.5)	21 (2.5)	-0.001
Anxiolytics	4484 (1)	5 (1)	0.001	4489 (1)	5 (1)	0.001	3962 (1.5)	13 (1.5)	0.007
Hypnotics	16312 (3.5)	18 (3.5)	-0.001	16331 (3.6)	18 (3.5)	-0.001	7886 (2.9)	25 (3)	0.003
Antidepressants	38003 (8.2)	42 (8.2)	0	38055 (8.3)	44 (8.4)	-0.001	25694 (9.6)	83 (9.9)	0.012
Psychostimulants	Redacted	<5	Redacted	Redacted	<5	Redacted	2148 (0.8)	7 (0.8)	0.004
Drugs for	22468 (4.9)	25 (4.9)	0.001	22456 (4.9)	25 (4.8)	0.002	13241 (4.9)	42 (5)	0.004

obstructive airway diseases									
Antiinfectives	23864 (5.2)	27 (5.3)	0.005	23849 (5.2)	31 (6)	0.006	15288 (5.7)	50 (6)	0.012
NSAIDs	13674 (3)	15 (2.9)	-0.002	13352 (2.9)	16 (3.1)	0.003	9804 (3.7)	32 (3.8)	0.01
Opioids	10841 (2.3)	12 (2.3)	0	10856 (2.4)	14 (2.7)	0	5925 (2.2)	20 (2.4)	0.013
No. of drugs prescribed									
None	273959 (59.2)	303 (59.2)	0	268927 (58.9)	303 (58.2)	-0.001	159707 (59.5)	492 (58.6)	-0.018
1-2 drugs	168105 (36.3)	187 (36.5)	0.004	167133 (36.6)	195 (37.4)	0.005	94589 (35.2)	301 (35.9)	0.014
3-4 drugs	18655 (4)	20 (3.9)	-0.008	18694 (4.1)	21 (4)	-0.008	12911 (4.8)	42 (5)	0.011
≥5 drugs	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Diagnosis within 1 year of pregnancy onset									
Diabetes Type 1	10514 (2.3)	12 (2.3)	0.006	9910 (2.2)	13 (2.5)	0.001	4618 (1.7)	15 (1.8)	0.007
Diabetes Type 2	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0
PCOS	10544 (2.3)	11 (2.1)	-0.011	10543 (2.3)	11 (2.1)	-0.011	4313 (1.6)	13 (1.5)	-0.005
Obesity	49432 (10.7)	56 (10.9)	0.01	48781 (10.7)	59 (11.3)	0.008	24953 (9.3)	81 (9.7)	0.015
Thyroid disorders	10022 (2.2)	11 (2.1)	-0.001	10014 (2.2)	11 (2.1)	-0.001	4749 (1.8)	15 (1.8)	0.002
Mood [affective] disorders	8123 (1.8)	9 (1.8)	0	8117 (1.8)	9 (1.7)	0.001	4718 (1.8)	15 (1.8)	0.003
Neurotic, stress-related and somatoform disorders	11569 (2.5)	13 (2.5)	0.003	11562 (2.5)	13 (2.5)	0.003	7437 (2.8)	24 (2.9)	0.006
Asthma	5448 (1.2)	6 (1.2)	-0.001	5454 (1.2)	6 (1.2)	-0.001	3359 (1.3)	11 (1.3)	0.006
Drug abuse	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Alcohol abuse	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0
Behavioural syndromes associated with physiological disturbances and physical factors	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Hypertension	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Ischaemic heart diseases	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0

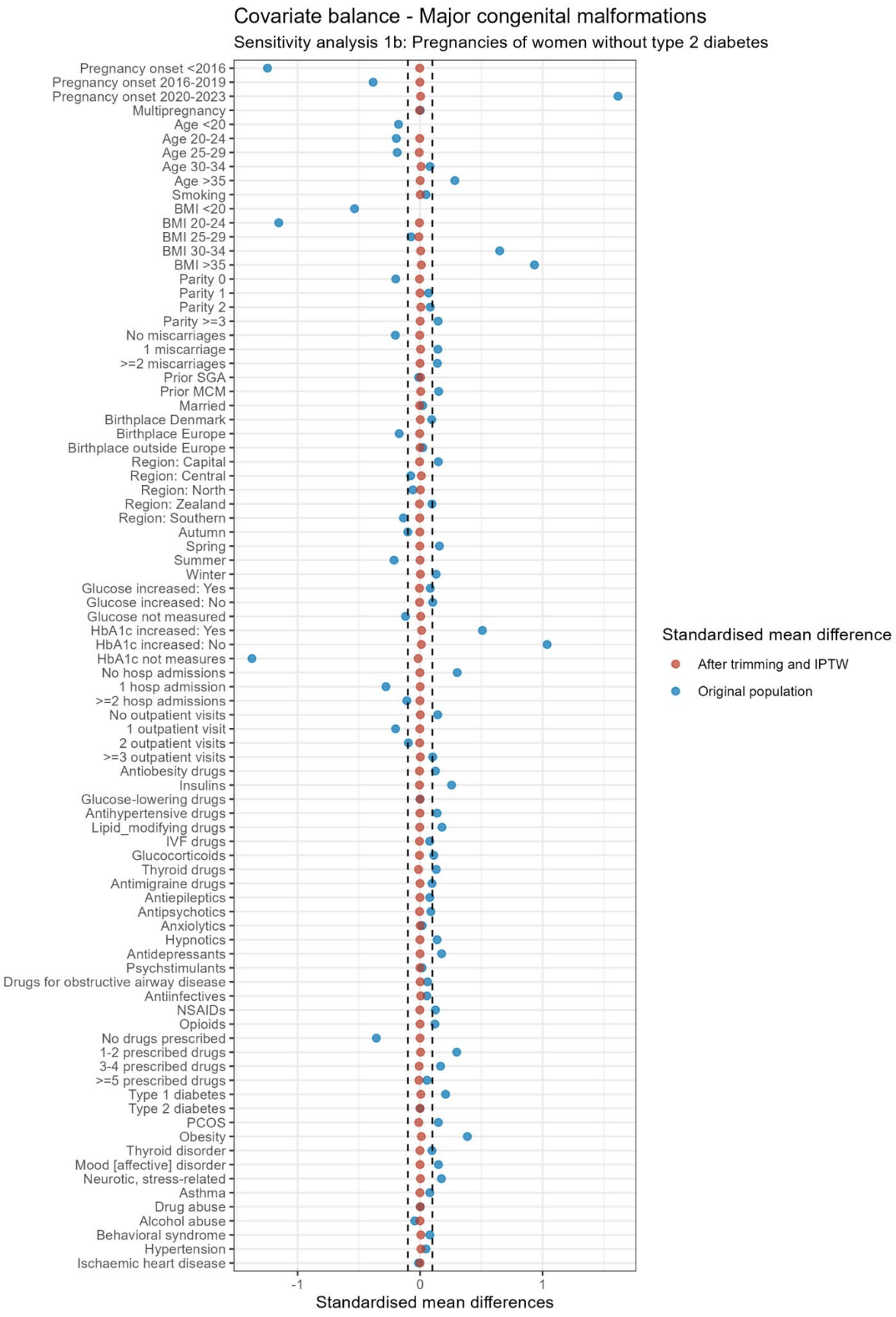
4.2.3. Supporting figures of PS distribution and covariate balance for the subpopulation without diabetes, sensitivity analysis 1b

Appendix figure 13. MCM population without T2D, PS distribution

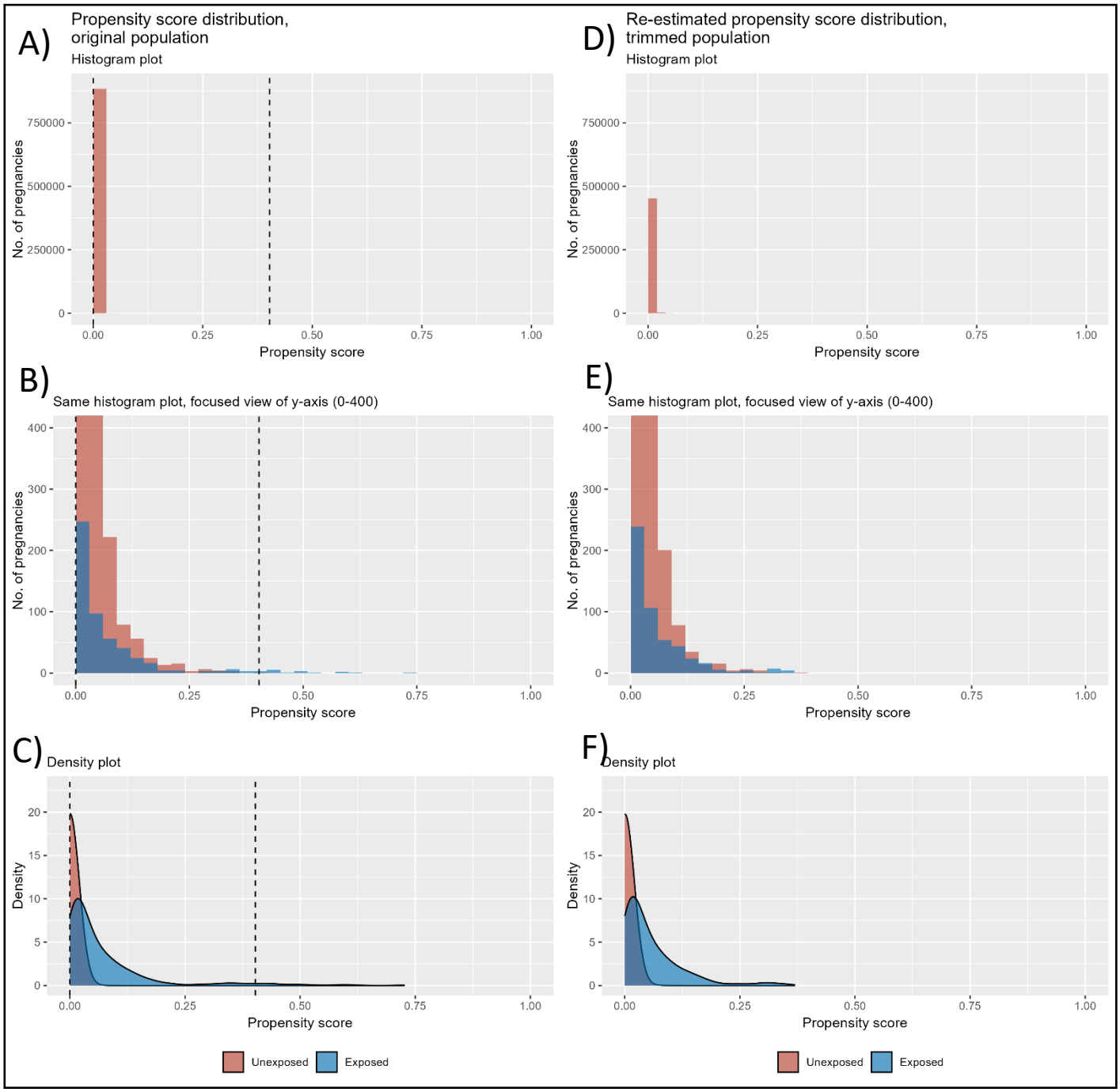


The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

Appendix figure 14. MCM population without T2D, covariate balance

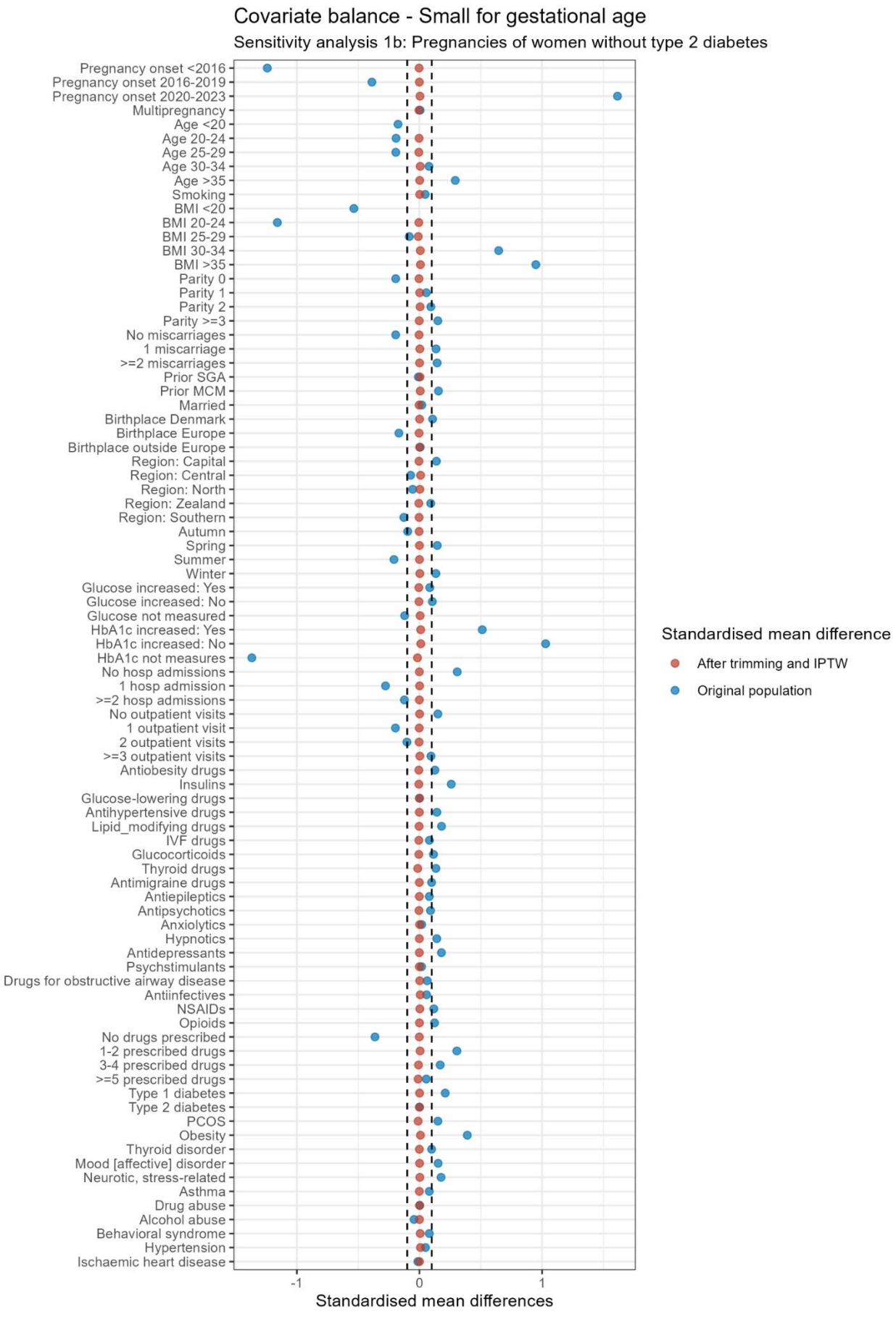


Appendix Figure 15. SGA population without T2D, PS distribution

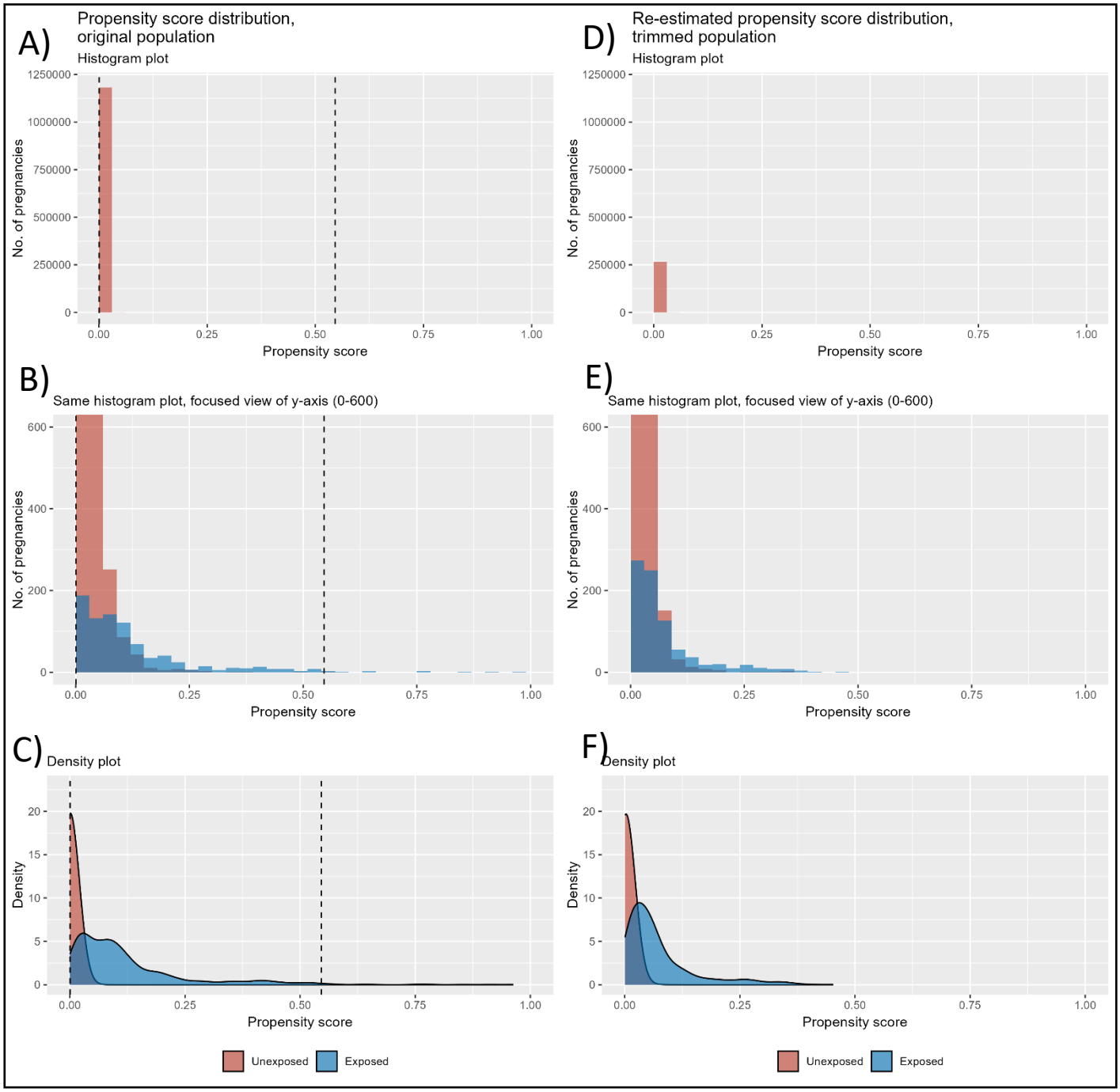


The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

Appendix Figure 16. SGA population without T2D, covariate balance

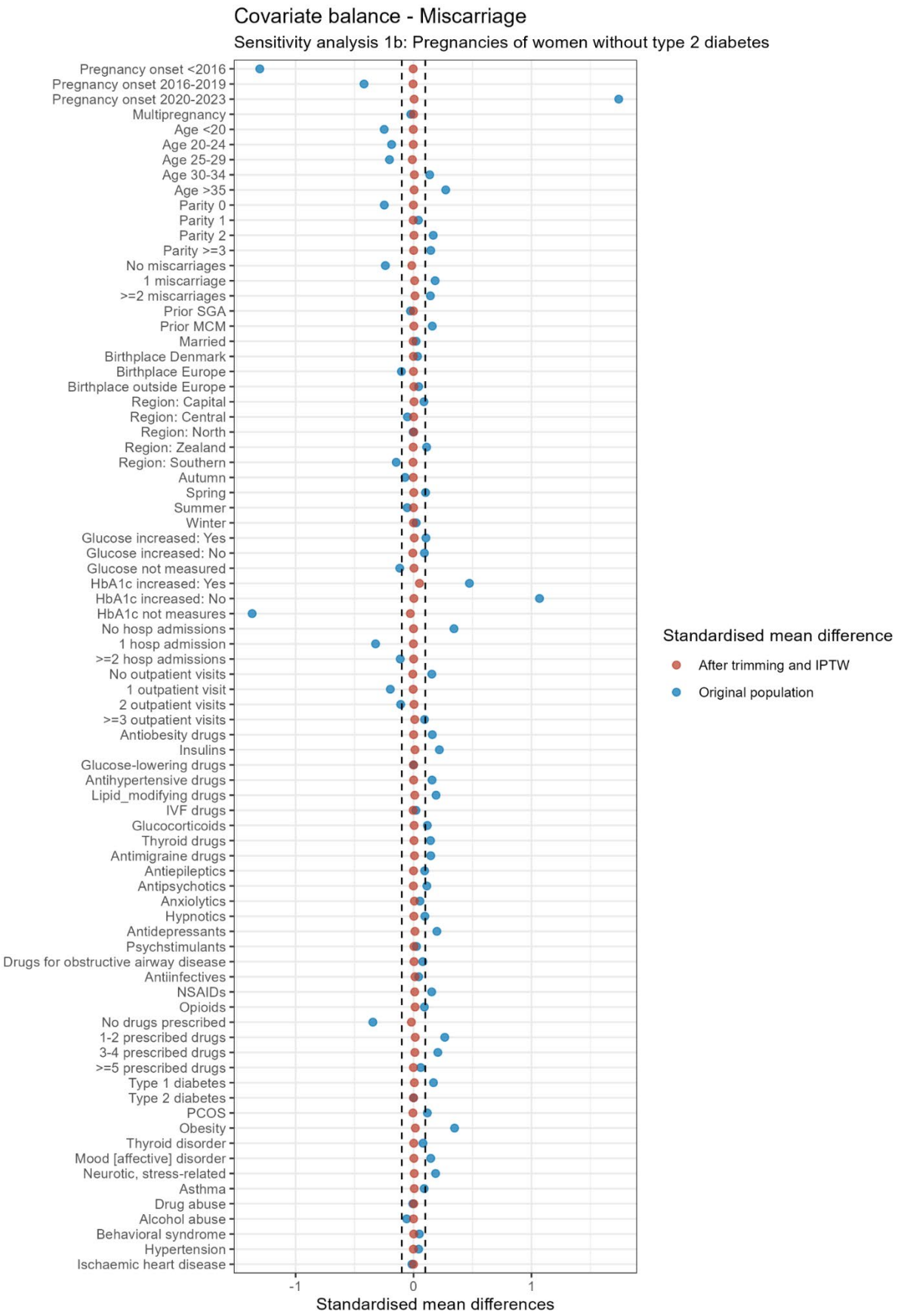


Appendix Figure 17. Miscarriage population without T2D, PS distribution



The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

Appendix Figure 18. Miscarriage population without T2D, covariate balance



Appendix 5. Sensitivity analysis 2. Pregnancies of users (exposed) vs. stoppers (unexposed, but prior GLP1RA users who filled a last prescription between 365 and 125 days before pregnancy)

5.1. Baseline characteristics, sensitivity analysis 2.

Appendix table 7. Subgroup analysis of pregnancies of GLP-1 RA stoppers vs non-stoppers: Baseline characteristics before IPTW.

