

# The Burden of Hyperglycemia First Detected in Pregnancy Among Indonesian Women

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## Research article

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# Abstract

**OBJECTIVE:** Despite improvements, Indonesian maternal health falls short of the Sustainable Development Goals. Using contemporary electronic healthcare records, this study explored the burden of Hyperglycemia First Detected in Pregnancy (HFDP) and its association with the determinants of maternal health in Indonesia.

**METHODS:** Electronic Health Records data were extracted on high-risk pregnant women without pre-existing diabetes who were screened for HFDP between 2014 and 2015 at two West Sumatera hospitals. Screening consisted of an oral glucose tolerance test (OGTT), grouping women into Diabetes In Pregnancy (DIP, glucose  $\geq 126$  mg/dl), Gestational Diabetes Mellitus (GDM, glucose 92-125 mg/dl), or high-risk women without elevated glucose levels (glucose  $< 92$  mg/dl); following the World Health Organization (WHO) standard. Maternal and neonatal outcomes, including mortality, were associated with the three diabetes statuses, using general and generalized linear models (depending on the type of outcome) adjusted for maternal age and parity.

**RESULT:** 3536 pregnant women were screened, of which 722 (21%) had HFDP; 655 (19%) were classified as GDM and 67 (2%) as DIP. Women with HFDP did not have a significantly higher risk of death: OR 1.36 (95%-CI 0.71-2.62) for GDM and 0.90 (95%-CI 0.12-6.67) for DIP. We did observe a significantly lower neonatal death rate for children born of GDM women, with three deaths (1%) compared to 178 (6%) in high-risk normal FBG women ( $p$ -value  $< 0.01$ ). This observation was not replicated when comparing DIP to normal FBG women (OR 0.58; 95%-CI 0.26-1.29).

**CONCLUSION:** The observed lack of difference in pregnancy outcomes between HFDP and pregnant women with normal fasting blood glucose levels (at the time of screening) reflects the considerable residual risk of these women. Nevertheless, have and calls for closer monitoring of high-risk women irrespective of their OGTT results. Larger sample-sized studies are warranted to replicate findings with sufficient accuracy to detect possibly smaller, but meaningful differences.

## Introduction

Due to continued improvements in Indonesian maternal health services, maternal mortality rates have reduced from 359 per 100,000 live births in 2012 to 305 per 100,000 live births in 2014 (1). Moreover, neonatal mortality slightly decreased from 20 per 1000 live births in 2002 to 19 per 1000 live births in 2012 (2, 3). While Indonesian maternal healthcare is improving, substantial efforts will be needed to reduce both maternal and child mortality further, meeting the Sustainable Development Goal (SDG) landmarks of fewer than 70 maternal deaths per 100,000 live births, and 12 neonatal deaths per 1,000 live births by 2030 (4, 5).

Indonesian maternal health services include measurements of maternal anthropometric traits, blood pressure, uterus height, fetal positioning, fetal presentation, fetal heart rate, tetanus immunization status, and basic laboratory tests (blood type, Hb and urine, HIV, syphilis, and malaria in endemic areas) (6).

Ultrasound scans, testing urine for protein to detect pre-eclampsia, and blood tests to detect hyperglycemia (oral glucose tolerance test, OGTT), are not standard antenatal care in Indonesia. The absence of routine screening for pre-eclampsia and hyperglycemia likely explains part of the elevated rate of pregnancy complications in Indonesian women.

Hyperglycemia First Detected In Pregnancy (HFDP) is associated with increased complications and worsening outcomes for both mother and child (7–9). HFDP includes both gestational diabetes (GDM, fasting plasma glucose 92–125 mg/dl) and diabetes in pregnancy (DIP, fasting plasma glucose  $\geq$  126 mg/dl). Whilst a clear potential driver of maternal, as well as child, morbidity, and mortality, only anecdotal evidence of the burden of HFDP in Indonesia exists. Notably, the problem is broadly acknowledged despite the absence of quantitative data on the magnitude of this problem.

This manuscript determines the association of HFDP with fetal and maternal outcomes in 3536 high-risk women referred to two West Sumatera hospitals between 2014 and 2015. As a secondary objective, we explored the influence of the timing of the oral glucose tolerance test (OGTT) screening on these associations.

## Methods

Electronic healthcare records (EHR) were reviewed, and data extracted on pregnant women without pre-existing diabetes who were screened for HFDP between 2014 and 2015 at two West Sumatera governmental tertiary referral-hospitals. First, is Achmad Mochtar Hospital (RSAM) located in Bukittinggi, which is a type B (intermediate level referral) hospital with 340 beds. The second one is M Djamil Hospital (RSMD) located in Padang, which is a type A (highest level referral) hospital. The screening was performed using an Oral Glucose Tolerance Test (OGTT). Based on their fasting blood glucose (FBG) levels, women were categorized into DIP, GDM, or normal glucose levels ( $< 92$  mg/dl), following the World Health Organization (WHO) reference (10, 11), and appendix 1. Notably, screening was geared towards high-risk women, irrespective of their pregnancy age. Women were perceived as high risk when they met one or more of the following risk factors; family history of diabetes, macrosomia, hyperemesis, high fever, seizure, bleeding, and pre-rupture of membranes. In the current study, screening time was grouped in: early (before 24 weeks), regular (24–31 weeks), or late-stage (after 31 weeks) (12).

Data were available concerning age, weight before pregnancy, weight before delivery, gestational weight gain (GWG), parity (nulliparity – multiparity), treatment (non-pharmacological, oral, insulin), gestational age at delivery, delivery mode (vaginal, cesarean), hospital stay (days), pregnancy hypertension (%), maternal death, neonatal death, baby length (cm), baby weight (grams).

To ascertain the burden of HFDP on pregnancy outcomes in this group of high-risk women, we compared pregnancy outcomes of women with HIP to outcomes in women with confirmed normal glucose levels at the screening. Where appropriate, differences were tested using Fisher's exact tests (for binary variables) or the Kruskal-Wallis test (for continuous variables). Next, we obtained effect estimates (mean difference and odds ratios (ORs)) and 95% confidence intervals adjusted for maternal age and parity using general

linear models and generalized linear models. Given the modest sample size, analyses were removed if the optimization algorithm failed to find a unique solution. All analyses were conducted using R (13), using the packages ggplot2 (14), tableone (15), dplyr (16), and magrittr (17).

Ethical approval was obtained from The Committee of the Research Ethics of the Faculty of Medicine, Universitas Andalas (Padang, Indonesia).

## Result

Complete records were available for 3903 women, excluding subjects with pre-existing DM ( $n = 15$ ), as well as low-risk women ( $n = 352$ ), leaving 3536 subjects (see Fig. 1). Screening-time stratified maternal characteristics and pregnancy outcomes are presented in Table 1. In all groups, the mean gestational age at delivery was less than 38 weeks. Women that were screened early went into labor after 37 weeks on average, with 37% of their babies being small for gestational age (Table 1). In addition, there was substantially more hypertension in women in the early screening group (43% versus 4% and 5% in the standard and late groups, respectively), as well as infant mortality (10% compared to 6% and 3% in the standard and late screening groups).