	Major congenital malformations[a]			Small for gestational age (SGA)[a]			Miscarriage/spontaneous abortion		
	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference
	GLP-1 RA stoppers, N = 357	GLP-1 RA users, N = 697		GLP-1 RA stoppers, N = 354	GLP-1 RA users, N = 691		GLP-1 RA stoppers, N = 520	GLP-1 RA users, N = 1087	
Maternal/pregnancy characteristics									
Year of pregnancy onset[b]									
<2016	42 (11.8)	69 (9.9)	-0.06	42 (11.9)	69 (10)	-0.06	59 (11.3)	109 (10)	-0.043
2016-2019	48 (13.4)	108 (15.5)	0.058	47 (13.3)	107 (15.5)	0.063	65 (12.5)	138 (12.7)	0.006
2020-2023	267 (74.8)	520 (74.6)	-0.004	265 (74.9)	515 (74.5)	-0.008	396 (76.2)	840 (77.3)	0.027
Multipregnancy	8 (2.2)	14 (2)	-0.016	8 (2.3)	14 (2)	-0.016	9 (1.7)	14 (1.3)	-0.036
Age at pregnancy onset, years									
<20	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Redacted	<5	Redacted
20-24	20 (5.6)	46 (6.6)	0.042	20 (5.6)	46 (6.7)	0.042	37 (7.1)	85 (7.8)	0.027
25-29	100 (28)	195 (28)	-0.001	100 (28.2)	192 (27.8)	-0.01	140 (26.9)	264 (24.3)	-0.06
30-34	139 (38.9)	258 (37)	-0.04	137 (38.7)	255 (36.9)	-0.037	177 (34)	400 (36.8)	0.058
≥35	98 (27.5)	198 (28.4)	0.021	97 (27.4)	198 (28.7)	0.028	166 (31.9)	336 (30.9)	-0.022
Smoking	53 (14.8)	95 (13.6)	-0.035	53 (15)	94 (13.6)	-0.039	Missing	Missing	Missing
BMI (kg/m^2)									
<20	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Missing	Missing	Missing
20-25	14 (3.9)	40 (5.7)	0.085	14 (4)	39 (5.6)	0.079	Missing	Missing	Missing
25-30	67 (18.8)	130 (18.7)	-0.003	66 (18.6)	127 (18.4)	-0.007	Missing	Missing	Missing
30-35	116 (32.5)	230 (33)	0.011	115 (32.5)	227 (32.9)	0.008	Missing	Missing	Missing
>35	160 (44.8)	297 (42.6)	-0.044	159 (44.9)	298 (43.1)	-0.036	Missing	Missing	Missing
Parity at pregnancy onset[c]									
0	165 (46.2)	294 (42.2)	-0.081	163 (46)	293 (42.4)	-0.073	227 (43.7)	429 (39.5)	-0.085
1	127 (35.6)	261 (37.4)	0.039	126 (35.6)	255 (36.9)	0.027	177 (34)	370 (34)	0
2	41 (11.5)	96 (13.8)	0.069	41 (11.6)	97 (14)	0.074	74 (14.2)	198 (18.2)	0.108
≥3	24 (6.7)	46 (6.6)	-0.005	24 (6.8)	46 (6.7)	-0.005	42 (8.1)	90 (8.3)	0.007
Prior registered miscarriages									
None	289 (81)	567 (81.3)	0.01	286 (80.8)	564 (81.6)	0.021	419 (80.6)	865 (79.6)	-0.025
1	54 (15.1)	100 (14.3)	-0.022	54 (15.3)	97 (14)	-0.034	80 (15.4)	171 (15.7)	0.01
≥2	14 (3.9)	30 (4.3)	0.019	14 (4)	30 (4.3)	0.019	21 (4)	51 (4.7)	0.032
Previous SGA outcome[d]	17 (4.8)	32 (4.6)	-0.008	17 (4.8)	32 (4.6)	-0.008	28 (5.4)	54 (5)	-0.019
Previous MCM outcome[d]	18 (5)	40 (5.7)	0.031	18 (5.1)	40 (5.8)	0.031	27 (5.2)	64 (5.9)	0.03
Married/registered partnership	148 (41.5)	302 (43.3)	0.038	147 (41.5)	299 (43.3)	0.035	216 (41.5)	440 (40.5)	-0.022
Maternal place of birth									
Denmark	305 (85.4)	600 (86.1)	0.019	303 (85.6)	597 (86.4)	0.023	430 (82.7)	919 (84.5)	0.05
Europe	18 (5)	30 (4.3)	-0.035	17 (4.8)	30 (4.3)	-0.022	29 (5.6)	57 (5.2)	-0.015

Outside of Europe	34 (9.5)	67 (9.6)	0.003	34 (9.6)	64 (9.3)	-0.012	61 (11.7)	111 (10.2)	-0.049
Region of residence									
The Capital Region	127 (35.6)	262 (37.6)	0.042	125 (35.3)	257 (37.2)	0.039	180 (34.6)	371 (34.1)	-0.01
Central Denmark	74 (20.7)	146 (20.9)	0.005	74 (20.9)	146 (21.1)	0.006	113 (21.7)	236 (21.7)	0
Northern Denmark	34 (9.5)	66 (9.5)	-0.002	34 (9.6)	66 (9.6)	-0.002	47 (9)	120 (11)	0.067
Region Zealand	63 (17.6)	101 (14.5)	-0.086	63 (17.8)	99 (14.3)	-0.095	90 (17.3)	176 (16.2)	-0.03
Southern Denmark	59 (16.5)	122 (17.5)	0.026	58 (16.4)	123 (17.8)	0.038	90 (17.3)	184 (16.9)	-0.01
Season of conception									
Winter	84 (23.5)	201 (28.8)	0.121	84 (23.7)	200 (28.9)	0.119	108 (20.8)	265 (24.4)	0.086
Spring	91 (25.5)	210 (30.1)	0.104	89 (25.1)	205 (29.7)	0.102	136 (26.2)	306 (28.2)	0.045
Summer	70 (19.6)	115 (16.5)	-0.081	70 (19.8)	115 (16.6)	-0.081	123 (23.7)	246 (22.6)	-0.024
Autumn	112 (31.4)	171 (24.5)	-0.153	111 (31.4)	171 (24.7)	-0.148	153 (29.4)	270 (24.8)	-0.103
Plasma glucose ≥11.0 mmol/L									
Yes	<5	Redacted	Redacted	<5	Redacted	Redacted	5 (1)	14 (1.3)	0.031
No	28 (7.8)	38 (5.5)	-0.096	28 (7.9)	38 (5.5)	-0.096	40 (7.7)	55 (5.1)	-0.108
Not measured	325 (91)	649 (93.1)	0.077	322 (91)	643 (93.1)	0.077	475 (91.3)	1018 (93.7)	0.088
HbA1c ≥48.0 mmol/mol									
Yes	43 (12)	151 (21.7)	0.259	43 (12.1)	151 (21.9)	0.261	70 (13.5)	213 (19.6)	0.166
No	166 (46.5)	350 (50.2)	0.074	164 (46.3)	345 (49.9)	0.072	244 (46.9)	556 (51.1)	0.085
Not measured	148 (41.5)	196 (28.1)	-0.283	147 (41.5)	195 (28.2)	-0.282	206 (39.6)	318 (29.3)	-0.219
No. of hospital admissions within 1 year of pregnancy onset									
None	334 (93.6)	646 (92.7)	-0.035	331 (93.5)	641 (92.8)	-0.029	483 (92.9)	1007 (92.6)	-0.009
1	14 (3.9)	36 (5.2)	0.06	14 (4)	36 (5.2)	0.06	24 (4.6)	56 (5.2)	0.025
≥2	9 (2.5)	15 (2.2)	-0.024	9 (2.5)	14 (2)	-0.035	13 (2.5)	24 (2.2)	-0.019
No. of outpatient visits within 1 year of pregnancy onset									
None	239 (66.9)	489 (70.2)	0.069	237 (66.9)	486 (70.3)	0.073	348 (66.9)	766 (70.5)	0.077
1	62 (17.4)	87 (12.5)	-0.137	61 (17.2)	87 (12.6)	-0.131	82 (15.8)	134 (12.3)	-0.099
2	29 (8.1)	43 (6.2)	-0.076	29 (8.2)	42 (6.1)	-0.082	41 (7.9)	67 (6.2)	-0.067
≥3	27 (7.6)	78 (11.2)	0.125	27 (7.6)	76 (11)	0.116	49 (9.4)	120 (11)	0.053
Prescription of drugs within 1 year of pregnancy onset									
Antiobesity preparations	10 (2.8)	10 (1.4)	-0.095	9 (2.5)	10 (1.4)	-0.078	14 (2.7)	20 (1.8)	-0.057
Insulins and analogues	22 (6.2)	59 (8.5)	0.089	22 (6.2)	59 (8.5)	0.089	39 (7.5)	79 (7.3)	-0.009
Antidiabetics, excl. GLP-1 RA	56 (15.7)	142 (20.4)	0.122	55 (15.5)	142 (20.5)	0.131	81 (15.6)	200 (18.4)	0.075
Antihypertensives	27 (7.6)	50 (7.2)	-0.015	27 (7.6)	50 (7.2)	-0.015	47 (9)	86 (7.9)	-0.04
Lipid-modifying drugs	20 (5.6)	41 (5.9)	0.012	20 (5.6)	41 (5.9)	0.012	39 (7.5)	74 (6.8)	-0.027
Drugs used in IVF treatment	72 (20.2)	72 (10.3)	-0.276	71 (20.1)	72 (10.4)	-0.271	99 (19)	89 (8.2)	-0.32
Glucocorticoids	8 (2.2)	24 (3.4)	0.072	8 (2.3)	24 (3.5)	0.073	16 (3.1)	37 (3.4)	0.018
Drugs for underactive thyroid	23 (6.4)	24 (3.4)	-0.139	23 (6.5)	24 (3.5)	-0.139	28 (5.4)	42 (3.9)	-0.072
Antimigraine drugs	16 (4.5)	30 (4.3)	-0.009	16 (4.5)	30 (4.3)	-0.009	23 (4.4)	57 (5.2)	0.038
Antiepileptics	<5	Redacted	Redacted	<5	Redacted	Redacted	5 (1)	20 (1.8)	0.075
Antipsychotics	9 (2.5)	12 (1.7)	-0.055	9 (2.5)	12 (1.7)	-0.056	16 (3.1)	28 (2.6)	-0.03

Anxiolytics	<5	Redacted	Redacted	<5	Redacted	Redacted	6 (1.2)	16 (1.5)	0.028
Hypnotics	11 (3.1)	27 (3.9)	0.043	11 (3.1)	27 (3.9)	0.043	22 (4.2)	39 (3.6)	-0.033
Antidepressants	36 (10.1)	72 (10.3)	0.008	35 (9.9)	72 (10.4)	0.018	51 (9.8)	124 (11.4)	0.052
Psychostimulants	5 (1.4)	6 (0.9)	-0.051	5 (1.4)	6 (0.9)	-0.051	7 (1.3)	15 (1.4)	0.003
Drugs for obstructive airway diseases	25 (7)	39 (5.6)	-0.058	25 (7.1)	39 (5.6)	-0.058	36 (6.9)	62 (5.7)	-0.05
Antiinfectives	22 (6.2)	43 (6.2)	0	22 (6.2)	43 (6.2)	0	32 (6.2)	70 (6.4)	0.012
NSAIDs	16 (4.5)	25 (3.6)	-0.045	16 (4.5)	24 (3.5)	-0.053	20 (3.8)	45 (4.1)	0.015
Opioids	8 (2.2)	18 (2.6)	0.022	8 (2.3)	18 (2.6)	0.022	14 (2.7)	28 (2.6)	-0.007
No. of drugs prescribed									
None	144 (40.3)	317 (45.5)	0.104	143 (40.4)	312 (45.2)	0.096	202 (38.8)	506 (46.6)	0.156
1-2 drugs	170 (47.6)	296 (42.5)	-0.104	169 (47.7)	295 (42.7)	-0.102	247 (47.5)	442 (40.7)	-0.138
3-4 drugs	38 (10.6)	73 (10.5)	-0.006	37 (10.5)	73 (10.6)	0.004	62 (11.9)	115 (10.6)	-0.043
≥5 drugs	5 (1.4)	11 (1.6)	0.015	5 (1.4)	11 (1.6)	0.015	9 (1.7)	24 (2.2)	0.034
Diagnosis within 1 year of pregnancy onset									
Diabetes Type 1	6 (1.7)	21 (3)	0.088	6 (1.7)	21 (3)	0.089	10 (1.9)	25 (2.3)	0.026
Diabetes Type 2	27 (7.6)	67 (9.6)	0.073	27 (7.6)	67 (9.7)	0.074	38 (7.3)	88 (8.1)	0.03
PCOS	15 (4.2)	26 (3.7)	-0.024	15 (4.2)	26 (3.8)	-0.024	18 (3.5)	31 (2.9)	-0.035
Obesity	42 (11.8)	89 (12.8)	0.031	41 (11.6)	89 (12.9)	0.04	58 (11.2)	123 (11.3)	0.005
Thyroid disorders	10 (2.8)	15 (2.2)	-0.042	10 (2.8)	15 (2.2)	-0.042	11 (2.1)	21 (1.9)	-0.013
Mood [affective] disorders	<5	Redacted	Redacted	<5	Redacted	Redacted	5 (1)	17 (1.6)	0.054
Neurotic, stress-related and somatoform disorders	<5	Redacted	Redacted	<5	Redacted	Redacted	6 (1.2)	27 (2.5)	0.1
Asthma	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted
Drug abuse	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Alcohol abuse	0 (0)	0 (0)	0	0 (0)	0 (0)	0	<5	Redacted	Redacted
Behavioural syndromes associated with physiological disturbances and physical factors	Redacted	<5	Redacted	Redacted	<5	Redacted	<5	Redacted	Redacted
Hypertension	Redacted	<5	Redacted	Redacted	<5	Redacted	8 (1.5)	5 (0.5)	-0.109
Ischaemic heart diseases	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Redacted	<5	Redacted

5.2. Adjusted characteristics after trimming and weighting, sensitivity analysis 2.

Appendix table 8. Subgroup analysis of pregnancies of GLP-1 RA stoppers vs non-stoppers: Baseline characteristics after IPTW.

	Major congenital malformations[a]			Small for gestational age (SGA)[a]			Miscarriage/spontaneous abortion		
	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference
	Pseudopopulation, stoppers, N = 352	GLP-1 RA users, N = 689		Pseudopopulation, stoppers, N = 349	GLP-1 RA users, N = 683		Pseudopopulation, stoppers, N = 513	GLP-1 RA users, N = 1059	
Maternal/pregnancy characteristics									
Year of pregnancy onset[b]									
<2016	36 (10.3)	68 (9.9)	-0.014	36 (10.3)	68 (10)	-0.011	57 (11.1)	105 (9.9)	-0.039

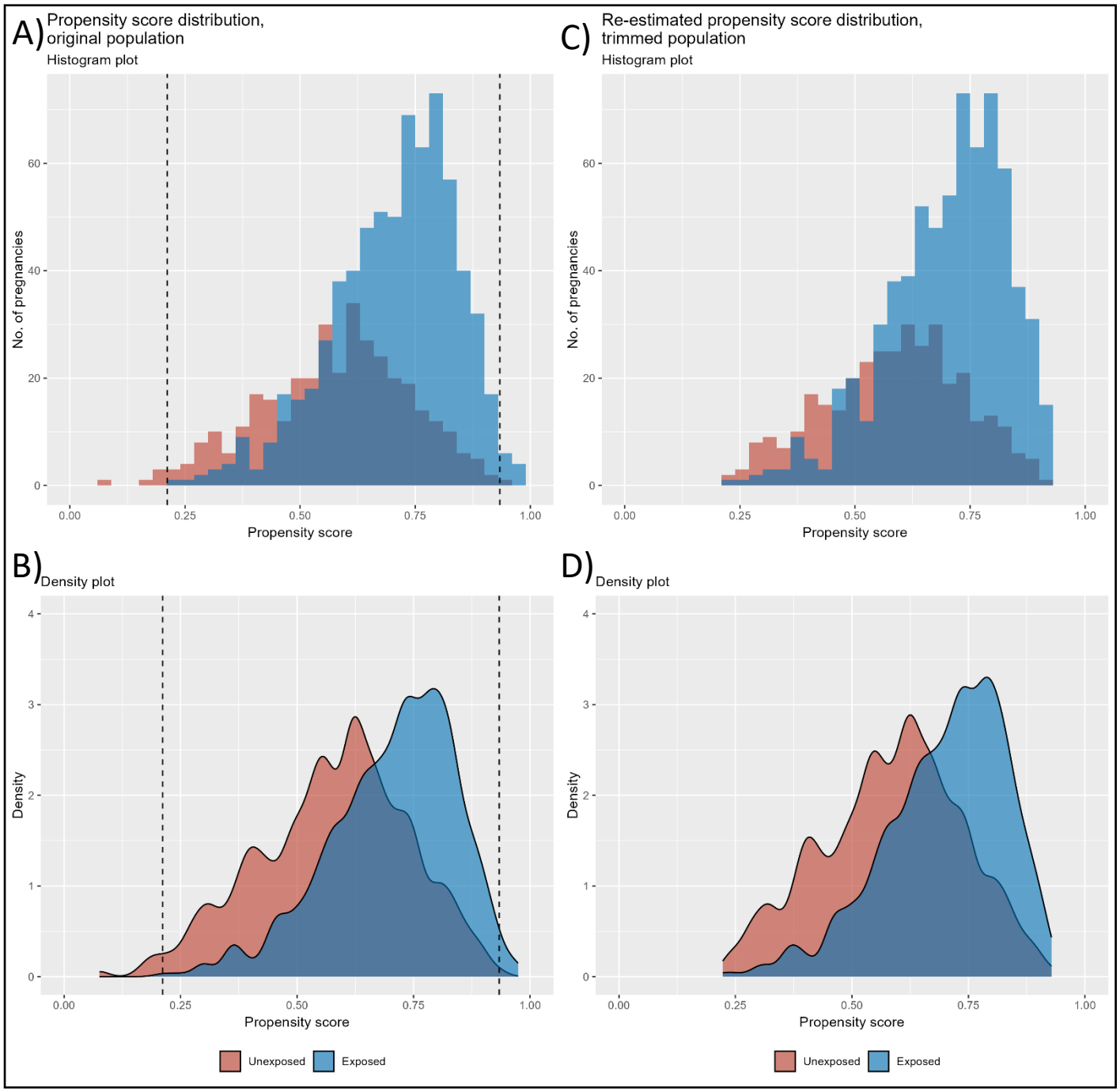
2016-2019	61 (17.3)	104 (15.1)	-0.062	61 (17.5)	103 (15.1)	-0.071	71 (13.8)	133 (12.6)	-0.037
2020-2023	255 (72.4)	517 (75)	0.06	252 (72.2)	512 (75)	0.065	385 (75.1)	821 (77.5)	0.057
Multipregnancy	7 (2)	14 (2)	0.002	7 (2)	14 (2)	0.003	6 (1.2)	14 (1.3)	0.007
Age at pregnancy onset, years									
<20									
20-24	19 (5.3)	46 (6.7)	0.057	18 (5.2)	46 (6.7)	0.064	39 (7.6)	83 (7.8)	0.009
25-29	106 (30.2)	194 (28.2)	-0.046	105 (30.2)	191 (28)	-0.049	127 (24.8)	261 (24.6)	-0.004
30-34	126 (35.9)	255 (37)	0.024	124 (35.5)	252 (36.9)	0.028	187 (36.5)	389 (36.7)	0.004
≥35	101 (28.6)	194 (28.2)	-0.01	102 (29.1)	194 (28.4)	-0.016	159 (31.1)	326 (30.8)	-0.006
Smoking	44 (12.4)	93 (13.5)	0.031	44 (12.6)	92 (13.5)	0.026	Missing	Missing	Missing
BMI (kg/m^2)									
<20	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Missing	Missing	Missing
20-25	31 (8.9)	40 (5.8)	-0.144	31 (8.8)	39 (5.7)	-0.143	Missing	Missing	Missing
25-30	70 (19.8)	128 (18.6)	-0.032	68 (19.5)	125 (18.3)	-0.031	Missing	Missing	Missing
30-35	110 (31.4)	226 (32.8)	0.031	109 (31.1)	223 (32.7)	0.032	Missing	Missing	Missing
>35	140 (39.9)	295 (42.8)	0.059	142 (40.6)	296 (43.3)	0.056	Missing	Missing	Missing
Parity at pregnancy onset[c]									
0	144 (40.9)	292 (42.4)	0.029	143 (40.9)	291 (42.6)	0.035	197 (38.5)	419 (39.6)	0.022
1	135 (38.4)	261 (37.9)	-0.011	133 (38)	255 (37.3)	-0.013	183 (35.6)	369 (34.8)	-0.016
2	48 (13.6)	90 (13.1)	-0.015	49 (13.9)	91 (13.3)	-0.017	93 (18.2)	184 (17.4)	-0.023
≥3	25 (7.1)	46 (6.7)	-0.018	25 (7.2)	46 (6.7)	-0.02	40 (7.7)	87 (8.2)	0.018
Prior registered miscarriages									
None	284 (80.7)	560 (81.3)	0.016	282 (80.8)	557 (81.6)	0.02	408 (79.5)	845 (79.8)	0.007
1	52 (14.9)	99 (14.4)	-0.014	52 (14.8)	96 (14.1)	-0.021	82 (16)	167 (15.8)	-0.006
≥2	16 (4.5)	30 (4.4)	-0.005	16 (4.4)	30 (4.4)	-0.002	23 (4.5)	47 (4.4)	-0.003
Previous SGA outcome[d]	14 (4)	32 (4.6)	0.032	13 (3.9)	32 (4.7)	0.038	23 (4.5)	52 (4.9)	0.018
Previous MCM outcome[d]	18 (5)	40 (5.8)	0.037	17 (5)	40 (5.9)	0.038	28 (5.5)	60 (5.7)	0.007
Married/registered partnership	151 (43)	295 (42.8)	-0.004	150 (43.1)	292 (42.8)	-0.007	212 (41.2)	427 (40.3)	-0.019
Maternal place of birth									
Denmark	305 (86.7)	595 (86.4)	-0.009	303 (86.8)	592 (86.7)	-0.003	434 (84.6)	895 (84.5)	-0.001
Europe	14 (4.1)	28 (4.1)	-0.001	15 (4.2)	28 (4.1)	-0.003	27 (5.2)	54 (5.1)	-0.005
Outside of Europe	33 (9.2)	66 (9.6)	0.011	32 (9.1)	63 (9.2)	0.005	52 (10.2)	110 (10.4)	0.005
Region of residence									
The Capital Region	132 (37.6)	257 (37.3)	-0.007	129 (36.9)	252 (36.9)	-0.001	175 (34.1)	360 (34)	-0.001
Central Denmark	77 (21.7)	146 (21.2)	-0.014	77 (22.1)	146 (21.4)	-0.017	108 (21.1)	231 (21.8)	0.017
Northern Denmark	34 (9.7)	65 (9.4)	-0.009	34 (9.7)	65 (9.5)	-0.006	60 (11.8)	114 (10.8)	-0.034
Region Zealand	43 (12.3)	101 (14.7)	0.064	43 (12.2)	99 (14.5)	0.061	79 (15.3)	173 (16.3)	0.027
Southern Denmark	66 (18.6)	120 (17.4)	-0.032	67 (19.1)	121 (17.7)	-0.036	91 (17.7)	181 (17.1)	-0.017
Season of conception									
Winter	98 (27.9)	198 (28.7)	0.02	98 (28.1)	197 (28.8)	0.017	123 (23.9)	254 (24)	0.001
Spring	105 (29.7)	207 (30)	0.007	102 (29.3)	202 (29.6)	0.005	144 (28.1)	297 (28)	-0.002
Summer	61 (17.3)	114 (16.5)	-0.019	61 (17.4)	114 (16.7)	-0.019	114 (22.2)	241 (22.8)	0.012
Autumn	88 (25.1)	170 (24.7)	-0.01	88 (25.1)	170 (24.9)	-0.005	132 (25.7)	267 (25.2)	-0.011
Plasma glucose ≥11.0 mmol/L									
Yes	5 (1.5)	10 (1.5)	-0.008	5 (1.6)	10 (1.5)	-0.008	6 (1.2)	14 (1.3)	0.009
No	19 (5.3)	38 (5.5)	0.01	19 (5.3)	38 (5.6)	0.01	26 (5.2)	55 (5.2)	0.001