Table 1  
Pregnancy characteristics and outcomes by time of screening

	Timing of glucose screening			p-value
	early (N = 411)	standard (N = 1797)	late (N = 1328)	
Age	32.91 (6.76)	33.11 (6.79)	33.36 (6.75)	0.402
Hospital stay (days)	4.77 (0.54)	4.82 (0.95)	4.83 (0.88)	0.479
Gestational age (weeks)	36.80 (2.77)	36.95 (2.53)	37.95 (1.96)	< 0.001
Maternal weight gain(kg)	10.35 (2.80)	10.47 (2.87)	10.50 (2.89)	0.673
Infant length (cm)	44.46 (3.86)	45.71 (3.32)	47.25 (2.58)	< 0.001
Infant weight (gr)	2592.87 (448.28)	2651.35 (433.80)	2869.53 (335.97)	< 0.001
Parity (%)				0.710
Nulliparity	242 (58.9)	1098 (61.1)	791 (59.6)	
Multiparity	169 (41.1)	698 (38.8)	537 (40.4)	
NA	0 (0.0)	1 (0.1)	0 (0.0)	
Caesarean section %	408 (99.3)	1783 (99.2)	1323 (99.6)	0.352
Gestational age groups (%)				< 0.01
Aterm (> 37 wks)	163 (39.7)	719 (40.0)	884 (66.6)	
Premature (34–37 wks)	31 (7.5)	115 (6.4)	6 (0.5)	
Preterm (< 34 wks)	217 (52.8)	963 (53.6)	438 (33.0)	
Infant weight groups (%)				< 0.01
Normal	258 (62.8)	1193 (66.4)	1207 (90.9)	
LGA	1 (0.2)	5 (0.3)	9 (0.7)	
SGA	152 (37.0)	599 (33.3)	112 (8.4)	
Maternal Hypertension (%)	178 (43.3)	72 (4.0)	61 (4.6)	< 0.001
Maternal death (%)	1 (0.2)	32 (1.8)	18 (1.4)	0.059
Neonatal death (%)	42 (10.2)	103 (5.7)	43 (3.2)	< 0.001
LGA large for gestational age; SGA small for gestational age; NA not available				

Table 2 shows pregnancy characteristics and outcomes per FBG category at screening (normal glucose, GDM, or DIP). Of the screened women, 67 had DIP, and 655 had GDM. Prevalence of GDM in pregnant women aged 20–49 who were screened by determining FBG was 18.5% (Table 2). Over 20% of pregnant women had higher FBG levels than normal.

Table 2  
Pregnancy characteristics and outcomes by FBG category

	FBG at screening			p-value
	Normal FBG (2814)	GDM (n = 655)	DIP (n = 67)	
Age	33.22 (6.78)	33.01 (6.71)	33.21 (6.96)	0.782
Hospital stay (days)	4.76 (0.63)	4.99 (0.16)	5.73 (4.85)	< 0.001
Gestational age (weeks)	37.35 (2.45)	37.20 (1.95)	36.51 (4.08)	0.009
Maternal weight gain (kg)	10.46 (2.83)	10.48 (2.89)	10.73 (4.27)	0.734
Infant length (cm)	46.12 (3.23)	46.28 (2.84)	45.63 (7.09)	0.239
Infant weight (gr)	2716.57 (402.78)	2752.83 (369.62)	2885.76 (1005.17)	0.001
Parity (%)				0.313
Nulliparity	1672 (59.4)	414 (63.2)	45 (67.2)	
Multiparity	1141 (40.5)	241 (36.8)	22 (32.8)	
NA	1 (0.0)	0 (0.0)	0 (0.0)	
Caesarean section %	2807 (99.8)	652 (99.5)	55 (82.1)	< 0.001
Gestational age groups (%)				< 0.001
Aterm (> 37 wks)	1403 (49.9)	321 (49.0)	42 (62.7)	
Premature (34-37wks)	142 (5.0)	2 (0.3)	8 (11.9)	
Preterm (< 34 wks)	1269 (45.1)	332 (50.7)	17 (25.4)	
Infant weight groups (%)				< 0.001
Normal	2107 (74.9)	508 (77.6)	43 (64.2)	
LGA	3 (0.1)	6 (0.9)	6 (9.0)	
SGA	704 (25.0)	141 (21.5)	18 (26.9)	
Maternal Hypertension (%)	176 (6.3)	129 (19.7)	6 (9.0)	< 0.001
Maternal death (%)	38 (1.4)	12 (1.8)	1 (1.5)	0.648
Neonatal death (%)	178 (6.3)	3 (0.5)	7 (10.4)	< 0.001
LGA large for gestational age; SGA small for gestational age.				