Not measured	328 (93.2)	641 (93)	-0.006	325 (93.1)	635 (93)	-0.006	480 (93.6)	990 (93.5)	-0.005
HbA1c ≥48.0 mmol/mol									
Yes	83 (23.6)	144 (20.9)	-0.073	84 (24.1)	144 (21.1)	-0.08	96 (18.7)	195 (18.4)	-0.008
No	169 (48.1)	349 (50.7)	0.051	166 (47.6)	344 (50.4)	0.055	260 (50.6)	547 (51.7)	0.021
Not measured	100 (28.3)	196 (28.4)	0.003	99 (28.3)	195 (28.6)	0.005	157 (30.7)	317 (29.9)	-0.015
No. of hospital admissions within 1 year of pregnancy onset									
None	327 (92.9)	639 (92.7)	-0.008	324 (92.9)	634 (92.8)	-0.004	473 (92.2)	984 (92.9)	0.029
1	18 (5.1)	36 (5.2)	0.008	18 (5.2)	36 (5.3)	0.005	27 (5.4)	54 (5.1)	-0.012
≥2	7 (2)	14 (2)	0.003	7 (1.9)	13 (1.9)	0	13 (2.5)	21 (2)	-0.034
No. of outpatient visits within 1 year of pregnancy onset									
None	251 (71.4)	487 (70.7)	-0.016	251 (71.9)	484 (70.9)	-0.022	358 (69.9)	752 (71)	0.025
1	41 (11.7)	86 (12.5)	0.022	40 (11.5)	86 (12.6)	0.031	62 (12.2)	131 (12.4)	0.006
2	22 (6.4)	43 (6.2)	-0.005	22 (6.3)	42 (6.1)	-0.004	36 (7.1)	67 (6.3)	-0.03
≥3	37 (10.6)	73 (10.6)	0.001	36 (10.4)	71 (10.4)	0.001	56 (10.9)	109 (10.3)	-0.02
Prescription of drugs within 1 year of pregnancy onset									
Antiobesity preparations	5 (1.3)	10 (1.5)	0.009	5 (1.3)	10 (1.5)	0.01	10 (2)	19 (1.8)	-0.015
Insulins and analogues	33 (9.3)	55 (8)	-0.051	33 (9.4)	55 (8.1)	-0.053	36 (6.9)	73 (6.9)	-0.001
Antidiabetics, excl. GLP-1 RA	76 (21.4)	138 (20)	-0.037	76 (21.7)	138 (20.2)	-0.039	93 (18.1)	188 (17.8)	-0.01
Antihypertensives	30 (8.6)	48 (7)	-0.064	31 (8.7)	48 (7)	-0.066	41 (7.9)	78 (7.4)	-0.02
Lipid-modifying drugs	21 (5.9)	40 (5.8)	-0.003	21 (6)	40 (5.9)	-0.006	37 (7.3)	72 (6.8)	-0.019
Drugs used in IVF treatment	39 (11.1)	72 (10.4)	-0.02	39 (11.3)	72 (10.5)	-0.021	46 (9.1)	89 (8.4)	-0.019
Glucocorticoids	11 (3.2)	24 (3.5)	0.018	11 (3.1)	24 (3.5)	0.023	18 (3.4)	35 (3.3)	-0.008
Drugs for underactive thyroid	12 (3.4)	23 (3.3)	-0.005	12 (3.5)	23 (3.4)	-0.005	21 (4.1)	40 (3.8)	-0.016
Antimigraine drugs	14 (4)	29 (4.2)	0.009	14 (4)	29 (4.2)	0.012	23 (4.4)	49 (4.6)	0.011
Antiepileptics	<5	Redacted	Redacted	<5	Redacted	Redacted	6 (1.1)	15 (1.4)	0.025
Antipsychotics	5 (1.4)	11 (1.6)	0.013	5 (1.5)	11 (1.6)	0.006	14 (2.8)	25 (2.4)	-0.025
Anxiolytics	<5	Redacted	Redacted	<5	Redacted	Redacted	5 (1)	13 (1.2)	0.019
Hypnotics	11 (3)	27 (3.9)	0.049	10 (3)	27 (4)	0.053	15 (2.9)	38 (3.6)	0.038
Antidepressants	28 (7.9)	67 (9.7)	0.061	27 (7.7)	67 (9.8)	0.071	48 (9.3)	112 (10.6)	0.042
Psychostimulants	<5	Redacted	Redacted	<5	Redacted	Redacted	6 (1.2)	13 (1.2)	0.005
Drugs for obstructive airway diseases	19 (5.3)	37 (5.4)	0.004	18 (5.3)	37 (5.4)	0.007	31 (6)	57 (5.4)	-0.024
Antiinfectives	16 (4.7)	42 (6.1)	0.059	16 (4.7)	42 (6.1)	0.06	33 (6.5)	66 (6.2)	-0.01
NSAIDs	11 (3)	25 (3.6)	0.032	10 (2.8)	24 (3.5)	0.034	22 (4.2)	42 (4)	-0.012
Opioids	6 (1.8)	18 (2.6)	0.051	6 (1.8)	18 (2.6)	0.053	12 (2.4)	27 (2.5)	0.011
No. of drugs prescribed									
None	163 (46.3)	316 (45.9)	-0.009	162 (46.3)	311 (45.5)	-0.016	241 (46.9)	501 (47.3)	0.008
1-2 drugs	152 (43.1)	294 (42.7)	-0.009	150 (43)	293 (42.9)	-0.003	210 (40.9)	433 (40.9)	-0.001
3-4 drugs	33 (9.3)	69 (10)	0.023	33 (9.4)	69 (10.1)	0.023	51 (9.9)	105 (9.9)	0.002
≥5 drugs	<5	Redacted	Redacted	<5	Redacted	Redacted	12 (2.3)	20 (1.9)	-0.029
Diagnosis within 1 year of pregnancy onset									
Diabetes Type 1	9 (2.5)	20 (2.9)	0.028	9 (2.5)	20 (2.9)	0.026	11 (2.1)	23 (2.2)	0.006
Diabetes Type 2	35 (10)	65 (9.4)	-0.022	36 (10.2)	65 (9.5)	-0.025	40 (7.8)	83 (7.8)	0.002
PCOS	16 (4.6)	26 (3.8)	-0.041	16 (4.6)	26 (3.8)	-0.043	18 (3.5)	31 (2.9)	-0.03
Obesity	52 (14.8)	85 (12.3)	-0.076	52 (14.9)	85 (12.4)	-0.074	58 (11.3)	115 (10.9)	-0.016

Thyroid disorders	10 (2.9)	14 (2)	-0.059	10 (2.9)	14 (2)	-0.054	9 (1.8)	19 (1.8)	0.003
Mood [affective] disorders	<5	Redacted	Redacted	<5	Redacted	Redacted	6 (1.2)	12 (1.1)	-0.006
Neurotic, stress-related and somatoform disorders	<5	Redacted	Redacted	<5	Redacted	Redacted	8 (1.5)	19 (1.8)	0.021
Asthma	<5	Redacted	Redacted	<5	Redacted	Redacted	6 (1.2)	9 (0.8)	-0.044
Drug abuse	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Alcohol abuse	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0
Behavioural syndromes associated with physiological disturbances and physical factors	Redacted	<5	Redacted	Redacted	<5	Redacted	<5	Redacted	Redacted
Hypertension	Redacted	<5	Redacted	Redacted	<5	Redacted	<5	Redacted	Redacted
Ischaemic heart diseases	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Redacted	<5	Redacted

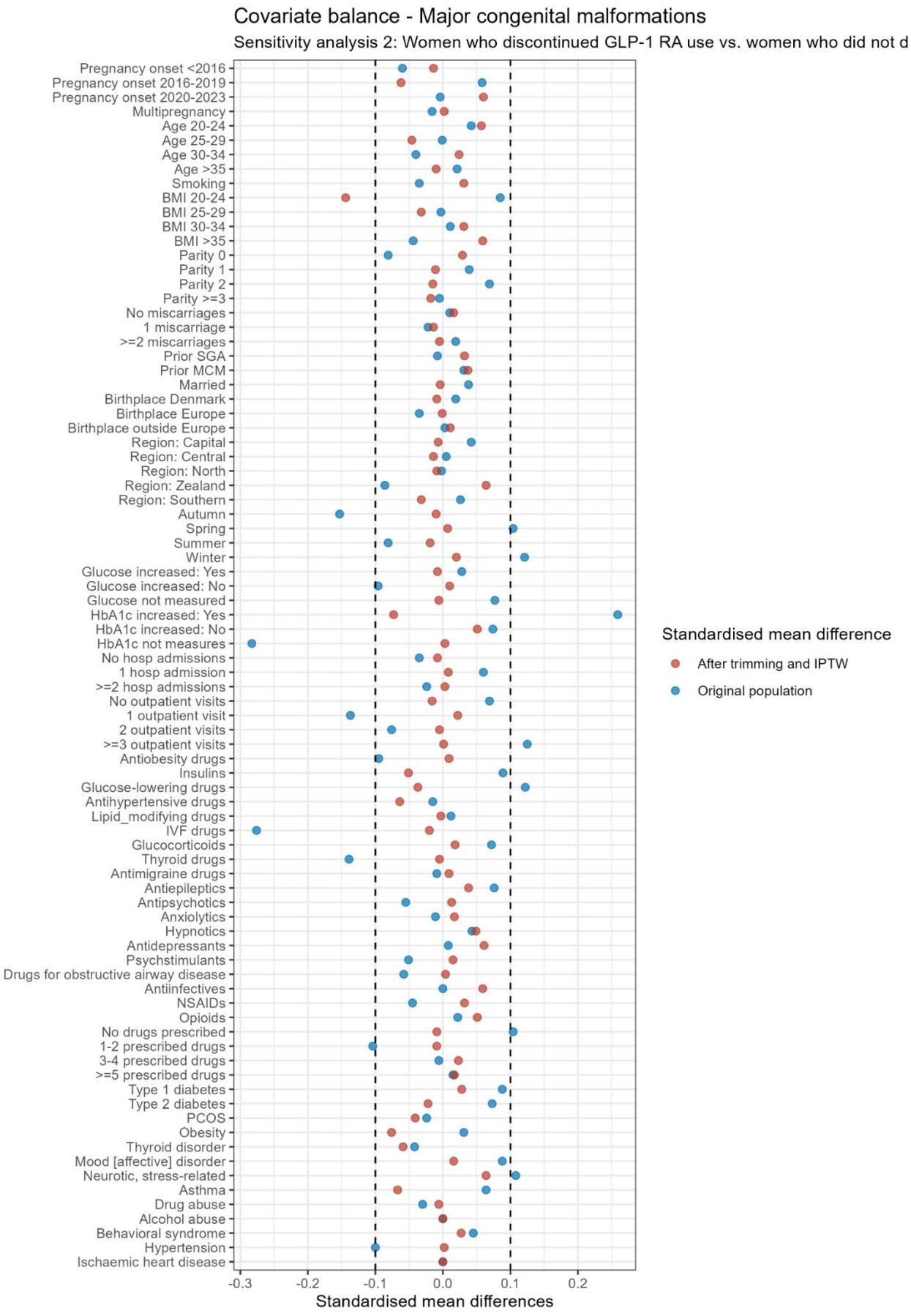
5.3. Supporting figures of PS distribution and covariate balance, sensitivity analysis 2

Appendix figure 19. Stoppers vs users, MCM population, PS distribution

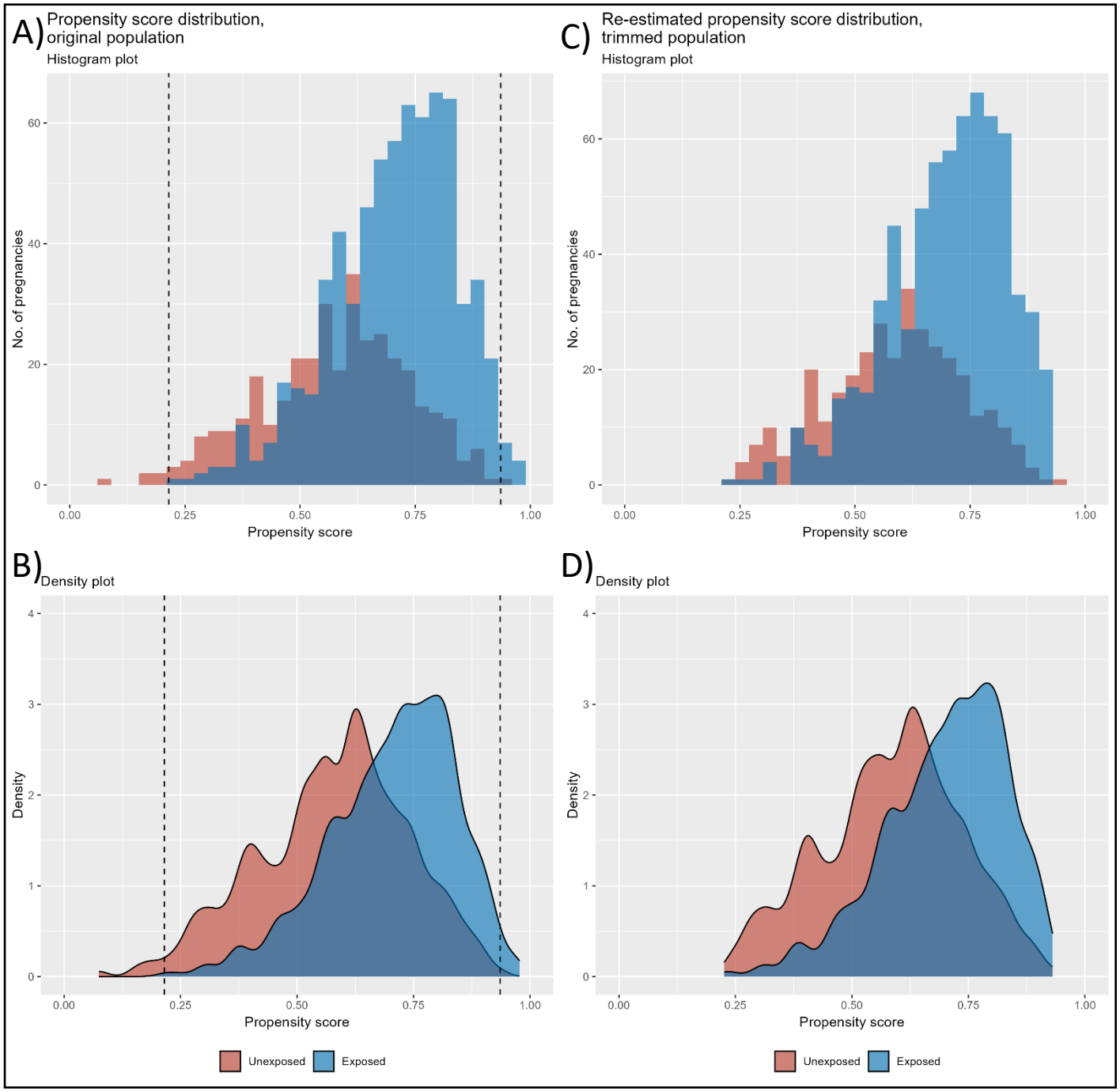


Unexposed: the stoppers.

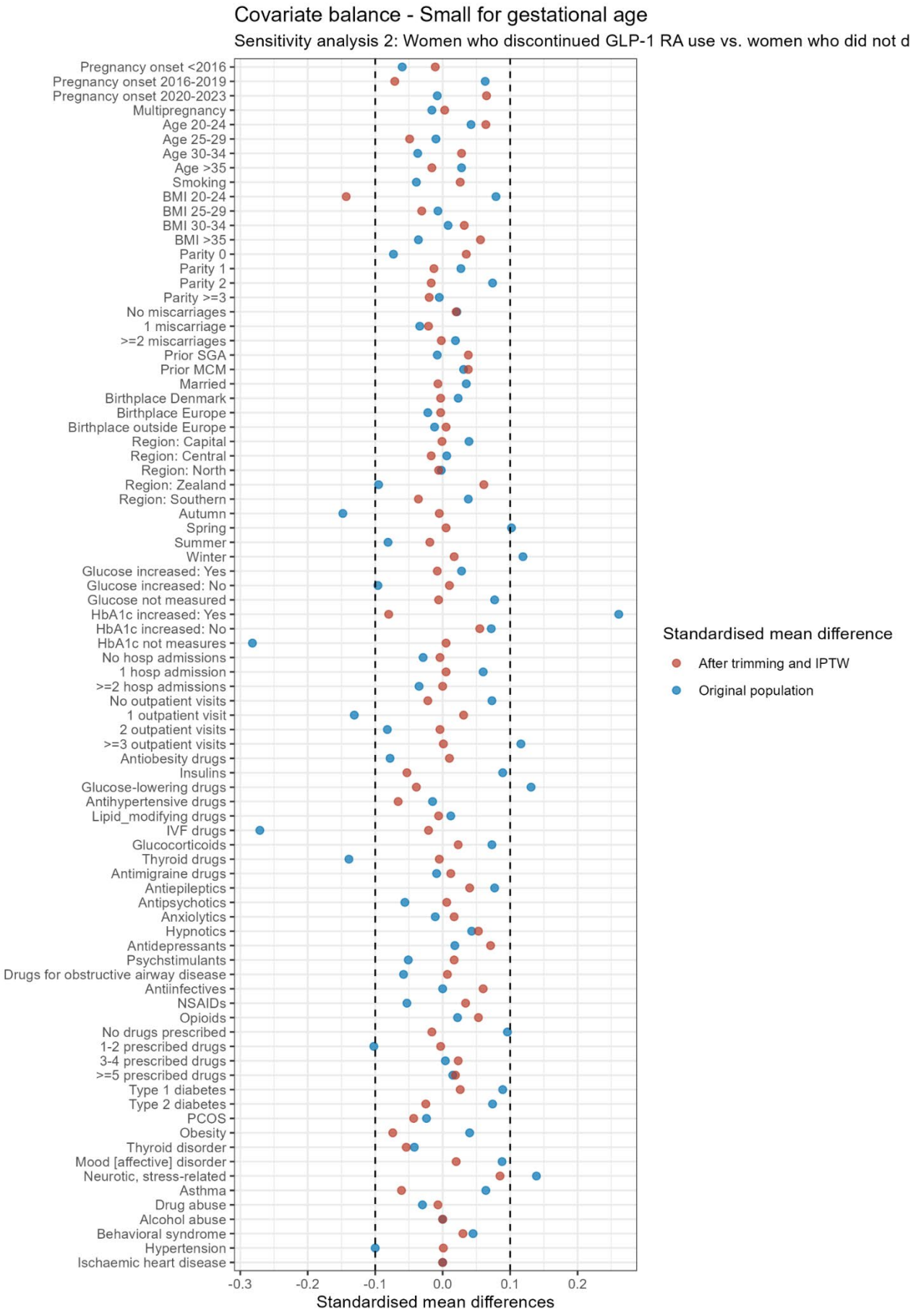
Appendix figure 20. Stoppers vs users, MCM population, covariate balance



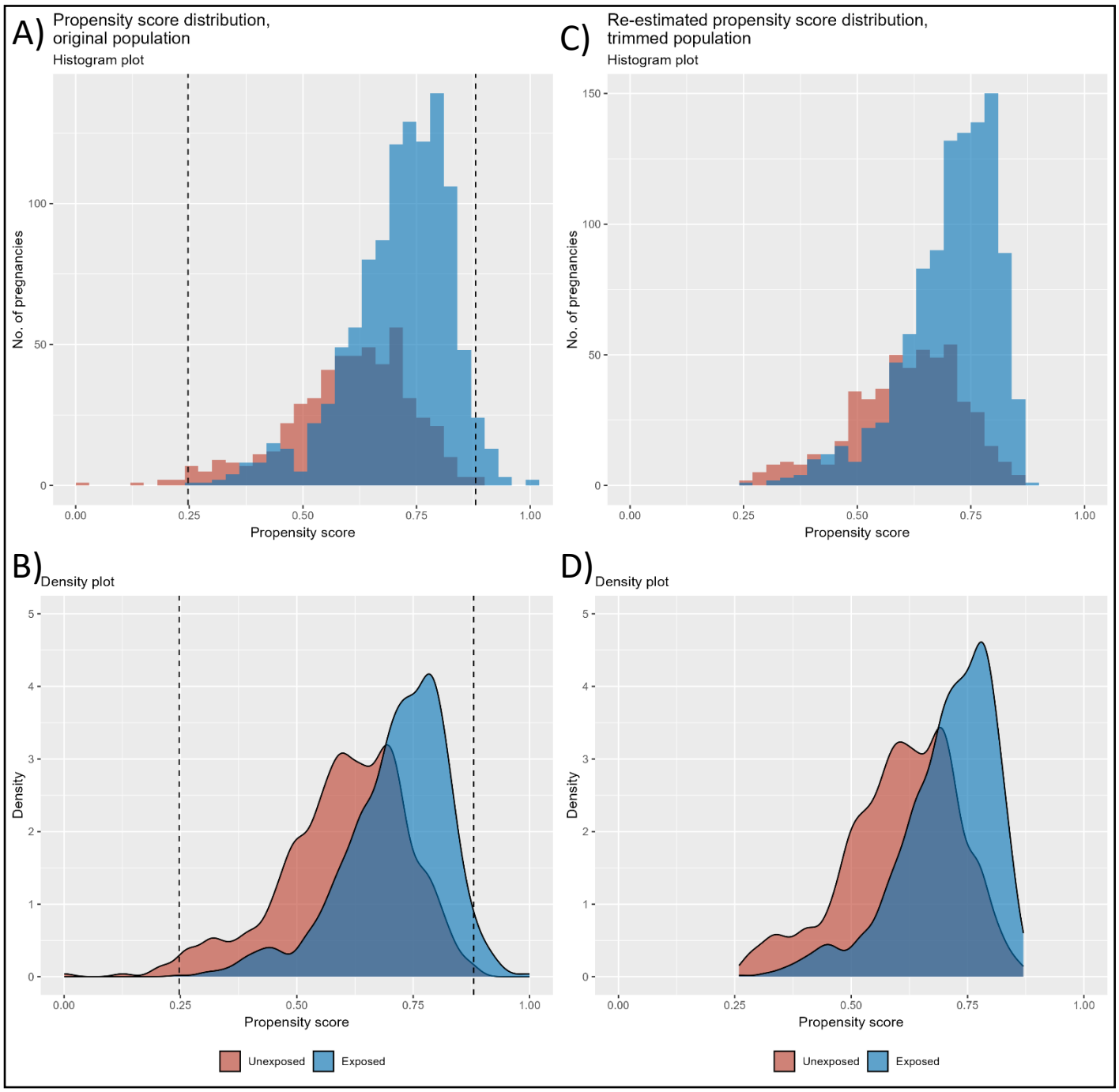
Appendix figure 21. Stoppers vs users, SGA population, PS distribution



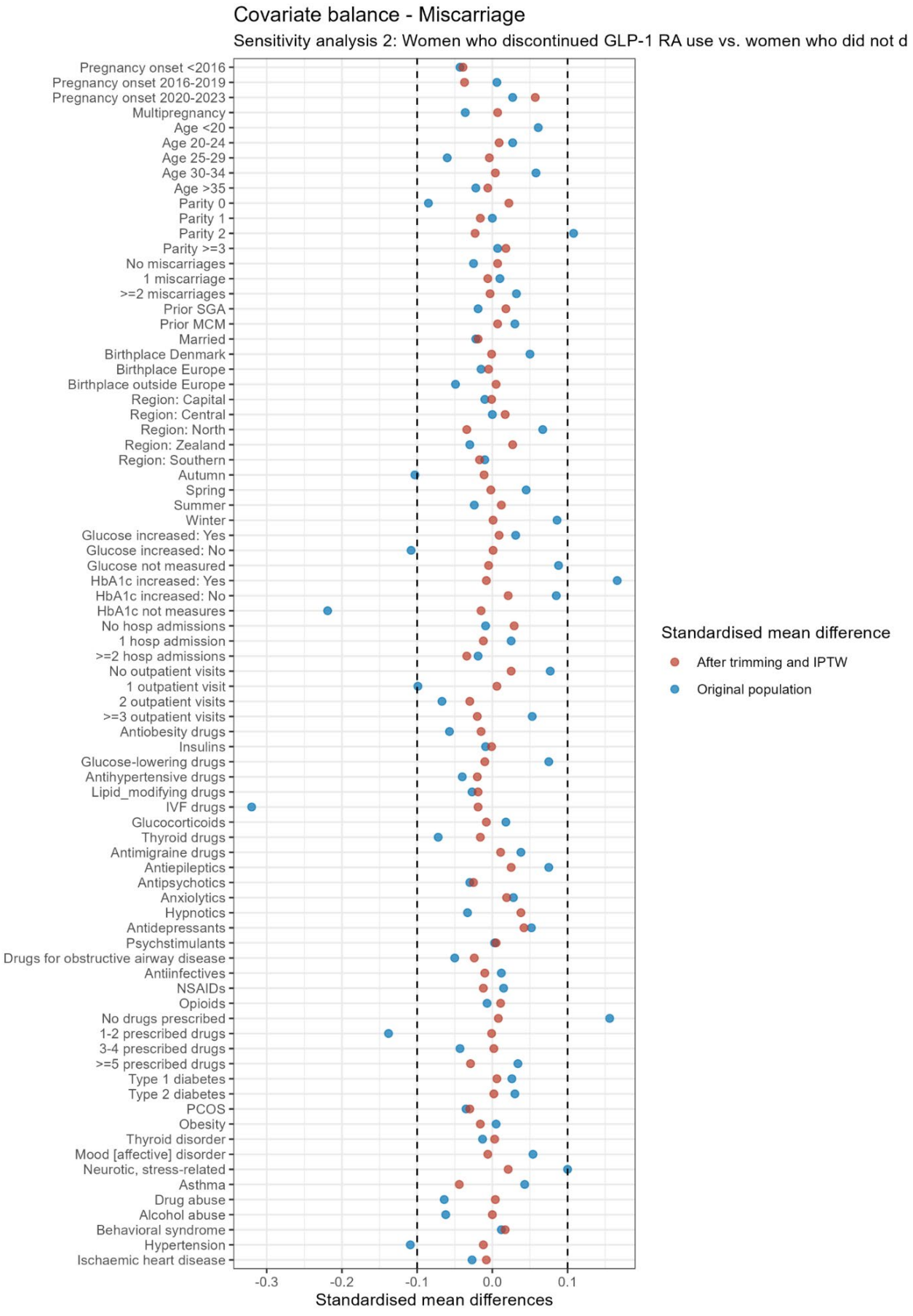
Appendix figure 22. Stoppers vs users, SGA population, covariate balance



Appendix figure 23. Stoppers vs users, miscarriage population, PS distribution



Appendix figure 24. Stoppers vs users, miscarriage population, covariate balance



Appendix 6. Sensitivity analysis 3. Exposure definition changed to begin at date of LMP

6.1. Baseline characteristics, sensitivity analysis 3.

Appendix table 9. Subgroup analysis of narrower expoure definition: Baseline characteristics before IPTW.