Table 3  
Treatment

Treatment	HFDP	
	GDM (N = 655)	DIP (N = 67)
Non pharmacology	499 (76.2)	11 (16.4)
Insulin	156 (23.8)	48 (71.6)
Oral	0 (0.0)	8 (11.9)

Table 4  
Comorbidities

Comorbidities	Screened (N = 3536)		
	Normal (N = 2814)	GDM (N = 655)	DIP (N = 67)
None	2544 (90.4)	513 (78.3)	52 (77.6)
Hypertension	169 (6.0)	128 (19.5)	5 (7.5)
Polyhydramnios	5 (0.2)	0 (0.0)	0 (0.0)
Hypercholesterolemia	2 (0.1)	2 (0.3)	1 (1.5)
Fetal distress	4 (0.1)	0 (0.0)	0 (0.0)
Fetal distress + hypertension	6 (0.2)	1 (0.2)	0 (0.0)
Anaemia	28 (1.0)	5 (0.8)	2 (3.0)
Kidney disease + hypertension	1 (0.0)	0 (0.0)	1 (1.5)
Pre-rupture membrane	50 (1.8)	3 (0.5)	3 (4.5)
Macrosomia	5 (0.2)	3 (0.5)	3 (4.5)
GDM Gestational Diabetes Mellitus, DIP Diabetes In Pregnancy			

Significant differences between these categories were found in birth weight, neonatal death, maternal hypertension, percentage of C-sections, and hospital days. In women with normal FBG and women with GDM, the percentage of C-sections was almost 100% compared to 82.1% in the DIP group.

Neonatal mortality was lowest in GDM and highest in the DIP group. The highest percentage of normal infant weight was found in GDM, but at the same time, GDM had the highest percentage of premature deliveries and maternal hypertension.

These analyses were subsequently repeated, accounting for variation in age and parity (Fig. 2). Overall, compared to high-risk women with normal FBG, women classified as GDM had decreased odds that their baby would be premature (OR 0.06; 95% CI 0.02–0.25) or would die (OR 0.07; 95% CI 0.02–0.21). On the



other hand, they were at increased risk of maternal hypertension (OR 3.66; 95% CI 2.86–4.68) and their baby being large for gestational age (LGA) (OR 8.17; 95% CI 2.03–32.80). With the exception of decreasing the risk of preterm babies (OR 0.45 95%; CI 0.25, 0.79), we did not observe any clear difference in outcomes between DIP and normal FBG within these high-risk pregnancies. The associations with Cesarean section, prematurity, maternal hypertension, and LGA differed between screening time (interaction p-value < 0.01)

The seemingly protective effect of GDM on neonatal death is rather surprising, even more so because it was mostly observed in the regular screening group, and not as much in those that were screened early (no data available for late screening). A possible explanation could be that women who are screened and detected as being GDM are treated earlier and monitored more closely. Therefore when complications arise, the intervention can be more timely and effective, preventing escalation and serious events. In addition, apart from the normal FBG classification, the women included in this study are still considered high-risk and therefore, other factors could have played a role in neonatal mortality.

Figure 3 describes the maternal age- and parity-adjusted results for continuous outcomes, finding that hospital stay was prolonged in DIP (MD 1.29, CI 1.13;1.49) and GDM (MD 0.23, CI 0.16;0.31) women (compared to the normal FBG group). Similarly, infant weight was increased for both groups, and gestational age was decreased in the DIP group (MD 0.68, CI 0.55;0.83). We did not observe a significant difference between the groups in maternal weight change, or infant height (with the exception for a decrease for late screened DIP women). All associations differed by screening time (interaction p-value < 0.01), with the exception of maternal height.

### Treatment of hyperglycemia

Out of the 67 DIP women, 48 (71.6%) used insulin, 8(11.9%) used oral drugs, and the remaining 11 (16.4%) did not use any pharmacological intervention. The primary aim of treating hyperglycemia in pregnancy is to reduce mortality and morbidity among women and their children. Advice to modify diet/lifestyle is often used as first-line treatment without pharmacological therapy. For those women requiring pharmacological treatment, insulin is traditionally being used (18).

In this study, the management of hyperglycemia appeared to be based on the glucose level. Of all 722 patients who had elevated glucose levels, pregnant women with GDM predominantly did not receive pharmacological treatment, while in women with DIP the majority used oral anti-diabetic drugs to reduce their blood glucose level (Table. 3).