	Major congenital malformations[a]			Small for gestational age (SGA)[a]			Miscarriage/spontaneous abortion		
	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference
	Unexposed, N = 900 376	GLP-1 RA users, N = 357		Unexposed, N = 895 768	GLP-1 RA users, N = 362		Unexposed, N = 1 194 817	GLP-1 RA users, N = 598	
Maternal/pregnancy characteristics									
Year of pregnancy onset[b]									
<2016	482301 (53.6)	37 (10.4)	-1.045	479073 (53.5)	37 (10.2)	-1.048	659684 (55.2)	63 (10.5)	-1.081
2016-2019	230043 (25.5)	49 (13.7)	-0.301	229380 (25.6)	54 (14.9)	-0.268	293292 (24.5)	69 (11.5)	-0.343
2020-2023	188032 (20.9)	271 (75.9)	1.319	187315 (20.9)	271 (74.9)	1.283	241841 (20.2)	466 (77.9)	1.413
Multipregnancy	17185 (1.9)	6 (1.7)	-0.017	16947 (1.9)	6 (1.7)	-0.018	17517 (1.5)	6 (1)	-0.042
Age at pregnancy onset, years									
<20	13548 (1.5)	0 (0)	-0.175	13446 (1.5)	0 (0)	-0.175	Redacted	<5	Redacted
20-24	108386 (12)	24 (6.7)	-0.183	107815 (12)	24 (6.6)	-0.187	164039 (13.7)	42 (7)	-0.221
25-29	317227 (35.2)	102 (28.6)	-0.143	315802 (35.3)	101 (27.9)	-0.159	384987 (32.2)	143 (23.9)	-0.186
30-34	306637 (34.1)	131 (36.7)	0.055	305105 (34.1)	133 (36.7)	0.056	374716 (31.4)	224 (37.5)	0.129
≥35	154578 (17.2)	100 (28)	0.262	153600 (17.1)	104 (28.7)	0.278	228056 (19.1)	188 (31.4)	0.287
Smoking	102171 (11.3)	52 (14.6)	0.096	101501 (11.3)	52 (14.4)	0.091	Missing	Missing	Missing
BMI (kg/m^2)									
<20	112004 (12.4)	0 (0)	-0.533	111424 (12.4)	0 (0)	-0.533	Missing	Missing	Missing
20-25	459681 (51.1)	20 (5.6)	-1.168	457279 (51)	20 (5.5)	-1.171	Missing	Missing	Missing
25-30	203364 (22.6)	61 (17.1)	-0.138	202398 (22.6)	63 (17.4)	-0.13	Missing	Missing	Missing
30-35	80335 (8.9)	125 (35)	0.664	79901 (8.9)	126 (34.8)	0.659	Missing	Missing	Missing
>35	44992 (5)	151 (42.3)	0.977	44766 (5)	153 (42.3)	0.976	Missing	Missing	Missing
Parity at pregnancy onset[c]									
0	411072 (45.7)	148 (41.5)	-0.085	408797 (45.6)	152 (42)	-0.074	547144 (45.8)	232 (38.8)	-0.142
1	338516 (37.6)	135 (37.8)	0.004	336994 (37.6)	134 (37)	-0.012	413901 (34.6)	188 (31.4)	-0.068
2	114894 (12.8)	53 (14.8)	0.06	114301 (12.8)	54 (14.9)	0.062	170674 (14.3)	122 (20.4)	0.162
≥3	35894 (4)	21 (5.9)	0.088	35676 (4)	22 (6.1)	0.096	63098 (5.3)	56 (9.4)	0.157
Prior registered miscarriages									
None	776693 (86.3)	290 (81.2)	-0.137	772779 (86.3)	292 (80.7)	-0.151	1030795 (86.3)	470 (78.6)	-0.203
1	103061 (11.4)	51 (14.3)	0.085	102474 (11.4)	54 (14.9)	0.103	134947 (11.3)	101 (16.9)	0.161
≥2	20622 (2.3)	16 (4.5)	0.121	20515 (2.3)	16 (4.4)	0.118	29075 (2.4)	27 (4.5)	0.114
Previous SGA outcome[d]	55273 (6.1)	16 (4.5)	-0.074	54969 (6.1)	16 (4.4)	-0.077	77448 (6.5)	27 (4.5)	-0.086
Previous MCM outcome[d]	27471 (3.1)	21 (5.9)	0.137	27339 (3.1)	21 (5.8)	0.134	36737 (3.1)	37 (6.2)	0.149
Married/registered partnership	370302 (41.1)	151 (42.3)	0.024	368448 (41.1)	157 (43.4)	0.045	458268 (38.4)	238 (39.8)	0.03
Maternal place of birth									
Denmark	754172 (83.8)	311 (87.1)	0.095	750368 (83.8)	315 (87)	0.092	1000004 (83.7)	505 (84.4)	0.021
Europe	69681 (7.7)	19 (5.3)	-0.098	69310 (7.7)	19 (5.2)	-0.101	90075 (7.5)	34 (5.7)	-0.075

Outside of Europe	76523 (8.5)	27 (7.6)	-0.034	76090 (8.5)	28 (7.7)	-0.028	104738 (8.8)	59 (9.9)	0.038
Region of residence									
The Capital Region	269972 (30)	137 (38.4)	0.178	268356 (30)	137 (37.8)	0.167	355851 (29.8)	212 (35.5)	0.121
Central Denmark	215121 (23.9)	85 (23.8)	-0.002	214267 (23.9)	85 (23.5)	-0.01	284632 (23.8)	139 (23.2)	-0.014
Northern Denmark	101263 (11.2)	28 (7.8)	-0.116	100658 (11.2)	28 (7.7)	-0.12	135785 (11.4)	62 (10.4)	-0.032
Region Zealand	113108 (12.6)	45 (12.6)	0.001	112475 (12.6)	46 (12.7)	0.005	153977 (12.9)	89 (14.9)	0.058
Southern Denmark	200912 (22.3)	62 (17.4)	-0.124	200012 (22.3)	66 (18.2)	-0.102	264572 (22.1)	96 (16.1)	-0.155
Season of conception									
Winter	222244 (24.7)	113 (31.7)	0.155	221263 (24.7)	113 (31.2)	0.146	293411 (24.6)	143 (23.9)	-0.015
Spring	215472 (23.9)	105 (29.4)	0.124	214143 (23.9)	105 (29)	0.116	287050 (24)	171 (28.6)	0.104
Summer	221773 (24.6)	53 (14.8)	-0.248	220529 (24.6)	55 (15.2)	-0.238	297067 (24.9)	137 (22.9)	-0.046
Autumn	240887 (26.8)	86 (24.1)	-0.061	239833 (26.8)	89 (24.6)	-0.05	317289 (26.6)	147 (24.6)	-0.045
Plasma glucose ≥11.0 mmol/L									
Yes	158 (0)	9 (2.5)	0.225	157 (0)	9 (2.5)	0.223	248 (0)	12 (2)	0.199
No	26918 (3)	16 (4.5)	0.079	26780 (3)	16 (4.4)	0.076	36760 (3.1)	24 (4)	0.051
Not measured	873300 (97)	332 (93)	-0.184	868831 (97)	337 (93.1)	-0.18	1157809 (96.9)	562 (94)	-0.14
HbA1c ≥48.0 mmol/mol									
Yes	2928 (0.3)	99 (27.7)	0.859	2905 (0.3)	100 (27.6)	0.857	4011 (0.3)	143 (23.9)	0.775
No	112719 (12.5)	170 (47.6)	0.829	112244 (12.5)	170 (47)	0.813	147244 (12.3)	292 (48.8)	0.863
Not measured	784729 (87.2)	88 (24.6)	-1.62	780619 (87.1)	92 (25.4)	-1.59	1043562 (87.3)	163 (27.3)	-1.529
No. of hospital admissions within 1 year of pregnancy onset									
None	775195 (86.1)	331 (92.7)	0.216	771315 (86.1)	334 (92.3)	0.199	1016793 (85.1)	554 (92.6)	0.242
1	99234 (11)	18 (5)	-0.221	98661 (11)	18 (5)	-0.224	139201 (11.7)	30 (5)	-0.242
≥2	25947 (2.9)	8 (2.2)	-0.041	25792 (2.9)	10 (2.8)	-0.007	38823 (3.2)	14 (2.3)	-0.055
No. of outpatient visits within 1 year of pregnancy onset									
None	611678 (67.9)	253 (70.9)	0.064	608656 (67.9)	254 (70.2)	0.048	801488 (67.1)	426 (71.2)	0.09
1	156523 (17.4)	44 (12.3)	-0.143	155686 (17.4)	44 (12.2)	-0.148	210303 (17.6)	72 (12)	-0.157
2	71582 (8)	23 (6.4)	-0.058	71158 (7.9)	24 (6.6)	-0.051	97834 (8.2)	33 (5.5)	-0.106
≥3	60593 (6.7)	37 (10.4)	0.13	60268 (6.7)	40 (11)	0.152	85192 (7.1)	67 (11.2)	0.142
Prescription of drugs within 1 year of pregnancy onset									
Antiobesity preparations	2201 (0.2)	5 (1.4)	0.128	2181 (0.2)	5 (1.4)	0.127	3193 (0.3)	12 (2)	0.165
Insulins and analogues	2306 (0.3)	39 (10.9)	0.477	2277 (0.3)	40 (11)	0.481	3158 (0.3)	52 (8.7)	0.416
Antidiabetics, excl. GLP-1 RA	9995 (1.1)	82 (23)	0.713	9931 (1.1)	84 (23.2)	0.718	11850 (1)	118 (19.7)	0.646
Antihypertensives	13216 (1.5)	28 (7.8)	0.306	13131 (1.5)	28 (7.7)	0.303	18710 (1.6)	51 (8.5)	0.322
Lipid-modifying drugs	2051 (0.2)	24 (6.7)	0.36	2038 (0.2)	24 (6.6)	0.357	2953 (0.2)	50 (8.4)	0.408
Drugs used in IVF treatment	67281 (7.5)	28 (7.8)	0.014	66867 (7.5)	31 (8.6)	0.04	79194 (6.6)	34 (5.7)	-0.039
Glucocorticoids	15122 (1.7)	9 (2.5)	0.059	15045 (1.7)	10 (2.8)	0.074	20140 (1.7)	18 (3)	0.088
Drugs for underactive thyroid	12836 (1.4)	13 (3.6)	0.141	12753 (1.4)	13 (3.6)	0.139	16164 (1.4)	21 (3.5)	0.14
Antimigraine drugs	18210 (2)	12 (3.4)	0.083	18119 (2)	13 (3.6)	0.095	23858 (2)	33 (5.5)	0.186
Antiepileptics	5146 (0.6)	7 (2)	0.124	5107 (0.6)	7 (1.9)	0.123	7810 (0.7)	15 (2.5)	0.149
Antipsychotics	6713 (0.7)	6 (1.7)	0.085	6671 (0.7)	7 (1.9)	0.104	12013 (1)	16 (2.7)	0.124
Anxiolytics	Redacted	<5	Redacted	Redacted	<5	Redacted	11172 (0.9)	10 (1.7)	0.065
Hypnotics	11849 (1.3)	13 (3.6)	0.15	11775 (1.3)	13 (3.6)	0.148	18331 (1.5)	22 (3.7)	0.135

Antidepressants	37396 (4.2)	38 (10.6)	0.25	37208 (4.2)	39 (10.8)	0.254	57118 (4.8)	73 (12.2)	0.269
Psychostimulants	Redacted	<5	Redacted	Redacted	<5	Redacted	7349 (0.6)	9 (1.5)	0.087
Drugs for obstructive airway diseases	32103 (3.6)	22 (6.2)	0.121	31917 (3.6)	22 (6.1)	0.118	43227 (3.6)	33 (5.5)	0.091
Antiinfectives	42075 (4.7)	23 (6.4)	0.077	41869 (4.7)	23 (6.4)	0.074	58951 (4.9)	39 (6.5)	0.068
NSAIDs	12306 (1.4)	12 (3.4)	0.132	12248 (1.4)	13 (3.6)	0.143	17007 (1.4)	27 (4.5)	0.183
Opioids	9326 (1)	9 (2.5)	0.113	9287 (1)	9 (2.5)	0.11	13837 (1.2)	16 (2.7)	0.111
No. of drugs prescribed									
None	667668 (74.2)	160 (44.8)	-0.626	664346 (74.2)	161 (44.5)	-0.634	881304 (73.8)	275 (46)	-0.591
1-2 drugs	217898 (24.2)	150 (42)	0.386	216707 (24.2)	152 (42)	0.385	291538 (24.4)	237 (39.6)	0.331
3-4 drugs	13661 (1.5)	43 (12)	0.428	13574 (1.5)	45 (12.4)	0.439	20106 (1.7)	74 (12.4)	0.428
≥5 drugs	>1148 (0.1)	<5 (<1.4)	0.13	Redacted	<5	Redacted	1869 (0.2)	12 (2)	0.18
Diagnosis within 1 year of pregnancy onset									
Diabetes Type 1	1243 (0.1)	15 (4.2)	0.282	1231 (0.1)	15 (4.1)	0.279	1730 (0.1)	17 (2.8)	0.224
Diabetes Type 2	594 (0.1)	41 (11.5)	0.505	590 (0.1)	41 (11.3)	0.501	863 (0.1)	56 (9.4)	0.449
PCOS	5090 (0.6)	14 (3.9)	0.228	5064 (0.6)	17 (4.7)	0.26	6077 (0.5)	20 (3.3)	0.207
Obesity	16986 (1.9)	48 (13.4)	0.445	16900 (1.9)	50 (13.8)	0.455	23248 (1.9)	71 (11.9)	0.399
Thyroid disorders	8208 (0.9)	11 (3.1)	0.156	8163 (0.9)	11 (3)	0.153	10364 (0.9)	13 (2.2)	0.107
Mood [affective] disorders	2148 (0.2)	5 (1.4)	0.129	2133 (0.2)	5 (1.4)	0.128	3527 (0.3)	8 (1.3)	0.116
Neurotic, stress-related and somatoform disorders	3633 (0.4)	7 (2)	0.144	3619 (0.4)	7 (1.9)	0.143	6136 (0.5)	17 (2.8)	0.182
Asthma	3969 (0.4)	5 (1.4)	0.101	3941 (0.4)	6 (1.7)	0.12	5490 (0.5)	9 (1.5)	0.106
Drug abuse	>1658 (0.2)	<5 (<1.4)	0.02	Redacted	<5	Redacted	Redacted	<5	Redacted
Alcohol abuse	886 (0.1)	0 (0)	-0.044	881 (0.1)	0 (0)	-0.044	2032 (0.2)	0 (0)	-0.058
Behavioural syndromes associated with physiological disturbances and physical factors	>971 (0.1)	<5 (<1.4)	0.13	Redacted	<5	Redacted	1374 (0.1)	5 (0.8)	0.105
Hypertension	>1267 (0.1)	<5 (<1.4)	0.07	Redacted	<5	Redacted	Redacted	<5	Redacted
Ischaemic heart diseases	73 (0)	0 (0)	-0.013	73 (0)	0 (0)	-0.013	128 (0)	0 (0)	-0.015

6.2. Adjusted characteristics after trimming and weighting, sensitivity analysis 3.

Appendix table 10. Subgroup analysis of narrower expoure definition: Baseline characteristics after trimming and IPTW.

	Major congenital malformations[a]			Small for gestational age (SGA)[a]			Miscarriage/spontaneous abortion		
	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference (%)	No. (%) of pregnancies		Standardised mean difference
	Pseudopopulation, unexposed, N = 86 952	GLP-1 RA users, N = 334		Pseudopopulation, unexposed, N = 80 163	GLP-1 RA users, N = 348		Pseudopopulation, unexposed, N = 77 675	GLP-1 RA users, N = 580	
Maternal/pregnancy characteristics									
Year of pregnancy onset[b]									
<2016	9116 (10.5)	36 (10.8)	0.009	8260 (10.3)	37 (10.6)	0.011	8246 (10.6)	63 (10.9)	0.01
2016-2019	11312 (13)	44 (13.2)	0.005	11629 (14.5)	52 (14.9)	0.012	8592 (11.1)	65 (11.2)	0.005
2020-2023	66524 (76.5)	254 (76)	-0.01	60274 (75.2)	259 (74.4)	-0.017	60837 (78.3)	452 (77.9)	-0.011
Multipregnancy	1460 (1.7)	6 (1.8)	0.009	1306 (1.6)	6 (1.7)	0.007	797 (1)	6 (1)	0.001

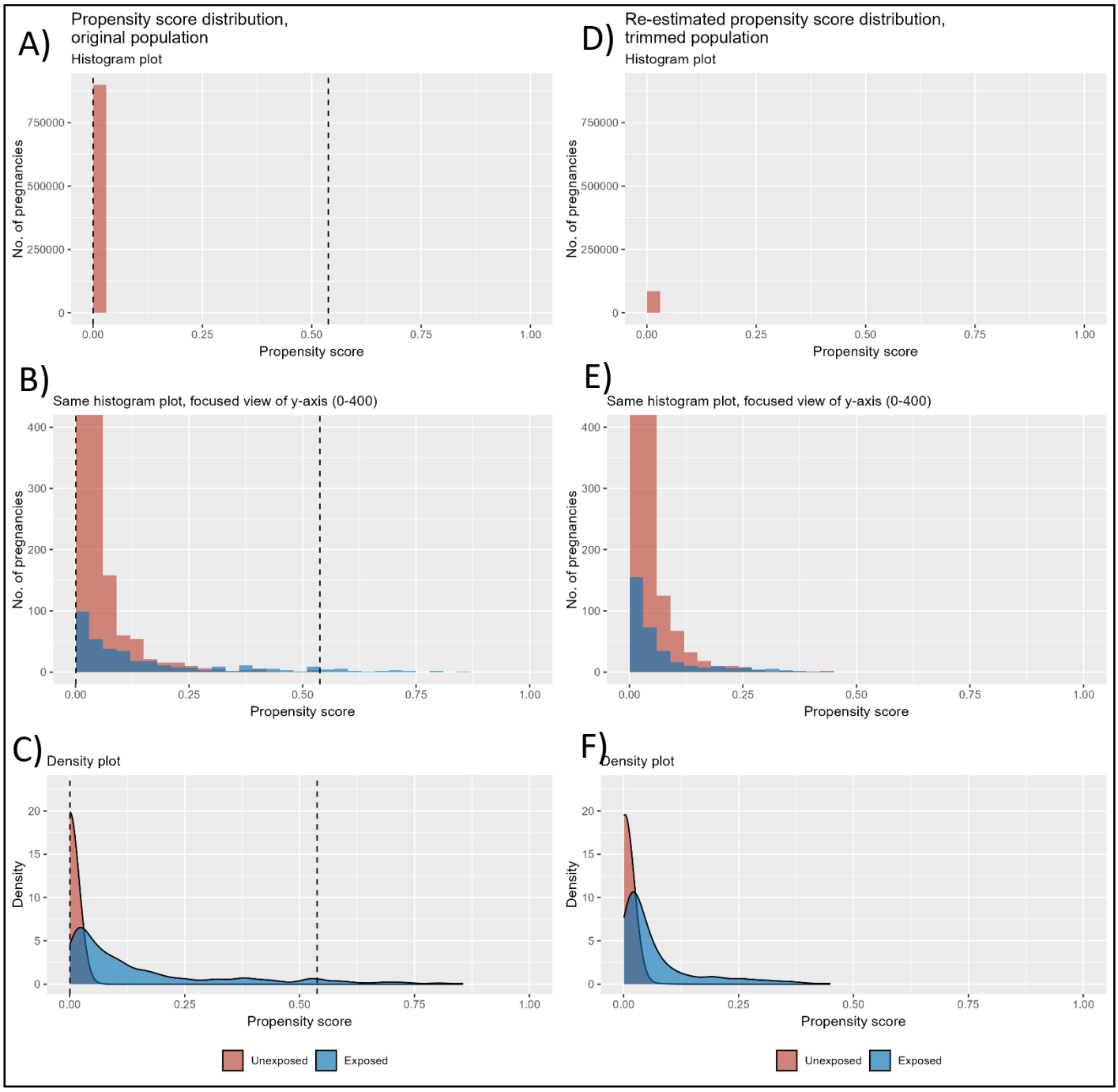
Age at pregnancy onset, years									
<20	0 (0)	0 (0)	0	0 (0)	0 (0)	0	Redacted	<5	Redacted
20-24	5794 (6.7)	22 (6.6)	-0.003	5322 (6.6)	23 (6.6)	-0.001	5649 (7.3)	42 (7.2)	-0.001
25-29	25989 (29.9)	100 (29.9)	0.001	23124 (28.8)	100 (28.7)	-0.002	18512 (23.8)	137 (23.6)	-0.005
30-34	30966 (35.6)	119 (35.6)	0	28796 (35.9)	126 (36.2)	0.006	29176 (37.6)	219 (37.8)	0.004
≥35	24203 (27.8)	93 (27.8)	0	22921 (28.6)	99 (28.4)	-0.003	24195 (31.1)	181 (31.2)	0.001
Smoking	12869 (14.8)	50 (15)	0.005	11464 (14.3)	50 (14.4)	0.002	Missing	Missing	Missing
BMI (kg/m^2)									
<20							Missing	Missing	Missing
20-25	5326 (6.1)	20 (6)	-0.005	4736 (5.9)	20 (5.7)	-0.007	Missing	Missing	Missing
25-30	16085 (18.5)	61 (18.3)	-0.006	14830 (18.5)	63 (18.1)	-0.009	Missing	Missing	Missing
30-35	30991 (35.6)	119 (35.6)	0	28350 (35.4)	123 (35.3)	0	Missing	Missing	Missing
>35	34550 (39.7)	134 (40.1)	0.008	32247 (40.2)	142 (40.8)	0.012	Missing	Missing	Missing
Parity at pregnancy onset[c]									
0	35742 (41.1)	137 (41)	-0.002	33504 (41.8)	145 (41.7)	-0.003	29738 (38.3)	223 (38.4)	0.003
1	32994 (37.9)	127 (38)	0.002	29649 (37)	129 (37.1)	0.002	24393 (31.4)	182 (31.4)	-0.001
2	12824 (14.7)	50 (15)	0.006	11789 (14.7)	52 (14.9)	0.007	16148 (20.8)	120 (20.7)	-0.002
≥3	5392 (6.2)	20 (6)	-0.009	5221 (6.5)	22 (6.3)	-0.008	7396 (9.5)	55 (9.5)	-0.001
Prior registered miscarriages									
None	71470 (82.2)	274 (82)	-0.004	65338 (81.5)	283 (81.3)	-0.005	61143 (78.7)	457 (78.8)	0.002
1	11646 (13.4)	45 (13.5)	0.002	11395 (14.2)	50 (14.4)	0.004	12902 (16.6)	96 (16.6)	-0.002
≥2	3836 (4.4)	15 (4.5)	0.004	3429 (4.3)	15 (4.3)	0.002	3630 (4.7)	27 (4.7)	-0.001
Previous SGA outcome[d]	4235 (4.9)	16 (4.8)	-0.004	3800 (4.7)	16 (4.6)	-0.007	3695 (4.8)	27 (4.7)	-0.005
Previous MCM outcome[d]	4720 (5.4)	19 (5.7)	0.012	4361 (5.4)	20 (5.7)	0.014	4744 (6.1)	36 (6.2)	0.004
Married/registered partnership	36535 (42)	140 (41.9)	-0.002	34643 (43.2)	150 (43.1)	-0.002	31095 (40)	232 (40)	-0.001
Maternal place of birth									
Denmark	76363 (87.8)	293 (87.7)	-0.003	70031 (87.4)	303 (87.1)	-0.009	65372 (84.2)	488 (84.1)	-0.001
Europe	4035 (4.6)	16 (4.8)	0.007	3868 (4.8)	18 (5.2)	0.016	4433 (5.7)	34 (5.9)	0.007
Outside of Europe	6553 (7.5)	25 (7.5)	-0.002	6265 (7.8)	27 (7.8)	-0.002	7869 (10.1)	58 (10)	-0.004
Region of residence									
The Capital Region	34381 (39.5)	133 (39.8)	0.006	30846 (38.5)	134 (38.5)	0.001	27767 (35.7)	207 (35.7)	-0.001
Central Denmark	19477 (22.4)	76 (22.8)	0.008	17949 (22.4)	80 (23)	0.014	17765 (22.9)	133 (22.9)	0.001
Northern Denmark	7133 (8.2)	28 (8.4)	0.006	6368 (7.9)	28 (8)	0.004	8082 (10.4)	60 (10.3)	-0.002
Region Zealand	11394 (13.1)	43 (12.9)	-0.007	10571 (13.2)	45 (12.9)	-0.008	11558 (14.9)	86 (14.8)	-0.001
Southern Denmark	14567 (16.8)	54 (16.2)	-0.016	14429 (18)	61 (17.5)	-0.012	12503 (16.1)	94 (16.2)	0.003
Season of conception									
Winter	27470 (31.6)	105 (31.4)	-0.003	24955 (31.1)	108 (31)	-0.002	18850 (24.3)	140 (24.1)	-0.003
Spring	24776 (28.5)	96 (28.7)	0.006	22884 (28.5)	101 (29)	0.011	22323 (28.7)	167 (28.8)	0.001
Summer	13698 (15.8)	51 (15.3)	-0.013	12732 (15.9)	53 (15.2)	-0.018	17624 (22.7)	131 (22.6)	-0.002
Autumn	21008 (24.2)	82 (24.6)	0.009	19592 (24.4)	86 (24.7)	0.006	18878 (24.3)	142 (24.5)	0.004
Plasma glucose ≥11.0 mmol/L									
Yes	Redacted	<5	Redacted	Redacted	<5	Redacted	1276 (1.6)	10 (1.7)	0.008
No	3802 (4.4)	15 (4.5)	0.006	3529 (4.4)	16 (4.6)	0.009	3243 (4.2)	24 (4.1)	-0.002

Not measured	82005 (94.3)	315 (94.3)	0	75626 (94.3)	328 (94.3)	-0.004	73156 (94.2)	546 (94.1)	-0.002
HbA1c ≥48.0 mmol/mol									
Yes	18967 (21.8)	76 (22.8)	0.03	18428 (23)	86 (24.7)	0.053	16160 (20.8)	126 (21.7)	0.028
No	44368 (51)	170 (50.9)	-0.003	39668 (49.5)	170 (48.9)	-0.013	39510 (50.9)	291 (50.2)	-0.015
Not measured	23617 (27.2)	88 (26.3)	-0.017	22067 (27.5)	92 (26.4)	-0.023	22005 (28.3)	163 (28.1)	-0.005
No. of hospital admissions within 1 year of pregnancy onset									
None	81197 (93.4)	311 (93.1)	-0.01	74308 (92.7)	321 (92.2)	-0.017	71812 (92.5)	536 (92.4)	-0.002
1	3913 (4.5)	15 (4.5)	0	3773 (4.7)	17 (4.9)	0.008	3961 (5.1)	30 (5.2)	0.004
≥2	1842 (2.1)	8 (2.4)	0.018	2082 (2.6)	10 (2.9)	0.017	1901 (2.4)	14 (2.4)	-0.003
No. of outpatient visits within 1 year of pregnancy onset									
None	62317 (71.7)	239 (71.6)	-0.003	56581 (70.6)	244 (70.1)	-0.01	55639 (71.6)	415 (71.6)	-0.002
1	10382 (11.9)	40 (12)	0.001	9670 (12.1)	43 (12.4)	0.009	9005 (11.6)	68 (11.7)	0.004
2	5781 (6.6)	22 (6.6)	-0.003	5533 (6.9)	24 (6.9)	0	4431 (5.7)	33 (5.7)	-0.001
≥3	8472 (9.7)	33 (9.9)	0.005	8379 (10.5)	37 (10.6)	0.006	8600 (11.1)	64 (11)	-0.001
Prescription of drugs within 1 year of pregnancy onset									
Antiobesity preparations	1309 (1.5)	5 (1.5)	-0.001	1172 (1.5)	5 (1.4)	-0.002	1375 (1.8)	10 (1.7)	-0.004
Insulins and analogues	7737 (8.9)	29 (8.7)	-0.01	7678 (9.6)	33 (9.5)	-0.004	6110 (7.9)	47 (8.1)	0.011
Antidiabetics, excl. GLP-1 RA	16929 (19.5)	65 (19.5)	0	16674 (20.8)	74 (21.3)	0.014	13597 (17.5)	104 (17.9)	0.014
Antihypertensives	5616 (6.5)	22 (6.6)	0.006	5353 (6.7)	24 (6.9)	0.01	5671 (7.3)	43 (7.4)	0.005
Lipid-modifying drugs	5043 (5.8)	19 (5.7)	-0.006	4497 (5.6)	19 (5.5)	-0.009	5299 (6.8)	41 (7.1)	0.012
Drugs used in IVF treatment	7244 (8.3)	27 (8.1)	-0.009	7240 (9)	30 (8.6)	-0.015	4467 (5.8)	33 (5.7)	-0.003
Glucocorticoids	2415 (2.8)	9 (2.7)	-0.005	2389 (3)	10 (2.9)	-0.007	2293 (3)	17 (2.9)	-0.001
Drugs for underactive thyroid	2958 (3.4)	11 (3.3)	-0.006	2802 (3.5)	12 (3.4)	-0.003	2740 (3.5)	20 (3.4)	-0.004
Antimigraine drugs	2920 (3.4)	11 (3.3)	-0.004	3007 (3.8)	13 (3.7)	-0.001	4266 (5.5)	32 (5.5)	0.001
Antiepileptics	1856 (2.1)	7 (2.1)	-0.003	1654 (2.1)	7 (2)	-0.004	1728 (2.2)	13 (2.2)	0.001
Antipsychotics	1617 (1.9)	6 (1.8)	-0.005	1688 (2.1)	7 (2)	-0.007	2157 (2.8)	16 (2.8)	-0.001
Anxiolytics	Redacted	<5	Redacted	Redacted	<5	Redacted	1381 (1.8)	10 (1.7)	-0.004
Hypnotics	3413 (3.9)	13 (3.9)	-0.002	3051 (3.8)	13 (3.7)	-0.004	2683 (3.5)	20 (3.4)	0
Antidepressants	8500 (9.8)	33 (9.9)	0.004	7932 (9.9)	35 (10.1)	0.006	8987 (11.6)	68 (11.7)	0.005
Psychostimulants	Redacted	<5	Redacted	Redacted	<5	Redacted	956 (1.2)	7 (1.2)	-0.002
Drugs for obstructive airway diseases	5494 (6.3)	21 (6.3)	-0.001	5073 (6.3)	22 (6.3)	0	4434 (5.7)	33 (5.7)	-0.001
Antiinfectives	5027 (5.8)	21 (6.3)	0.021	4587 (5.7)	22 (6.3)	0.026	4526 (5.8)	34 (5.9)	0.001
NSAIDs	3111 (3.6)	12 (3.6)	0.001	2970 (3.7)	13 (3.7)	0.002	3462 (4.5)	26 (4.5)	0.001
Opioids	1691 (1.9)	7 (2.1)	0.011	1787 (2.2)	9 (2.6)	0.025	1985 (2.6)	15 (2.6)	0.002
No. of drugs prescribed									
None	41737 (48)	159 (47.6)	-0.008	37532 (46.8)	160 (46)	-0.017	36956 (47.6)	273 (47.1)	-0.01
1-2 drugs	34937 (40.2)	136 (40.7)	0.011	32519 (40.6)	144 (41.4)	0.017	31006 (39.9)	233 (40.2)	0.005
3-4 drugs	9405 (10.8)	36 (10.8)	-0.001	9310 (11.6)	41 (11.8)	0.006	8612 (11.1)	66 (11.4)	0.011
≥5 drugs	Redacted	<5	Redacted	Redacted	<5	Redacted	1101 (1.4)	8 (1.4)	-0.004
Diagnosis within 1 year of pregnancy onset									
Diabetes Type 1	3638 (4.2)	14 (4.2)	0	3217 (4)	14 (4)	0.001	2129 (2.7)	16 (2.8)	0.001

Diabetes Type 2	6986 (8)	25 (7.5)	-0.028	7185 (9)	31 (8.9)	-0.003	5898 (7.6)	45 (7.8)	0.008
PCOS	3524 (4.1)	13 (3.9)	-0.01	3915 (4.9)	16 (4.6)	-0.016	2548 (3.3)	19 (3.3)	0
Obesity	10313 (11.9)	39 (11.7)	-0.006	10215 (12.7)	44 (12.6)	-0.003	8857 (11.4)	66 (11.4)	-0.001
Thyroid disorders	2378 (2.7)	9 (2.7)	-0.003	2277 (2.8)	10 (2.9)	0.002	1791 (2.3)	13 (2.2)	-0.004
Mood [affective] disorders	1395 (1.6)	5 (1.5)	-0.01	1228 (1.5)	5 (1.4)	-0.009	1098 (1.4)	8 (1.4)	-0.003
Neurotic, stress-related and somatoform disorders	1762 (2)	7 (2.1)	0.005	1581 (2)	7 (2)	0.003	2295 (3)	17 (2.9)	-0.001
Asthma	Redacted	<5	Redacted	1291 (1.6)	6 (1.7)	0.01	1175 (1.5)	9 (1.6)	0.003
Drug abuse	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Alcohol abuse	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0
Behavioural syndromes associated with physiological disturbances and physical factors	Redacted	<5	Redacted	Redacted	<5	Redacted	668 (0.9)	5 (0.9)	0
Hypertension	Redacted	<5	Redacted	Redacted	<5	Redacted	Redacted	<5	Redacted
Ischaemic heart diseases	0 (0)	0 (0)	0	0 (0)	0 (0)	0	0 (0)	0 (0)	0

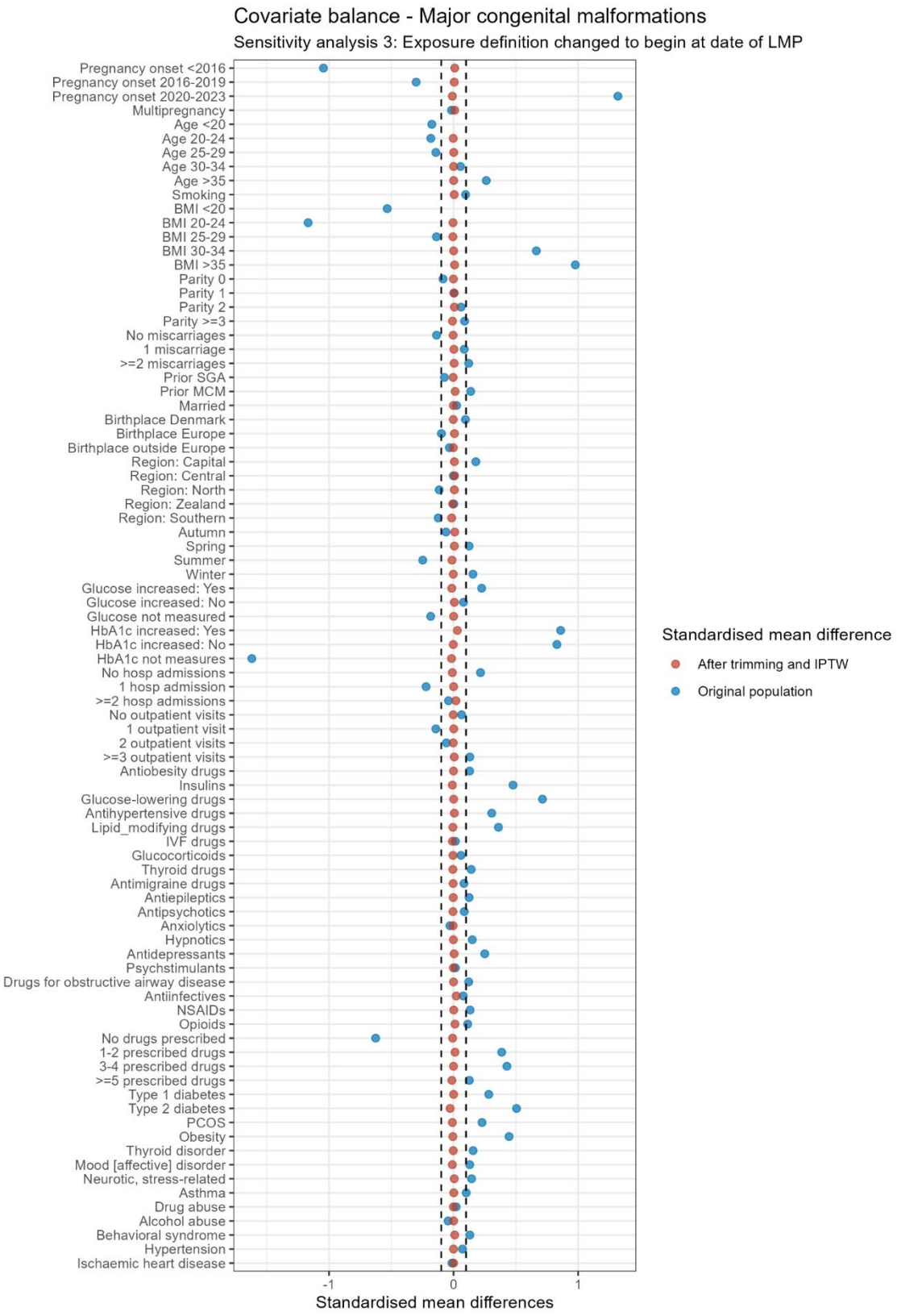
6.3. Supporting figures, sensitivity analysis 3.

Appendix figure 25. Narrowed exposure definition, MCM population, PS distribution

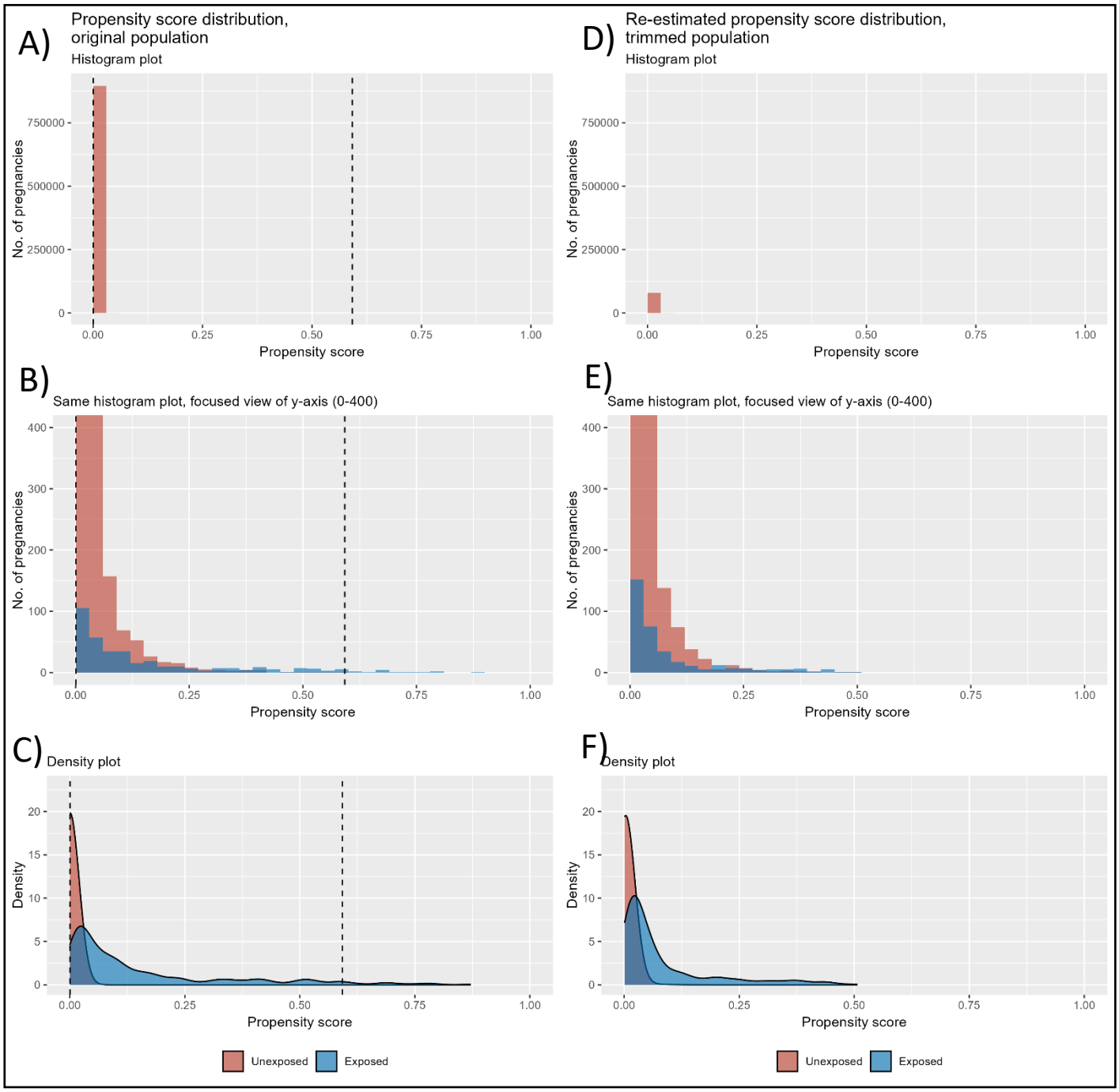


The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

Appendix figure 26. Narrowed exposure definition, MCM population, covariate balance

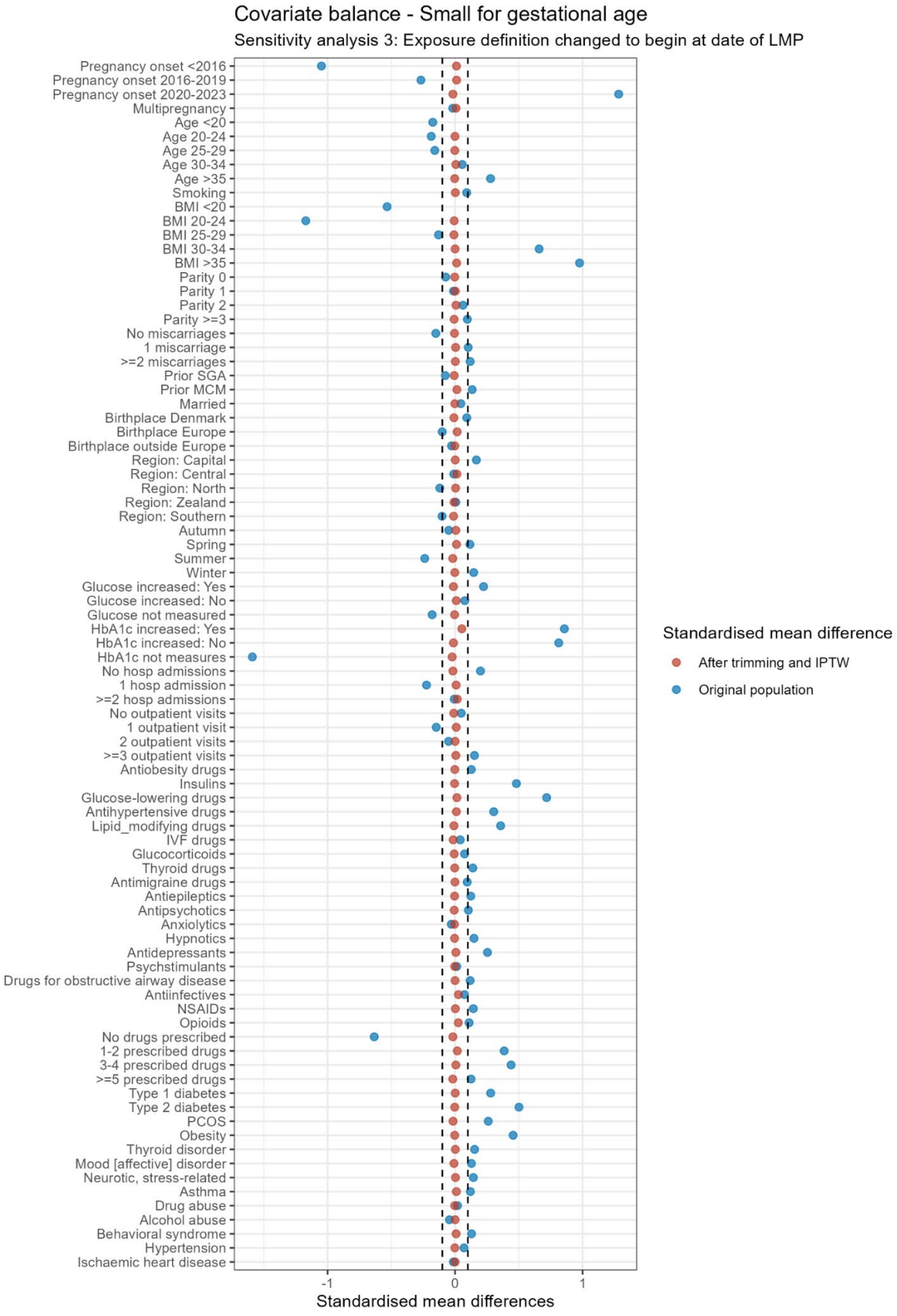


Appendix figure 27. Narrowed exposure definition, SGA population, PS distribution

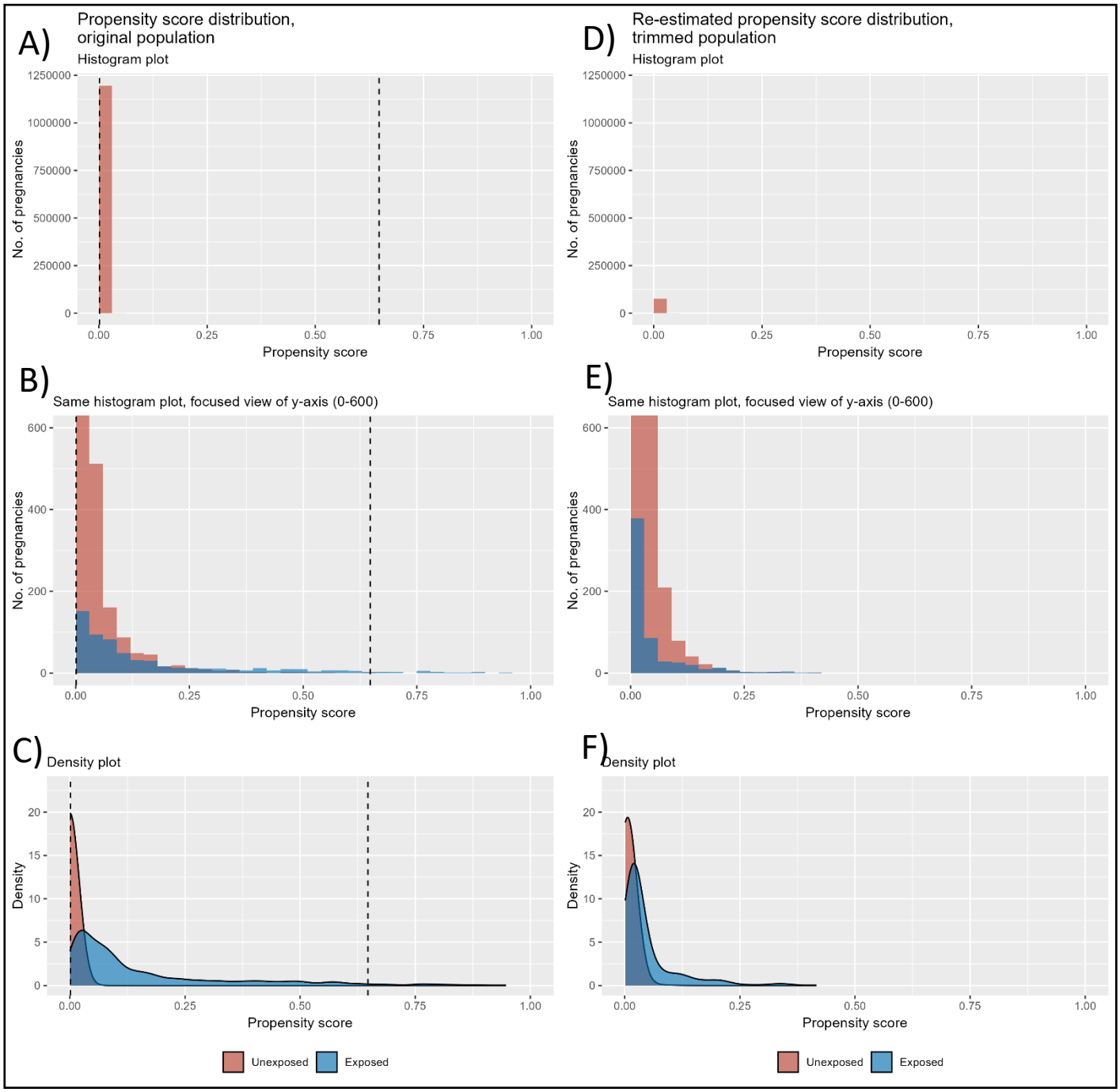


The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

Appendix figure 28. Narrowed exposure definition, SGA population, covariate balance