### Comorbidities

The large majority (90%) of normal FBG women did no experience any comorbidities, 169 (6%) experienced hypertension, 28 (1%) anemia, 50 (1.8%) suffered from a pre-ruptured membrane, with other comorbidities occurring at frequencies less than 1%. For GDM women, 78% remained comorbidity free during their pregnancy, 128 (20%) suffered from hypertension, with the remaining events occurring in less

than 1% of the pregnancies. Also, most (78%) of the DIP women did not experience any comorbidities, whereas 5 (7.5%) were diagnosed with hypertension, one subject had kidney disease-related hypertension, 3 (4.5%) had pre-ruptured membranes, 2 (3%) had children with macrosomia, 2 (3%) experienced anemia, and a single woman suffered from hypercholesterolemia.

## Discussion

Although the present study showed differences between pregnant women with GDP, DIP, and normal FBG, and also associations were found between the timing of screening and various pregnancy characteristics and outcomes, we could not quantify or demonstrate an unequivocal burden of HFDP, nor any advantage of early screening. There are several possible explanations for this finding. The first is that this was a retrospective study, and so the decision to screen early or late was made based on clinical judgment, and not by randomization, or standardized guideline, as OGTT is not performed routinely in antenatal care in Indonesia. It is therefore quite likely that the group screened early consisted of women having multiple risk factors or already showing symptoms, which made their treating physician refer them for screening at this stage. A potential benefit of early screening would have to be demonstrated in a larger and unselected population. Also, the group screened early is very small compared to those screened later, which probably hampered the statistical power. As for the counterintuitive 'protective' effect of GDM on neonatal death, as said in the previous section, this could be an artefact of the GDM cases identified being monitored more closely and treated with insulin or non-pharmacological therapy. In addition, the women in this study who had normal FBG were not low-risk pregnancies, as they were already referred to a tertiary hospital for a check-up. This is best demonstrated by the fact that also in the normal FBG group, 50% of babies were born preterm or prematurely, and practically 100% was delivered by C-section. This is not representative of the general population of the cities where hospital A and B are situated (see Appendix 2), where 25% (max) of babies are delivered with a C-section. From Appendix 2, it is also apparent that there are substantial differences in neonatal and infant death between the two cities, and these differences are echoed in our study population (see appendix 5). It would have been useful to perform the study for the two hospitals separately, but then patient numbers in the DIP and early screening groups would be too low for meaningful analysis. What the data did show is that pregnant women with GDM were three times more likely to also have hypertension, and length of stay in hospital was increased for GMD and DIP compared to the women with normal FBG. Also, a higher rate of neonatal deaths was observed in the DIP group. The high incidence of hypertension as a comorbidity in HFDP in this study may be indicative of a relationship between hypertension and hyperglycemia in pregnancy. It is indeed known that an increase in blood sugar can affect vascular activity (19). However, the contribution of changes in insulin secretion and resistance to the pathophysiologic features of hypertension in pregnancy is not clear (20). So, even though we can assume that there is a relationship between HFDP and hypertension in pregnancy, we cannot say how this has affected or confounded our findings. Several cohort studies of substitute markers for insulin resistance in early pregnancy suggest that insulin resistance predisposes to new-onset hypertension in pregnancy (21).

In our study population, more than 75% of patients identified as having GDM received non-pharmacological therapy. This is reflective of current clinical standards, where clinicians increasingly tend to start with non-pharmacological therapy through lifestyle modification, sometimes in combination with insulin (7), since GDM involves only slightly elevated FBG levels. Notably, oral antidiabetics such as glyburide are equally efficient as insulin for the treatment of HIP (22, 23), especially if dietary interventions failed (23). In this study, more pregnant women experienced late screening for hyperglycemia, and the level of blood glucose was higher, and it requests insulin immediately. This probably explains the relatively low use of oral antidiabetics in our study sample (0% in GDM, 12% in DIP).

There were considerable differences between hospital A and B with respect to the proportion of GDM and the number of deaths. Hospital A (Bukittinggi) only detected 2% GDM cases compared to 65% in hospital B (Padang), in regular screening (and similar for late screening). Also, in Bukittinggi, there were more cases of neonatal death (for regular screening: 7% Bukittinggi vs. 2% Padang). These differences can also be observed in the populations of the respective regions as collected by the statistical bureau and basic health research west Sumatera (2, 24, 25) (see appendix 6), in the sense that neonatal mortality is substantially higher in Bukittinggi (76 per 1000 live births compared to 18 Padang). This could be partly explained as a regional difference but may also be triggered by the fact that Padang Hospital is tertiary and, therefore, top-referral hospital. So, cases that would go undetected in Bukittinggi may be detected in Padang, explaining mostly the difference in GDM cases.