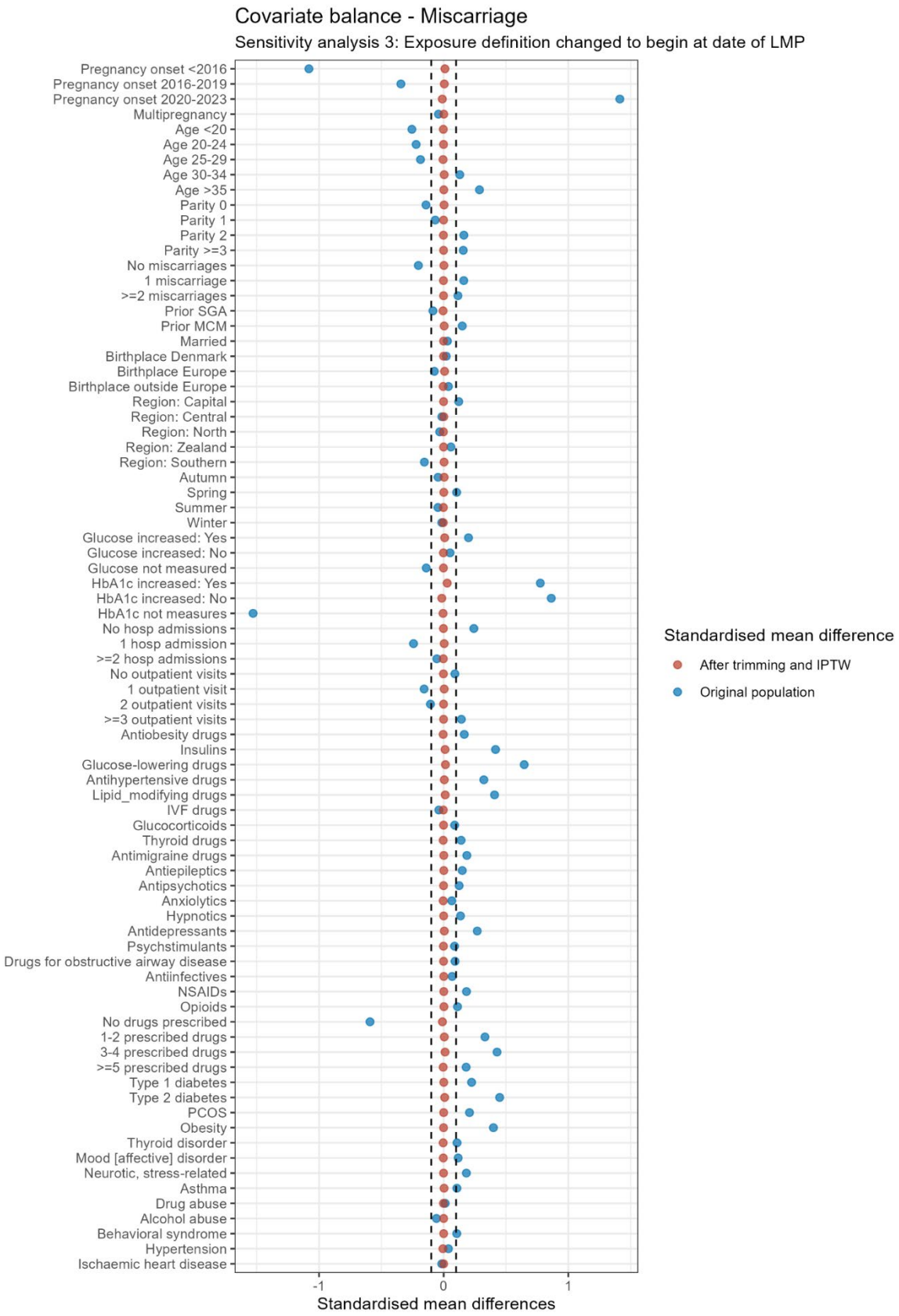


Appendix figure 29. Narrowed exposure definition, miscarriage population, PS distribution



The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

Appendix figure 30. Narrowed exposure definition, miscarraige population, covariate balance



Appendix 7. Sensitivity analysis 4. Investigation of the effect of dropping BMI and smoking variables from the PS model of the MCM population

7.1. Baseline MCM population characteristics and adjusted characteristics after trimming and IPTW, sensitivity analysis 4

Appendix table 11. Analysis of major congenital malformations without the covariates BMI and smoking included in the propensity score

	Baseline characteristics before trimming and IPTW			Baseline characteristics after trimming and IPTW		
	No. (%) of pregnancies		Standardised mean difference	No. (%) of pregnancies		Standardised mean difference
	Unexposed, N = 900 036	GLP-1 RA users, N = 697		Pseudopopulation, unexposed, N = 222 937	GLP-1 RA users, N = 676	
Maternal/pregnancy characteristics						
Year of pregnancy onset[b]						
<2016	482269 (53.6)	69 (9.9)	-1.063	21438 (9.6)	67 (9.9)	0.011
2016-2019	229984 (25.6)	108 (15.5)	-0.251	33645 (15.1)	106 (15.7)	0.016
2020-2023	187783 (20.9)	520 (74.6)	1.276	167854 (75.3)	503 (74.4)	-0.02
Multipregnancy	17177 (1.9)	14 (2)	0.007	4314 (1.9)	14 (2.1)	0.01
Age at pregnancy onset, years						
<20	13548 (1.5)	0 (0)	-0.175	0 (0)	0 (0)	0
20-24	108364 (12)	46 (6.6)	-0.188	15034 (6.7)	45 (6.7)	-0.003
25-29	317134 (35.2)	195 (28)	-0.157	63420 (28.4)	191 (28.3)	-0.004
30-34	306510 (34.1)	258 (37)	0.062	81467 (36.5)	250 (37)	0.009
≥35	154480 (17.2)	198 (28.4)	0.27	63016 (28.3)	190 (28.1)	-0.004
Smoking	102128 (11.3)	95 (13.6)	0.069	*22566 (10.1)*	*92 (13.6)*	*0.113*
BMI (kg/m^2)						
<20	112004 (12.4)	0 (0)	-0.533	*13927 (6.2)*	*0 (0)*	*-0.32*
20-25	459661 (51.1)	40 (5.7)	-1.163	*85268 (38.2)*	*40 (5.9)*	*-0.828*
25-30	203295 (22.6)	130 (18.7)	-0.097	*58843 (26.4)*	*127 (18.8)*	*-0.183*
30-35	80230 (8.9)	230 (33)	0.619	*35633 (16)*	*225 (33.3)*	*0.431*
>35	44846 (5)	297 (42.6)	0.985	*29266 (13.1)*	*284 (42)*	*0.732*
Parity at pregnancy onset[c]						
0	410926 (45.7)	294 (42.2)	-0.07	93475 (41.9)	285 (42.2)	0.005
1	338390 (37.6)	261 (37.4)	-0.003	83931 (37.6)	254 (37.6)	-0.002
2	114851 (12.8)	96 (13.8)	0.03	30843 (13.8)	94 (13.9)	0.002
≥3	35869 (4)	46 (6.6)	0.117	14688 (6.6)	43 (6.4)	-0.01
Prior registered miscarriages						
None	776416 (86.3)	567 (81.3)	-0.134	181534 (81.4)	550 (81.4)	-0.002
1	103012 (11.4)	100 (14.3)	0.087	32040 (14.4)	97 (14.3)	-0.001
≥2	20608 (2.3)	30 (4.3)	0.113	9363 (4.2)	29 (4.3)	0.005
Previous SGA outcome[d]	55257 (6.1)	32 (4.6)	-0.069	10950 (4.9)	32 (4.7)	-0.008
Previous MCM outcome[d]	27452 (3.1)	40 (5.7)	0.131	12248 (5.5)	39 (5.8)	0.012
Married/registered partnership	370151 (41.1)	302 (43.3)	0.045	96507 (43.3)	292 (43.2)	-0.002
Maternal place of birth						
Denmark	753883 (83.8)	600 (86.1)	0.065	192385 (86.3)	584 (86.4)	0.003
Europe	69670 (7.7)	30 (4.3)	-0.145	9246 (4.1)	29 (4.3)	0.007
Outside of Europe	76483 (8.5)	67 (9.6)	0.039	21306 (9.6)	63 (9.3)	-0.008
Region of residence						
The Capital Region	269847 (30)	262 (37.6)	0.161	84941 (38.1)	258 (38.2)	0.001

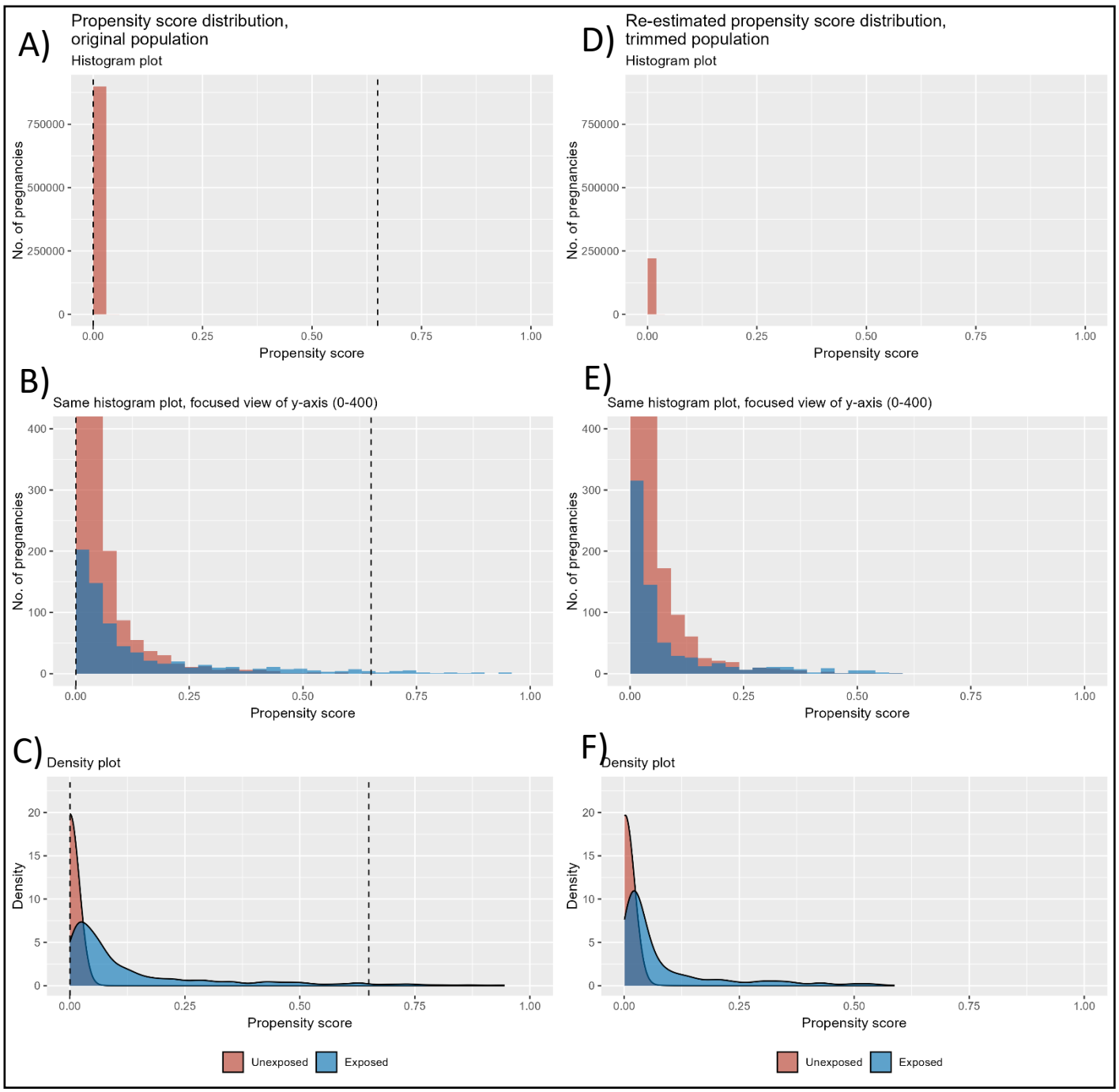
Central Denmark	215060 (23.9)	146 (20.9)	-0.071	45529 (20.4)	140 (20.7)	0.007
Northern Denmark	101225 (11.2)	66 (9.5)	-0.058	19857 (8.9)	62 (9.2)	0.009
Region Zealand	113052 (12.6)	101 (14.5)	0.056	33469 (15)	100 (14.8)	-0.006
Southern Denmark	200852 (22.3)	122 (17.5)	-0.121	39141 (17.6)	116 (17.2)	-0.01
Season of conception						
Winter	222156 (24.7)	201 (28.8)	0.094	63492 (28.5)	193 (28.6)	0.002
Spring	215367 (23.9)	210 (30.1)	0.14	67623 (30.3)	205 (30.3)	0
Summer	221711 (24.6)	115 (16.5)	-0.202	37567 (16.9)	112 (16.6)	-0.007
Autumn	240802 (26.8)	171 (24.5)	-0.051	54254 (24.3)	166 (24.6)	0.005
Plasma glucose ≥11.0 mmol/L						
Yes	157 (0)	10 (1.4)	0.168	2222 (1)	7 (1)	0.005
No	26896 (3)	38 (5.5)	0.123	12201 (5.5)	36 (5.3)	-0.007
Not measured	872983 (97)	649 (93.1)	-0.18	208514 (93.5)	633 (93.6)	0.005
HbA1c ≥48.0 mmol/mol						
Yes	2876 (0.3)	151 (21.7)	0.726	39401 (17.7)	131 (19.4)	0.059
No	112539 (12.5)	350 (50.2)	0.89	116241 (52.1)	349 (51.6)	-0.01
Not measured	784621 (87.2)	196 (28.1)	-1.491	67295 (30.2)	196 (29)	-0.025
No. of hospital admissions within 1 year of pregnancy onset						
None	774880 (86.1)	646 (92.7)	0.215	207715 (93.2)	627 (92.8)	-0.017
1	99216 (11)	36 (5.2)	-0.216	10776 (4.8)	34 (5)	0.009
≥2	25940 (2.9)	15 (2.2)	-0.047	4446 (2)	15 (2.2)	0.017
No. of outpatient visits within 1 year of pregnancy onset						
None	611442 (67.9)	489 (70.2)	0.048	158225 (71)	476 (70.4)	-0.013
1	156480 (17.4)	87 (12.5)	-0.138	27249 (12.2)	84 (12.4)	0.006
2	71562 (8)	43 (6.2)	-0.07	14251 (6.4)	43 (6.4)	-0.001
≥3	60552 (6.7)	78 (11.2)	0.157	23212 (10.4)	73 (10.8)	0.014
Prescription of drugs within 1 year of pregnancy onset						
Antiobesity preparations	2196 (0.2)	10 (1.4)	0.131	3234 (1.5)	10 (1.5)	0.003
Insulins and analogues	2286 (0.3)	59 (8.5)	0.411	16838 (7.6)	52 (7.7)	0.007
Antidiabetics, excl. GLP-1 RA	9935 (1.1)	142 (20.4)	0.655	39444 (17.7)	123 (18.2)	0.017
Antihypertensives	13194 (1.5)	50 (7.2)	0.284	13342 (6)	43 (6.4)	0.019
Lipid-modifying drugs	2034 (0.2)	41 (5.9)	0.333	10054 (4.5)	31 (4.6)	0.005
Drugs used in IVF treatment	67237 (7.5)	72 (10.3)	0.101	23906 (10.7)	70 (10.4)	-0.013
Glucocorticoids	15107 (1.7)	24 (3.4)	0.112	7846 (3.5)	24 (3.6)	0.002
Drugs for underactive thyroid	12825 (1.4)	24 (3.4)	0.131	7115 (3.2)	21 (3.1)	-0.005
Antimigraine drugs	18192 (2)	30 (4.3)	0.131	9452 (4.2)	29 (4.3)	0.003
Antiepileptics	5144 (0.6)	9 (1.3)	0.075	3091 (1.4)	9 (1.3)	-0.005
Antipsychotics	6707 (0.7)	12 (1.7)	0.089	3820 (1.7)	11 (1.6)	-0.007
Anxiolytics	7162 (0.8)	7 (1)	0.022	2091 (0.9)	6 (0.9)	-0.006
Hypnotics	11835 (1.3)	27 (3.9)	0.161	7976 (3.6)	25 (3.7)	0.007
Antidepressants	37362 (4.2)	72 (10.3)	0.24	21277 (9.5)	66 (9.8)	0.008
Psychostimulants	4115 (0.5)	6 (0.9)	0.05	1960 (0.9)	6 (0.9)	0.001
Drugs for obstructive airway diseases	32086 (3.6)	39 (5.6)	0.097	12158 (5.5)	38 (5.6)	0.008
Antiinfectives	42055 (4.7)	43 (6.2)	0.066	12477 (5.6)	40 (5.9)	0.014
NSAIDs	12293 (1.4)	25 (3.6)	0.143	7482 (3.4)	23 (3.4)	0.003
Opioids	9317 (1)	18 (2.6)	0.116	5324 (2.4)	17 (2.5)	0.009
No. of drugs prescribed						
None	667511 (74.2)	317 (45.5)	-0.612	106534 (47.8)	316 (46.7)	-0.022

1-2 drugs	217752 (24.2)	296 (42.5)	0.395	92921 (41.7)	287 (42.5)	0.016
3-4 drugs	13631 (1.5)	73 (10.5)	0.384	21004 (9.4)	66 (9.8)	0.014
≥5 drugs	1142 (0.1)	11 (1.6)	0.158	2479 (1.1)	7 (1)	-0.01
Diagnosis within 1 year of pregnancy onset						
Diabetes Type 1	1237 (0.1)	21 (3)	0.232	6058 (2.7)	19 (2.8)	0.007
Diabetes Type 2	568 (0.1)	67 (9.6)	0.457	15864 (7.1)	50 (7.4)	0.015
PCOS	5078 (0.6)	26 (3.7)	0.22	8671 (3.9)	26 (3.8)	-0.003
Obesity	16945 (1.9)	89 (12.8)	0.427	25483 (11.4)	77 (11.4)	-0.002
Thyroid disorders	8204 (0.9)	15 (2.2)	0.101	4212 (1.9)	13 (1.9)	0.003
Mood [affective] disorders	2143 (0.2)	10 (1.4)	0.132	3466 (1.6)	10 (1.5)	-0.007
Neurotic, stress-related and somatoform disorders	3625 (0.4)	15 (2.2)	0.156	4768 (2.1)	14 (2.1)	-0.006
Asthma	3966 (0.4)	8 (1.1)	0.08	2096 (0.9)	7 (1)	0.01
Drug abuse	Redacted	<5	Redacted	Redacted	<5	Redacted
Alcohol abuse	886 (0.1)	0 (0)	-0.044	0 (0)	0 (0)	0
Behavioural syndromes associated with physiological disturbances and physical factors	Redacted	<5	Redacted	Redacted	<5	Redacted
Hypertension	Redacted	<5	Redacted	Redacted	<5	Redacted
Ischaemic heart diseases	73 (0)	0 (0)	-0.013	0 (0)	0 (0)	0

Gray area: Despite not included in the PS model, BMI and smoking is still included in the characteristics table to show the effect of dropping the variables.

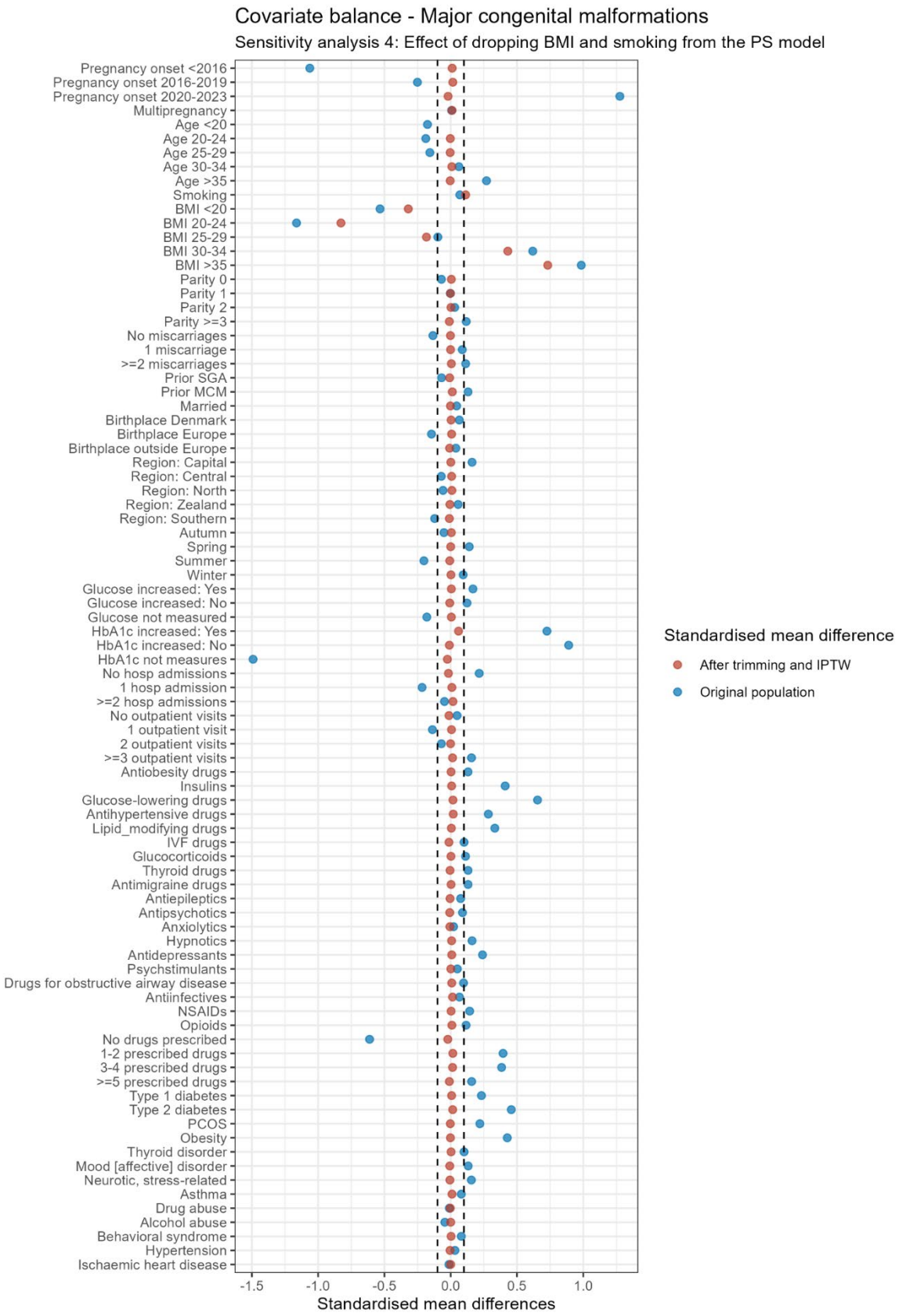
7.2. Supporting figures, sensitivity analysis 4

Appendix figure 31. MCM population, PS distribution



The overlap in PS distributions is presented by three different layouts: A) Overview of all data; B) A focused view of the y-axis; C) A density plot of all data. Dashed vertical lines in the figures on the left indicate the minimum and maximum range of the common overlap region. D), E) and F): PS distribution, re-estimated after the exclusion of observations outside the common region.

Appendix figure 32. MCM population, covariate balance



Appendix 8. The study protocol

Protocol for the study:

Adverse pregnancy and birth outcomes in women exposed to glucagon-like peptide-1 receptor agonists – A nationwide register-based study

Version 1.6, dated 5. February 2024.

Table of Contents

1. List of abbreviations

BMI	Body mass index
CED	Cohort entry date
CI	Confidence interval
CRS	The Danish Civil Registration System
DAC	The Data Analytics Centre
DKMA	The Danish Medicines Agency
DNPR	Danish National Prescription Registry
EU	European Union
FDA	The American Food and Drug Administration
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
ICD-10	International Statistical Classification of Diseases, 10th Revision
INN	International non-proprietary name
CLIR	The Clinical Laboratory Information Register
GW	Gestational week
LMP	Last menstrual period date (first day of the last menstrual period)
MA	Marketing authorisation
MAH	Marketing authorisation holder
MBR	The Danish Medical Birth Register
MCM	Major congenital malformation
NPR	The Danish National Patient Register
PCOS	Polycystic ovary syndrome
PS	Propensity score
SDS	Danish health data authority
SGA	Small for gestational age
TOPFA	Terminations of pregnancy due to foetal anomaly

2. Responsible parties

Denmark

- Helle Gerda Olsen: Postgraduate MSc student, pharmacovigilance assessor, DKMA
- Elvira Vaclavik Bräuner: daily supervisor, epidemiologist, Data Analytics Center (DAC), DKMA
- Elena Dudukina: daily supervisor, pharmacoepidemiologist, DAC, DKMA
- Stine Hasling Mogensen: team manager and scientific senior adviser, DAC, DKMA
- Jon Trærup Andersen: clinical adviser, Professor in clinical pharmacology / pharmacoepidemiology, Bispebjerg Hospital.

The Netherlands

- Olaf Klungel: examinator/tutor, Professor in pharmacoepidemiology, Utrecht University

3. Kort populærvidenskabelig beskrivelse af forskningsprojekt (plain language Danish summary of the research project)

Svær overvægt er i dag blandt de største sundhedsmæssige udfordringer i den vestlige verden. Lægemidlerne i klassen GLP-1 receptor agonister (GLP-1 RA, på dansk også kaldet GLP-1 analoge lægemidler) blev oprindeligt udviklet til behandling af type 2 diabetes, men er samtidig kendt for at have en vægtreducerende virkning. To produkter i klassen er siden blevet markedsført specifikt som behandling mod overvægt og svær overvægt, nemlig Saxenda (liraglutid) i 2015 og Wegovy (semaglutid) i 2022.

Der er sparsom viden om sikkerheden ved brug af GLP-1 analoge lægemidler under graviditet. Dyrestudier har vist fosterskadende effekter, og derfor frarådes kvinder at bruge produkterne, hvis de er gravide eller planlægger at blive gravide. Siden markedsføringen af de to lægemidler mod overvægt og svær overvægt er forbruget i Danmark imidlertid steget markant, også blandt kvinder i den fødedygtige alder. Trods anbefalingerne bliver nogle kvinder alligevel gravide imens de er i gang med behandlingen.

For at kunne rådgive disse kvinder bedre, er der brug for mere viden om de eventuelle risici der kan forekomme i graviditeter der er opstået under samtidig behandling med GLP-1 analoge lægemidler. Ved hjælp af de allerede tilgængelige data i danske registre frem til nu, vil mit projekt undersøge risikoen for udvikling af alvorlige misdannelser blandt disse graviditeter. Fokus vil være på risikoen for afbrydelse af graviditeten pga. fostermisdannelser, samt risikoen for spontan abort og lav gestationsaldersjusteret fødselsvægt ved brug af GLP-1 analoge lægemidler før og under graviditeten.

4. Abstract

Obesity are among the major health challenges in the Western world. Glucagon-like peptide-1 receptor agonist (GLP-1 RA) medicines were originally developed for the treatment of diabetes type 2, but they also have weight-reducing potential, and two products in this class have until today been developed and approved specifically to treat overweight and obesity, i.e. Saxenda (liraglutide) in 2015 and Wegovy (semaglutide) in 2022.

To date, limited information about the safety of GLP-1 RA in pregnancy is available. Animal studies have shown reproductive toxicity, and women are therefore advised to stop treatment if they plan to become pregnant or in the case of pregnancy. Since the launch of GLP-1 RA as weight reducing therapy, drug dispensing has been increasing notably in Denmark, including among women of fertile age. Despite clinical recommendations, some women may still become pregnant during treatment.

To be able to counsel women with overweight or obesity appropriately, this study will address the knowledge gaps by investigating an association between GLP-1 RA use before conception or during pregnancy and potential risks of adverse pregnancy and birth outcomes. We will utilise nationwide Danish health registry data to investigate the risks of spontaneous abortion, termination of pregnancy due to foetal anomaly and small for gestational age among pregnancies exposed to GLP-1 RA pre-conceptionally or during pregnancy versus no exposure to GLP-1 RA pre-conceptionally or during pregnancy. In a separate analysis, we will investigate the risk of any major congenital malformation among pregnancies exposed to GLP-1 RA pre-conceptionally or in first trimester versus pregnancies unexposed to GLP-1 RA pre-conceptionally or in first trimester.

5. Amendments and updates

Table 1. Amendments and updates.

Number	Date	Section of study protocol	Reason for amendment / update
1.0	24 June 2023		Protocol submitted for SDS
1.1	21 August 2023	Throughout	To enable more detailed and operational method descriptions
1.2	4 October 2023	Throughout	To incorporate comments and feedback from Elvira, Elena and Jon
1.3	06 November 2023	Throughout	To incorporate comments and feedback from Elvira and Elena
1.4	27 November 2023	9.6.2. Sensitivity analyses	Additional sensitivity analyses added after feedback from Olaf, and use of lab values has been clarified.
1.5	11 January 2024	9.2.4 Exclusion criteria	List of teratogens for exclusion aligned with existing definitions.
1.6	**05 February 2024**	**9.2.4 Exclusion criteria**	**To solve possible confusion: Clearer distinction between malformations of known cause (to be excluded up front) and those minor malformations that during data cleaning needs to be excluded from the major malformations (in accordance with EUROCAT definitions).** **Multiple pregnancies will be added as an additional exclusion criterium, this is for data analytical simplicity and in line with other research groups.**

6. Milestones

Table 2. Milestones.

Milestone	Planned date
Data access requested	26 June 2023
Interim assessment	24 November 2023
Data access granted	*Tentatively expected 23 December 2023*
Data analysis completed	*Tentatively expected 15 March 2024*
Final report of study results	*Tentatively expected 1 May 2024*
Oral presentation	*Tentatively expected 1 July 2024*
Manuscript submission to peer reviewed international journal	*Tentatively expected 15 July 2024*

7. Rationale and background

Obesity and overweight are among the major health challenges in the Western world (1). Glucagon-like peptide-1 receptor agonist (GLP-1 RA) drugs were originally developed for the treatment of type 2 diabetes (2). Weight-loss was observed during GLP1-RA treatment as a side effect (3), which led to further drug development specifically for use among overweight and obese persons (2).

The first drug in the class of GLP-1 RA, exenatide, was approved in the EU in 2006 for the treatment of type 2 diabetes mellitus (4). Other approvals of GLP-1 agonists for the same indication have since followed, i.e. for liraglutide in 2009 (5), lixisenatide in 2013 (6), dulaglutide in 2014 (7), and semaglutide in 2018 (8). It is widely recognised that GLP-1 agonists approved for diabetes are also used off-label for the treatment of obesity and overweight (9–11), but to date, only two GLP-1 RA, have received regulatory approval for the obesity and overweight as indications, namely liraglutide and semaglutide in 2015 (12) and 2022 (13), respectively.

Due to GLP-1 agonists' effectiveness (14), some call them "miracle drugs" (9,10), and their utilisation is now increasing notably worldwide (9,15). Although weight reduction is maintained while on treatment (16), but to achieve a lasting effect long-term continued treatment may be necessary.

In Denmark in the period from 2018 to 2022, the sale of the entire class of GLP-1 RA medicines have increased over 4-fold among women of all age groups, whereas sales have increased 7-fold among women aged 25-44 years (**reference: Medstat**).

Common to all EU-approved GLP-1 RAs is the current lack of data on the utilisation and safety during pregnancy in humans (4–8,12,13). During preclinical development, studies on animals showed reproductive toxicity across all GLP-1 RA substances, which were deemed as possibly related to the anorexigenic effect on the mother (4–8,12,13), whereas for semaglutide and lixisenatide, few malformations were noticed in the animal's offspring without a biologic mechanism identified (6,8). The possibility for these adverse events being random findings was considered in the assessment of the marketing authorisation applications, but eventually it was concluded that a causal relation could not be ruled out (6,8). In all EU product information (PI) documents, women are advised to use contraception during GLP-1 RA treatment or to discontinue treatment either when planning to become pregnant or immediately at the time the pregnancy is clinically confirmed (17–23).

Despite these recommendations and considering the growing population of GLP-1 RA users, some women may inadvertently become pregnant during the course of their treatment. Several factors could play a role in this regard. Firstly, women with high BMI are not necessarily recognised as patients with a chronic disease in the traditional sense, and may, therefore, not receive the same level of medical counselling and attention as other patient groups. Secondly, women with polycystic ovary syndrome (PCOS) may be prescribed GLP-1 RA to lose weight as part of their infertility treatment (24,25), but, paradoxically, once the drug exerts its effect, fertility may recur. Since contraception counselling could be less prioritized by healthcare practitioners among women with a history of infertility, this group of women may be at an increased risk of inadvertent GLP-1 RA use periconceptionally and during pregnancy. Lastly, discontinuation of GLP-1 RA treatment may lead to regaining of up to two-thirds of the previous weight loss within the first year (16), and, thus, a proportion of women with severe obesity may prefer to continue their treatment despite a concurrent intent to achieve pregnancy. Taken together, these are all aspects which stress the necessity to investigate a potential association between exposure to GLP-1 RAs periconceptionally and in pregnancy and the risks of adverse pregnancy and birth outcomes.

To further stress the gap in knowledge, at the time of designing the present study, no observational studies on this associated have been completed, nor has the European Medicines Agency (EMA) requested any post-authorisation safety studies in pregnancy for any of the GLP-1 RA agents (4–8,12,13). Only for the

product Wegovy, has the American Food and Drug Administration (FDA) issued two post market requirements with regard to use in pregnancy including:

- A prospective product-specific registry study to collect information based on voluntary consent from pregnant women exposed at any time during pregnancy, which will be compared to an unexposed reference population; with an estimated study completion date of 30-12-2032 (NCT05872022, same as EUPAS104613).
- A retrospective study using administrative insurance claims data, but the details on the study design and statistical analysis plan are not publicly available; the estimated study completion date is 15-08-2027 (NCT05503927).

In addition, an investigator-initiated observational multicentre study utilizing data from "Participating centres of the European Network of Teratogen Information Services (ENTIS)" has been registered in the ENCePP database with an anticipated study size of 200, and a final study report was expected on 30-06-2023. Only little additional information has been provided in the EU PAS Register (EUPAS50643).

Due to an unmet and growing need for data on the possible association between periconceptional or pregnancy exposure to GLP-1 RAs and adverse pregnancy and birth outcomes, a well-conducted observational study is required.

The aim of the present study is to investigate the association between periconceptional or pregnancy exposure to GLP-1 RA and the risks of adverse pregnancy and birth outcomes in an observational study using Danish nationwide and prospectively collected healthcare data in a context of universal and tax-supported healthcare system. The results of the present study may be used to support informed counselling of women who may become pregnant while continuing GLP-1 RA treatment.

8. Research question and objectives

Primary objective:

1. To investigate the association between periconceptional or pregnancy exposure to GLP-1 RA and the adverse pregnancy and birth outcomes: spontaneous abortion, any major congenital malformation (MCM), and small for gestational age (SGA) as compared to pregnancies unexposed to GLP-1 RA periconceptionally or during pregnancy.

The exposure window covering 3 months before conception and first trimester (T1) will be used for the investigation of any MCM as the outcome, and 3 months before conception and entire duration of the pregnancy will be used as an exposure window for the remaining outcomes.

The research question: Is periconceptional or pregnancy exposure to GLP-1 RA medicines associated with increased risks of adverse pregnancy and birth outcomes?

- Null-hypothesis: Exposure to GLP-1 RA periconceptionally or during pregnancy is not associated with an increased risk of adverse pregnancy and/or birth events.
- Alternative hypothesis: Exposure to GLP-1 RA periconceptionally or during pregnancy is associated with an increased risk of adverse pregnancy and/or birth events.

Secondary objectives:

1. To apply the primary objective for individual substances in the class of GLP-1 RAs (i.e., liraglutide, semaglutide, dulaglutide, exenatide, lixisenatide) if sufficient number of events is accrued.

2. To provide a quantitative description of GLP-1 RA drug utilisation prior to as well as during early and late pregnancy.

9. Research methods

9.1. Study design

For ethical reasons, a non-interventional design is required. Considering that GLP-1 RA have been approved in the EU since 20 November 2006, information has been accumulating within existing national registries, including the Danish, that can be utilised for this investigation. Hence, the study design will be a nationwide retrospective register-based study, utilising secondary data.

We will use a cohort study design for the investigation of adverse pregnancy outcomes (spontaneous abortion) and prevalence study design for the investigation of adverse birth outcomes (any MCM and SGA).

9.2. Setting

9.2.1. Source population

The study will apply existing secondary data from Danish nationwide registries:

- the Danish Civil Registration System (CRS)
- the Danish National Patient Register (NPR)
- the Danish National Prescription Registry (DNPR)
- the Danish Medical Birth Register (MBR)
- the Clinical Laboratory Information Register (CLIR)

The CRS provides a unique personal identifier assigned to every legal resident of Denmark at birth or immigration since 1968 and enables linkage between all registries at an individual level (28).

The NPR stores data on all in-hospital encounters since 1995, including the date of the encounter and primary and secondary diagnoses recorded according to ICD-10. Virtually all in-hospital medical care in Denmark, including encounters at outpatient specialist clinics, is provided by the public hospitals (29).

The DNPR provides data on all prescription medications dispensed in the community pharmacies since 1995 (30).

The MBR provides maternal, pregnancy, and childbirth-related characteristics including the date of delivery, gestational age at birth, status of a birth (live vs stillbirth), maternal age at delivery, smoking status at 1st prenatal visit on all deliveries ending in a live or stillbirth in Denmark since 1997. The maternal BMI is recorded in MBR since 2004 (31).

The CLIR provides information about biochemical and immunological analyses performed at the major clinical biochemistry and clinical immunology laboratories in Denmark since 2008 (32); however a complete national coverage was first fully established in Q3 2015 with regard to clinical biochemical analyses (32).

9.2.2. Study population

The study population will consist of pregnancies registered with a birth outcome (live or still) in MBR between 04 October 2007 (i.e. 23 weeks after launch date of 26 April 2007) and 31 December 2023 OR with an abortion outcome (spontaneous or induced) in NPR between 10 May 2007 (i.e. 2 weeks after 26 April 2007) and 31 Dec 2023.

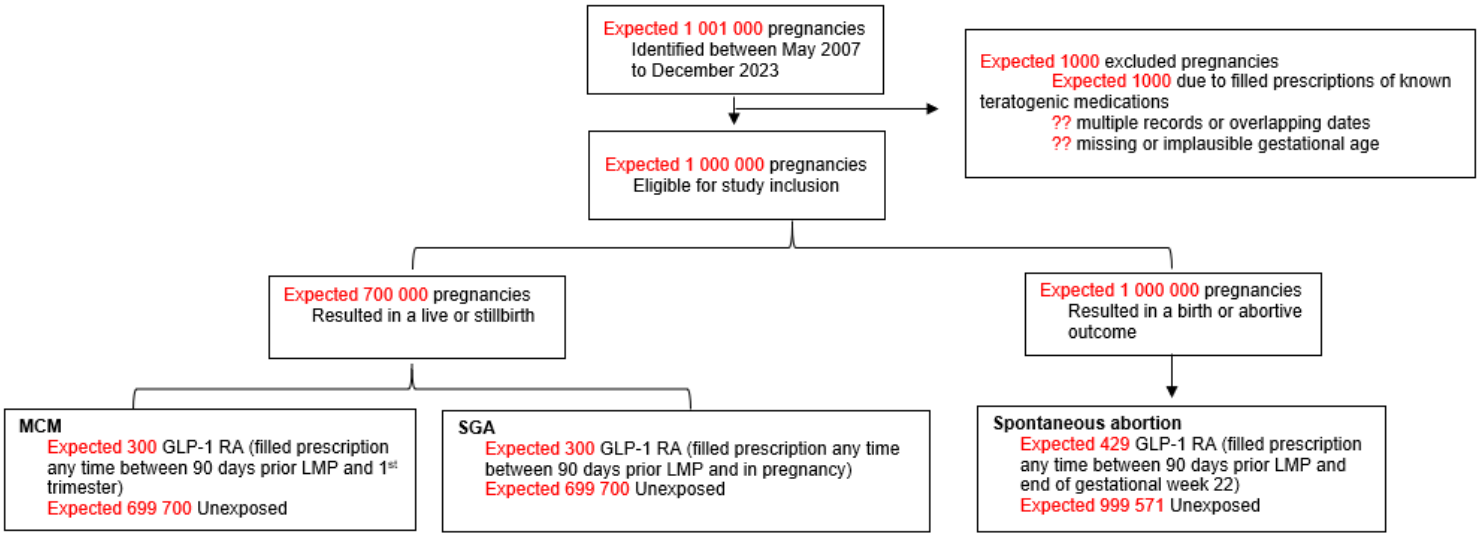
The unit of analysis will be the single pregnancy. A multi-foetal pregnancy will be addressed as a single pregnancy unit.

For each individual pregnancy, the date of last menstrual period, (first day of the last menstrual period, LMP) will be calculated as date of birth minus gestational age in days available in the MBR for births or in NPR for pregnancies ending in abortion. Date of LMP will be used as cohort entry date (CED) (equivalent to the 'index date' or 'start of follow up' for the investigation of spontaneous abortion as the outcomes). Hence, the study population will constitute all pregnancies with date of LMP between 26 April 2007 (i.e. first launch of a GLP-1 RA product in Denmark) and xx XXXXX 2023.

The same woman will be able to enter the study population several times if she had >1 recorded pregnancy during the study period. The presence of multiple pregnancies of the same woman will be addressed during the statistical analyses.

The overall population is merged by pregnancies recorded in either NPR alone (if a pregnancy ended before gestational week (GW) 23) or in the MBR in addition to NPR (if a pregnancy lasted beyond GW 23). Since the MBR contains important baseline characteristics (including smoking status and BMI) that are not covered by the NPR, the outcome analyses of MCM and SGA will be performed on the subset of data from MBR. Hence, the following sub-populations will be defined as outlined in Figure 1 below:

Figure 1. Definitions of subpopulations for the individual outcome analyses. Note that the expected numbers represent an approximation and is solely for illustrative purposes. Refer to section 9.4 for further details on the expected study size.



9.2.3. Study period

For the primary objective, the period during which pregnancies can enter the study spans the date from first launch of a GLP-1 RA in Denmark, i.e. from 26 April 2007, and until the most recent data access possible.

For the secondary objective, the study period will be narrowed to the date of first authorisation, or, if available, to the date of first launch in Denmark, for each individual substance:

- 26 April 2007 for exenatide
- 30 June 2009 for liraglutide

- 01 February 2013 for lixisenatide
- 21 March 2014 for albiglutide (until MA was retracted on 29 October 2018)
- 21 November 2014 for dulaglutide
- 08 February 2018 for semaglutide

9.2.4. Exclusion criteria

Pregnancies excluded:

- Any pregnancy exposed to known teratogens during pregnancy (33) (from LMP date to pregnancy end date, both dates inclusive), as outlined in the table 3 below.
- Any pregnancy with birth defects resulting from a known cause according to EUROCAT definitions (33,34)
- Any pregnancy of a woman who has an invalid personal identifier (an invalid CRS number)
- Any pregnancy of a woman who was not a resident of Denmark 12 months prior to LMP.
- Any pregnancy with missing information on gestational age.
- Any multiple pregnancy.

Table 3. List of known teratogenic substances (33).

Drug	**Anatomical Therapeutic Chemical (ATC) codes**
Warfarin	B01AA03
Antineoplastic drugs	L01DA L01AB01 L01AA02 M04AC01 L01AA01 L01DB01 L01BB02 L01BA01 L04AX03 L01CA01 L01CA02
Lithium	N05AN01
Topical or systemic retinoids, including isotretinoin	D10BA01 D10AD54 D10BA04 D05BB D11AH04
Misoprostol	A02BB01 G02AD06 M01AE56 M01AB55
Thalidomide	L04AX02
Valproic acid	N03AG01

9.3. Variables

9.3.1. Exposure of interest

The exposure of interest is the class of GLP-1 RA medicines (ATC code: A10BJ) as outlined in the table below. Redeeming a prescription does not infer that the medicine is taken, but this is the underlying assumption in this study. The exposure is defined as at least one redeemed prescription of any GLP-1 RA within the exposure time window of interest.

Table 4. Overview of EU-approved GLP-1 RA medicines.

MA date	Date of with-drawal	Product name	INN	Formulation	Recommended posology	MAH	Indication
20-11-2006	NA	Byetta	exenatide	Prefilled pens that provide either 5 or 10 micrograms of exenatide in each dose. For s.c. injection.	5-10 mg s.c. twice daily	AstraZeneca	Diabetes Mellitus, Type 2
30-06-2009	NA	Victoza	liraglutide	pre-filled pens (6 mg/ml). One pre-filled pen contains 18 mg liraglutide in 3 ml, hence contains 30 doses of 0.6 mg, 15 doses of 1.2 mg or 10 doses of 1.8 mg.	0.6-1.8 mg s.c. once daily	Novo Nordisk A/S	Diabetes Mellitus, Type 2
17-06-2011	NA	Bydureon	exenatide	2 mg powder and solvent for prolonged-release suspension for s.c. injection	2mg s.c. once weekly	AstraZeneca	Diabetes Mellitus, Type 2
01-02-2013	NA	Lyxumia	lixisenatide	Prefilled pens (10-20 mg solutions)	10-20 mg s.c. once daily	Sanofi Winthrop Industrie	Diabetes Mellitus, Type 2
21-03-2014	29-10-2018	Eperzan	albiglutide	30 mg or 50 mg powder and solvent for solution for s.c. injection	30-50 mg once weekly	GlaxoSmithKline Trading Services Limited	Diabetes Mellitus, Type 2
21-11-2014	NA	Trulicity	dulaglutide	prefilled pens (solutions: 0.75 mg, 1.5 mg, 3 mg, 4.5 mg)	0.75-4.5 mg s.c. once weekly	Eli Lily	Diabetes Mellitus, Type 2
23-03-2015	NA	Saxenda	liraglutide	Pre-filled pens, contains 18 mg liraglutide in 3 ml.	0.6-3.0 mg s.c. once daily	Novo Nordisk A/S	Obesity and overweight
08-02-2018	NA	Ozempic	semaglutide	Prefilled pens (0.25-2 mg solutions)	0.25-1 mg s.c. once weekly	Novo Nordisk A/S	Diabetes Mellitus

03-04-2020	NA	Rybelsus	semaglutide	Tablets (3, 7 and 14 mg)	3-14 mg p.o. once daily	Novo Nordisk A/S	Diabetes Mellitus, Type 2
06-01-2022	NA	Wegovy	semaglutide	Prefilled pens (0.25-2.4 mg solutions)	0.25-2.4 mg s.c. once weekly	Novo Nordisk A/S	Obesity and overweight
NA	*NA*	*NA*	*Beinaglutide, A10BJ07*	*NA*	*NA*	*NA*	*NA*

NA: Not applicable

Definition of the duration of exposure

The largest package sizes of GLP-1 RA medicines provide for three months of treatment.; i.e. each filled prescription is assumed to correspond to 3 months of continuous use, starting from the date of the filling of the prescription.

The exposure time windows are the following:

- SAB outcome: [LMP -90 days; LMP +154 days]
- MCM outcome: [LMP -90 days; LMP +97 days] (35)
- SGA outcome: [LMP -90 days; LMP +pregnancy end]

Graphic representations of the exposure risk periods are provided below for each of the outcomes.

Figure 2. Assessment of MCM.

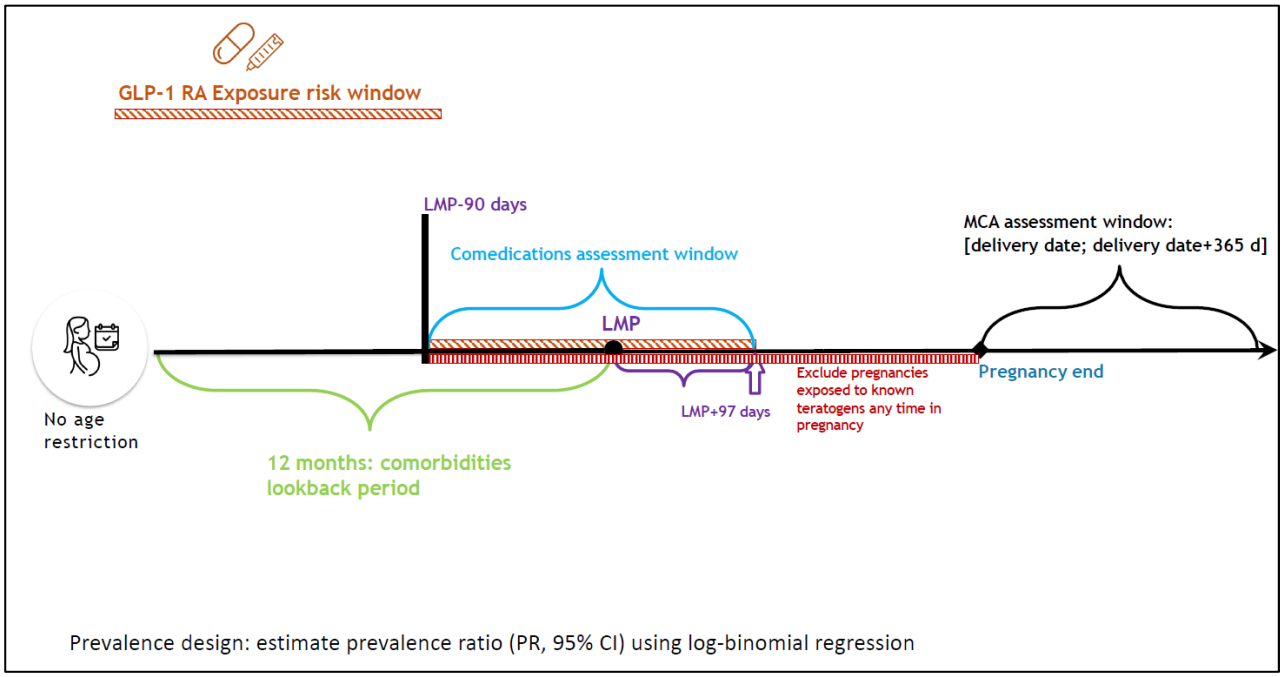


Figure 3. Assessment of SGA and low birth weight.

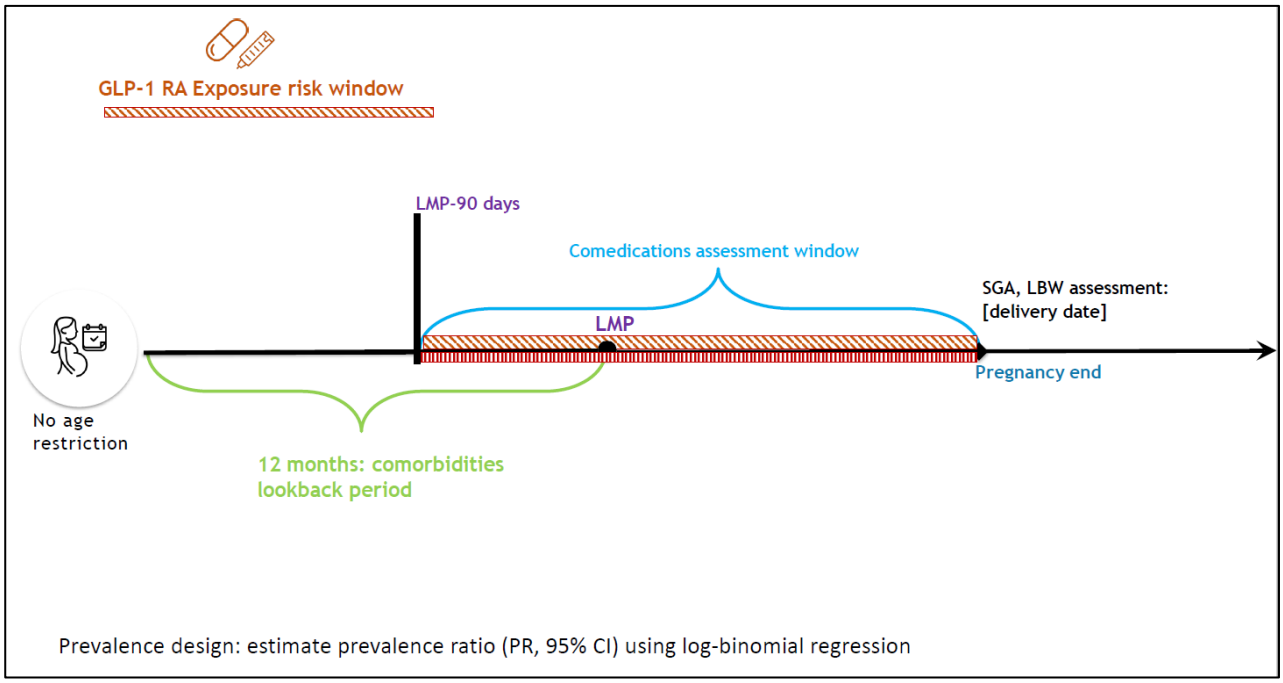
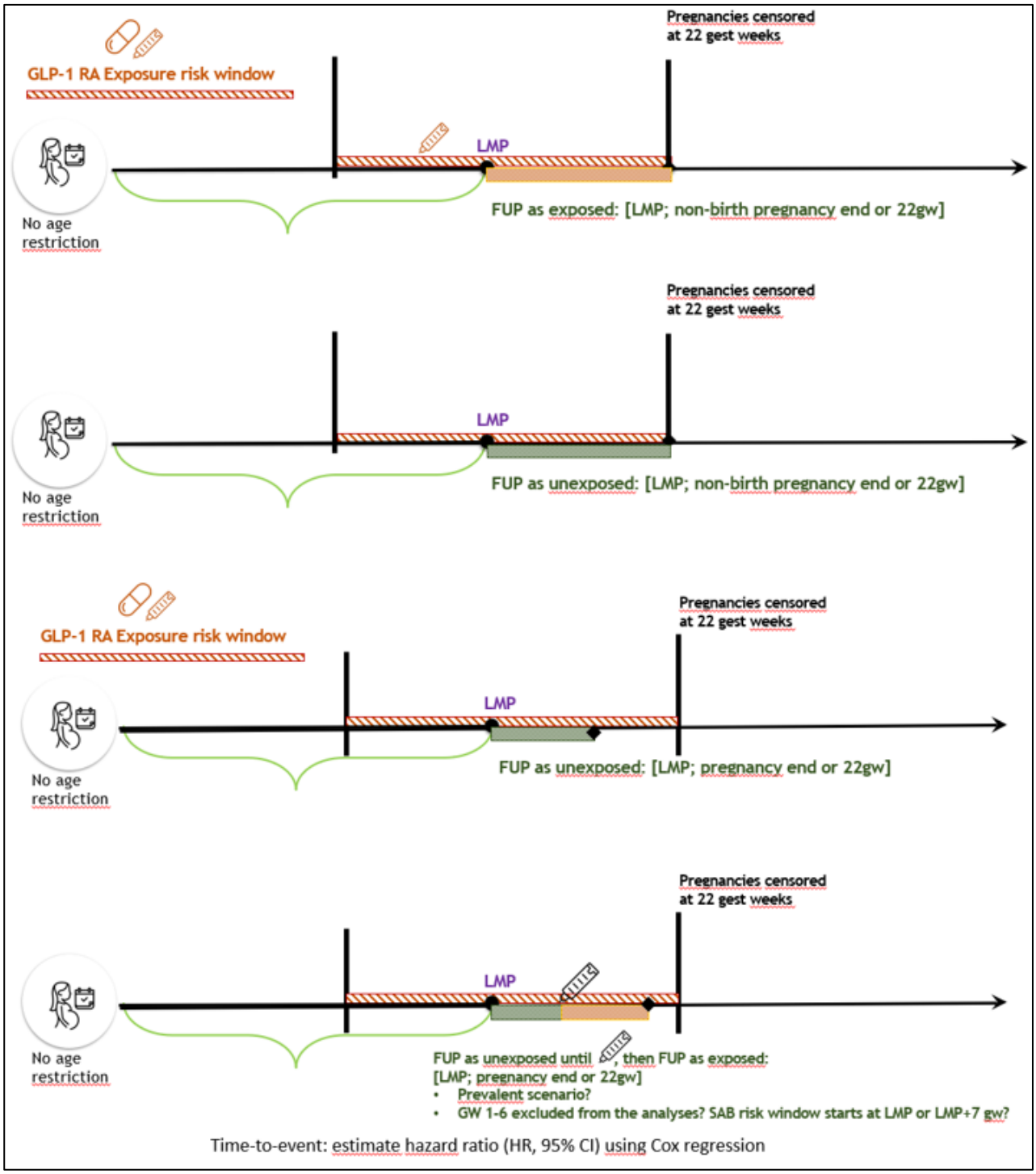


Figure 4. Assessment of spontaneous abortion in various exposure scenarios.



9.3.2. Endpoints of interest

Spontaneous abortion

Spontaneous abortions are defined as pregnancies ending in foetal death before the end of gestational week 22, according to ICD-10 classification codes.

Any MCM

MCM will be measured as a single composite outcome: 'any MCM,' and will be defined according to EUROCAT classification system (34). Each pregnancy can have more than one foetus, and each foetus can have more than one malformation, yet a pregnancy with malformations will be counted only once in the analysis of overall malformation prevalence. Descriptive analysis of malformation subtypes may be considered; the analyses would then be conducted on the level of the single foetus.

Livebirths will be followed through 1 year of age to ensure completeness of data on MCM, as diagnosis may be recorded with a delay (36).

SGA

SGA is defined as below the lowest 10th percentile of the gestational age–specific and sex-specific birth weight in the MBR subpopulation of all births.

9.3.3. Baseline maternal/pregnancy characteristics and demographics

A look-back period of 365 days since the LMP (LMP-365 days; LMP-1 day) will be used to establish pre-pregnancy drug use. Co-morbidities will be ascertained using the diagnostic history of the pregnant woman using the same look-back period. If for a certain variable >1 value has been recorded during the look back period, the value closest to LMP will be applied.

Table 5. Maternal/pregnancy characteristics and demographics variables.

Variables	Definition	ICD-10 / ATC code	Data source
Maternal/pregnancy characteristics at pregnancy onset			
Year of pregnancy	<2014, 2014-2018, 2019-2023		NPR
Age at pregnancy onset	<20, 20-24, 25-29, 30-34, >35		NPR
Smoking at the first prenatal visit	yes/no		MBR
BMI, kg/m^2	<20, 20-24, 25-29, 30-34, >35		MBR
Multiple birth pregnancy	Yes/no		MBR
Parity	1, ≥2		MBR
Previous pregnancies with same foetal outcome	yes/no		MBR
Married or defacto	Yes/no		CRS
Place of birth	Denmark, Europe, outside Europe		NPR
Region of residence	Capital Region of Denmark, Region Zealand, Southern Denmark, Central Denmark Region, North Denmark		NPR
Season of conception	Winter, Spring, Summer, Autumn		NPR
HbA1c >48 mmol/mol	yes/no		CLIR
Prescription of drugs within 1 year of pregnancy onset			

Systemic glucocorticoids	yes/no	H02AB, H02B	DNPR
Antidepressants	yes/no	N06A, N06C	DNPR
Insulins and analogues	yes/no	A10A	DNPR
Blood glucose lowering drugs excl. insulins and GLP-1 RA	yes/no	A10B except A10BJ	DNPR
Antihypertensives	yes/no	C02 (antihypertensives), C03 (diuretics), C07 (beta blockers), C08 (calcium channel blockers), C09 (agents acting on the RAS (ACE-inhib + ARBs)	DNPR
Lipid modifying agents		C10	
Antiobesity preparations	yes/no	A08A	DNPR
Antiinfectives for systemic use	yes/no	J01-J05	DNPR
Antipsychotics	yes/no	N05A	DNPR
Anxiolytics		N05B	
Hypnotics and sedatives		N05C	
Psychostimulants		N06B	
Drugs for obstructive airway diseases	yes/no	R03	DNPR
Drugs for underactive thyroid / thyroid hormones	yes/no	H03AA	DNPR
Drugs used in IVF treatment	yes/no	G03G, G03DA, G03XA, H01AA, H01CA, H01CC, L02AE	DNPR
NSAIDs	yes/no	M01A except M01AX	DNPR
Opioids	yes/no	N02A	DNPR
Antimigraine drugs	yes/no	N02C	
Antiepileptics	yes/no	N03	
Number of unique drugs prescribed at least once	1-2, 3-4, ≥ 5		DNPR

Morbidities diagnosed within 1 year of pregnancy onset

Asthma	yes/no	J45	NPR
Ischaemic heart diseases	yes/no	I21-I25	NPR
Diabetes Type 1	yes/no	E10.9, E10.9A	NPR
Diabetes Type 2	yes/no	E11	NPR
Hypertension	yes/no	I10-I15	NPR
Obesity	yes/no	E66, E68	NPR
PCOS	yes/no	E28.2, N97.0	NPR
Mood [affective] disorders	yes/no	F30-F39	NPR
Neurotic, stress-related and somatoform disorders	yes/no	F40-F48	NPR
Behavioural syndromes associated with physiological disturbances and physical factors	yes/no	F50-F59	NPR
Thyroid disorders	yes/no	E00-E07	NPR
Rheumatic diseases	yes/no	M36	
No. of hospital admissions	none, 1,2, ≥3		NPR
No. of outpatient visits	none, 1,2, ≥3		NPR

9.4. Study size and precision

9.4.1. Study size

Considering the current low level of evidence, exclusion of large risks of adverse pregnancy and birth outcomes could be relevant; moreover, the results of the present study may be valuable for future meta-analyses investigating an association between periconceptional and pregnancy exposure to GLP-RAs and adverse pregnancy and birth outcomes.

The sample size and estimates precision will be determined by the availability of data until current date. In Denmark, 971 705 live births have been registered between 2007 and 2023 (37). According to publicly available excerpts from the NPR and the MBR (38), 0.1 pregnancy out of 1000 pregnancies were exposed to a GLP-1 RA before 2017, corresponding to approximately 6 exposed pregnancies per year. In the period from 2017-2020, the exposure doubled to 0.2 per 1000 pregnancies, corresponding to 12 exposed pregnancies per year. Since 2020, number of pregnancies exposed to GLP-1 RAs increased up to 0.4 (~25 pregnancies) and 0.7 (~41 pregnancies) per 1000 pregnancies in 2021 and 2022, respectively. Based on the overall national trend of GLP-1 RA use (15), the exposure to GLP-1 RAs periconceptually and in pregnancy may be expected to continue to rise further into 2023.

Taken together, around 300 GLP-1 RA exposed pregnancies ending in still- or live birth is estimated from the subset of data defined by the MBR before the end of 2024.

Pregnancies ending in spontaneous or induced abortion before 22 weeks of gestation will be additionally included in this study. In a survey on Danish registry data from 2014, 70% of all registered pregnancies ended in a live birth, 0.3% in a stillbirth, 13% in spontaneous abortion, and 17% in termination of pregnancy

(39). Using these proportions, the expected number of pregnancies exposed to GLP-1 RA and ending in spontaneous or induced abortion will be 129.

Hence, the size of the total, combined exposed pregnancy population (NPR + MBR registries) is expected to be approximately 429 pregnancies, and the total population approximately 1 000 000 pregnancies.

9.4.2. Precision estimation

In case of no true effect of GLP-1 RA on the outcome MCM (i.e. a prevalence proportion ratio of 1), and given a background prevalence proportion of 3%, a population of 300 exposed births, the estimated precision (40) will be 3.62 with a point estimate of 1 and a 95%CI of 0.53 – 1.90. Hence, the least detectable difference is estimated to be a 1.9-fold increased prevalence of MCM among exposed births.

Similarly, for SGA, given a Danish background prevalence for SGA of 3.9% (41), and in case of no true effect, the estimated precision is 3.08 with a point estimate of 1 and a 95%CI of 0.57-1.74.

For spontaneous abortion, given a background prevalence of spontaneous abortions of 13% (39), an estimated exposed population of 429, and in case of no true effect, the estimated precision is 1.63 with a point estimate of 1 and a 95%CI of 0.78-1.28.

9.5. Data management

Data management will be conducted on the Danish Health Data Authority secure server (SDS) in compliance with national data security and privacy guidelines. SDS will ensure that data is pseudo-anonymised to protect individuals' identities. Once electronic access has been granted, the dataset will be analysed using R software (reference needed). No sensitive data, defined as counts <5 individuals or other data identifying individuals, are allowed to be presented in the report tables.

9.6. Data analysis

9.6.1. Computation of a propensity score

Following exclusion of pregnancies according to the exclusion criteria, the three subopulations will be defined for the individual outcome analyses in accordance with Figure 1 in section 9.2.2. Study population.

For each subpopulation, to control for confounding, a logistic regression model will be developed from all available variables with a known potential impact on the outcome (refer to Table 5). This model will be used to estimate a propensity score value between 0 and 1 for each pregnancy. Briefly, a propensity score is an estimate of the likelihood of exposure for each individual, given a set of known risk factors for the outcome (42).

9.6.2. Inverse probability of treatment (IPT) weighting

We will compare pregnancies exposed to GLP-1 RA with pregnancies unexposed whose distribution of risk factors is similar to that of the exposed population. With this approach, the target of inference will be the average GLP-1 RA effect among GLP-1 RA exposed pregnancies, i.e. the average treatment effect among the treated (ATT).

Each pregnancy will receive a weight according to the inverse of the probability of its actual exposure status to create a pseudo-population, i.e. IPTW = 1/(X*PS + (1-X)*(1-PS)), where X can be 0 or 1. This will be done for each subpopulation assessment separately, refer to the Figure in section 9.2.2. Study population.

Covariate balance between exposed and unexposed before and after IPT weighting will be investigated by assessment of standardised differences, to assess the performance of the IPT weights. A cut-off of 10% will be used for the standardized mean difference. Non-overlapping areas will be investigated, and, if feasible they will be asymmetrically trimmed at the 99th percentile, and variables balance will be reassessed. If sufficient balance is not initially achieved, common model diagnostic techniques will be applied to modify and specify the propensity score model, e.g. via transformation of variables based on visual inspections of QQ plots.

9.6.1. Statistical analysis

Measures of proportion will be hazard ratio for pregnancy outcomes (spontaneous abortion), and prevalence proportion ratio for birth outcomes (MCM and SGA).

Spontaneous abortion will be modelled in a time-to-event framework with gestational age in days as the underlying time unit. Unadjusted and adjusted hazard ratios with corresponding 95% confidence intervals (CIs) will be computed using Cox proportional hazards regression to allow for censoring of induced abortions and to consider time-varying changes in exposure status during follow-up. The unit of observation will be a single pregnancy.

For MCM and SGA, unadjusted and adjusted prevalence proportions will be calculated as number of pregnancies ending in the given birth outcome divided by the total number of pregnancies at risk. Unadjusted and adjusted prevalence proportion ratios with corresponding 95% Wald CIs will be computed using log-binomial regression.

9.6.1. Descriptive analyses

Characteristics of exposed pregnancies

In accordance with the secondary objective, the pregnancy population will be described in terms of number of pregnancies exposed per indication and per product, and number of pregnancies with prescriptions filled prior to pregnancy onset, vs. in first, second, and third trimester of pregnancy.

TOPFA and stillbirth

In 2018-2022, the average yearly number of abortions occurring GW ≥ 12 was 467 (reference: esundhed.dk), and approximately half of these is assumed to being due to foetal/neonatal illness. With an average of 60 000 births per year, the background prevalence for TOPFA is therefore estimated as (234/60 000 pregnancies) 0.39%. Considering the rarity of this outcome, inferential analysis is disregarded. The number of pregnancies terminated after GW 12 in accordance with article 94 of the Danish Health Act (late abortion permitted by dedicated council), i.e. pregnancies registered with ICD-10 code: DO059, will be collected and presented descriptively by exposure group. The same will apply to the outcome of stillbirths with a background prevalence of 0.3% (39).

Subcategories of malformations

For cases of TOPFA and MCM, subcategories of ICD-10 codes will be described in a table, if sufficient number of events is accrued (for TOPFA, ICD-10 codes O35-O36 will apply).

9.6.2. Sensitivity analyses

To address the robustness of the study results for the primary study objective, a number of sensitivity analyses will be performed:

Stratifications

To investigate the possibility of existing residual confounding by indication, stratification will be performed in two ways:

- by date of first approval of the obesity indication (i.e. corresponding to LMP before vs. after 23-03-2015).
- by fulfilled criteria for diabetes type 2 versus not fulfilled criteria for diabetes type 2. A diagnosis code of type 2 diabetes alone is not sufficient to recognise subjects with type 2 diabetes since GLP-1 RAs approved solely for type 2 diabetes may sometimes be prescribed to patients without type 2 diabetes, in order to receive the reimbursement provided for the type 2 diabetes indication, as there is currently no reimbursement for the obesity indication. Sometimes off-label prescriptions can also happen due to recurrent problems with medicine availability.
  Hence at least one the following criteria from the period of 365 days prior to LMP date should be fulfilled to classify a woman as having type 2 diabetes:
  1. An ICD-10 code: E11
  2. ATC-codes A10A, A10B. A10BJ02 liraglutid (“Saxenda”) and A10BJ06 semaglutid ("Ozempic”, ”Rybelsus”, ”Wegovy flextouch”) is only included if prescribed concomitantly with other antidiabetic medicine/ OR a HbA1c value above 47 mmol/mol. A10BJ02 and A10BJ06, when prescribed alone, can be prescribed for overweight as an indication and not diabetes.
  3. HbA1c value above 48.0 mmol/mol

  Secondly, to sort out any cases of type 1 diabetes, pregnancies with an insulin prescription 365 days prior to pregnancy onset should be identified in the subset, and for each of these cases it should be clarified whether the insulin prescription during the look back period happened in relation to a previous pregnancy of the same woman, since insulin could be prescribed to pregnant women with type 2 diabetes.

The pregnancy subgroup of GLP-1 RA stoppers

Substantial heterogeneity is expected both within the exposure/non-exposure groups and between groups. To address the risk of any unmeasured confounding by indication in the main analysis, the utility of a subgroup within the main reference group, namely the prior users of GLP-1 RAs, has been considered. This subgroup is expected to share many similarities with the current users which could be a strength for the control of possible unmeasured confounding, although they also differ in some important aspects. For instance, stoppers and current users are assumed to have overall comparable distributions of BMI and comorbidities. On the other hand, stoppers are likely to have a higher proportion of planned pregnancies than current users, since stopping treatment is recommended in case a pregnancy is planned. Since stopping GLP-1 RA treatment will be followed by a period of weight regain (43), the stoppers will be further into their weight-regain curve than the current users, hence a change in weight over time is an unmeasurable but potentially confounding time-varying variable. Due to this expected weight regain, a potentially negative effect of stopping treatment before pregnancy is also a possibility, albeit not part of the research question of this study. Stoppers could also have stopped due to adverse events, which could be an indicator of increased frailty as a source of residual confounding. Lastly, the number of stoppers is likely much smaller than the total number of unexposed pregnancies which could cause increased uncertainty in the estimates.

This subgroup of "stoppers" is therefore investigated not as its own research objective, but as sensitivity analyses to address the robustness of the study results using two different perspectives:

- the association between GLP-1 RA exposure and all study outcomes will be investigated in pregnancies exposed to GLP-1 RA versus pregnancies of pre-conceptional stoppers of GLP-1 RA, defined as pregnancies with prior GLP-1 RA use during [LMP -365 days; LMP -125 days (i.e. prescription of 90 days+ 35 days wash-out)].
- the association between pre-conceptional GLP-1 RA exposure and all study outcomes will be investigated in pregnancies of pre-conceptional stoppers of GLP-1 RA, defined as pregnancies with prior GLP-1 RA use during [LMP -365 days; LMP -125 days (i.e. prescription of 90 days+ 35 days wash-out)] versus unexposed pregnancies without pre-conceptional use.

Impact of defining exposure start based on days' prescription (44)

The beginning of the exposure window aligns with the number of days' supply in a single GLP-1 RA prescription based on the assumption that the medicine is taken as prescribed. However, if some women stop using the GLP-1 RA before their medication is used up, there is a risk that some truly unexposed pregnancies could be misclassified as exposed, which would introduce a bias towards the null. To investigate the potential impact, a sensitivity analysis will be performed that narrows the exposure window to begin at the date of LMP.

Impact of not adjusting for BMI and smoking

Since some potentially important confounding variables (i.e. BMI and smoking) are available only within the birth subpopulation (i.e. the population from the MBR), adjustment for these variables will not be possible for the miscarriage outcome analysis which utilises the full pregnancy population (i.e. NPR plus MBR). To quantify the impact of this potential bias, the PS-IPTW analysis of the MCM and SGA outcomes will be repeated with these variables excluded from the PS.

9.7. Quality control

The availability and quality of data will be checked initially by standard descriptive procedures to identify missing and erroneous data and to verify the consistency of the dataset. For instance, variables with values exceeding typical ranges and missing values will be flagged. The frequency of missing data, and whether missing data are random processes or could be linked to key characteristics such as year of pregnancy, will be analysed descriptively.

In 2019 the structure of the MBR and the NPR changed which requires harmonisation of data before and after 2019 in these two data sources.

9.8. Limitations

The design is challenged by the fact that considerable heterogeneity exists between users in the various indications. Particularly for the obesity/overweight and off-label indications, the identification of a relevant comparison population of nonusers with potentially comparable baseline characteristics is challenging. Restriction to a single indication, as a means to achieve less heterogeneity, is not considered feasible in the main analysis, since the number of exposed pregnancies is likely too low in our dataset to allow for meaningful interpretation within a single indication. Whereas the PS IPTW analysis may only account for any imbalances among the measured confounders, any unmeasured confounders may bias the results.

Specifically, the BMI and smoking status are only available in the MBR registry; hence they are not available for pregnancies ending in spontaneous abortion, for which information is exclusively obtained from the

NPR registry. For this reason, the outcome assessment of spontaneous abortion could be biased by unmeasured confounding due to BMI and smoking. The magnitude of the bias will be further investigated within sensitivity analyses.

Due to the high costs of being in GLP-1 RA treatment, income is a confounding factor and is unavailable in this study. To reduce the unmeasured confounding by socioeconomic status, we use the region of residence as a proxy. A strong correlation between GLP-1 RA use and region of residence has been observed in Denmark (reference: Danish medical bulletin who wrote about the large difference in GLP-1 RA prescriptions across municipality).

The robustness of the results obtained for the primary objective of the study will be investigated by a sensitivity analysis that compares the users to a subset of the reference population of nonusers, namely the pregnancies who have had prior GLP-1 RA exposure before pregnancy onset, i.e. the GLP-1 RA stoppers (refer to section 9.6.5. Sensitivity analysis). This subset of the reference population is assumed to be more comparable at baseline with regard to e.g. BMI, smoking status and income status, than could be the case for the overall nonuser reference population.

The outcome “Any MCM” is a composite, heterogeneous outcome. Its ability to reveal any risks of specific types of malformations is limited and may lead to bias towards the null, and hence a false reassuring conclusion (26).

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