Ideally, all pregnant women who visit advanced health care facilities are entitled to a blood glucose examination because of a high-risk pregnancy. However, this also requires that pregnant women are informed about and know how to benefit from maternal healthcare services. In Indonesia, this is often not the case. A study on health knowledge of pregnant women in Banten, Indonesia, presented that pregnant women in Indonesia do not have adequate knowledge about the conditions that need to be handled by healthcare professionals and danger signs during pregnancy (26). One effort to improve the knowledge of pregnant women is the Kesehatan Ibu dan Anak/ Maternal-Child Health (KIA/MCH) book (27, 28). This book is provided free of charge to every pregnant woman in Indonesia. It contains guidelines and information on pregnancy development, childbirth, and child development until the age of two years. However, according to basic health research 2013, KIA book ownership is still quite rare at 31.7% (29). Improving the dissemination of the KIA book would greatly increase the awareness and knowledge of pregnant women about their health condition.

#### Strengths and limitations:

This was the first Indonesian study after the changes in WHO criteria on hyperglycemia in pregnancy. Data collection was based on the systematic extraction of medical health records from two referral hospitals, which were located in the densely populated mainland and coastal area of West Sumatera. This study is addressing global priority areas for women and their babies in a developing country with reasonably good societal conditions.

A further limitation of this study is that we have focused on women who were referred for screening, and regrettable, we do not have information on the referral reason. As such, the inference should be limited to high-risk women, and it is unlikely that our results generalize to all women irrespective of the perceived risk of HFDP. Additional limitations include the lack of a reference value for FBG in women of childbearing age in the general Indonesian population. Therefore, we cannot be completely sure that applying the WHO cutoff values accurately identified those in need of treatment. It is difficult to say whether this caused bias and, if so, in what direction. Second, for pregnant women in the region, there was no information available on maternal age and parity even though we have delivery age in ranges of ten years.

#### Further research

These findings are of paramount importance for the attention of researchers, policymakers, and decision-making organizations to facilitate the development of interventions to health care facilities for mothers and babies. In our study sample of women referred for screening, normal FBG levels did not always mean normal conditions, so even when women are not classified as GDM or DIP, we still have to see them as high-risk. Further investigation to identify the magnitude and interaction among maternal status, education, access to health facilities, neonatal conditions, health, nutritional status, and wellbeing is required. Regulation and efficient organization of blood glucose screening is needed, particularly in developing countries.

## Conclusion

This study shows the high mortality rate of mothers suffering from hyperglycemia, and the tendency of hyperglycemic women to give birth to preterm children, both potentially indicative of poor awareness of the availability of maternal services, including glucose screening while pregnant. The information provided in this study could be used as a basis to develop effective approaches to complications associated with hyperglycemia in pregnancy in both mothers and their offspring.

## Declarations

#### Ethical Issues

The research protocol for this study was approved by the Committee of the Research Ethics of the Faculty of Medicine, Andalas University No: 146/KEP/FK/2015

#### Conflict of Interest

Prof Maarten J Postma received grants and honoraria from various pharmaceutical industries and consultancy companies, all unrelated to this study, but potentially concerning companies interested in the subject matter of this study. Also, he holds stocks in the Dutch companies Ingress Health (Rotterdam) and Pharmacoeconomics Advice Groningen (PAG Ltd). All other authors declare that they have no conflict

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## Author Contributions

Najmiatul Fitria performed the data collection and was responsible for drafting the first version of the manuscript. Bobby Indra Utama was responsible for reviewing the manuscript and patient's report. Antoinette van Asselt supervised the project and critically revised the paper. Ivan Surya Pradipta and Armand F Schmidt provided advice on and performed statistical analyses reported in this paper. Maarten J. Postma supervised the project and reviewed various versions of the manuscript.

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## Figures

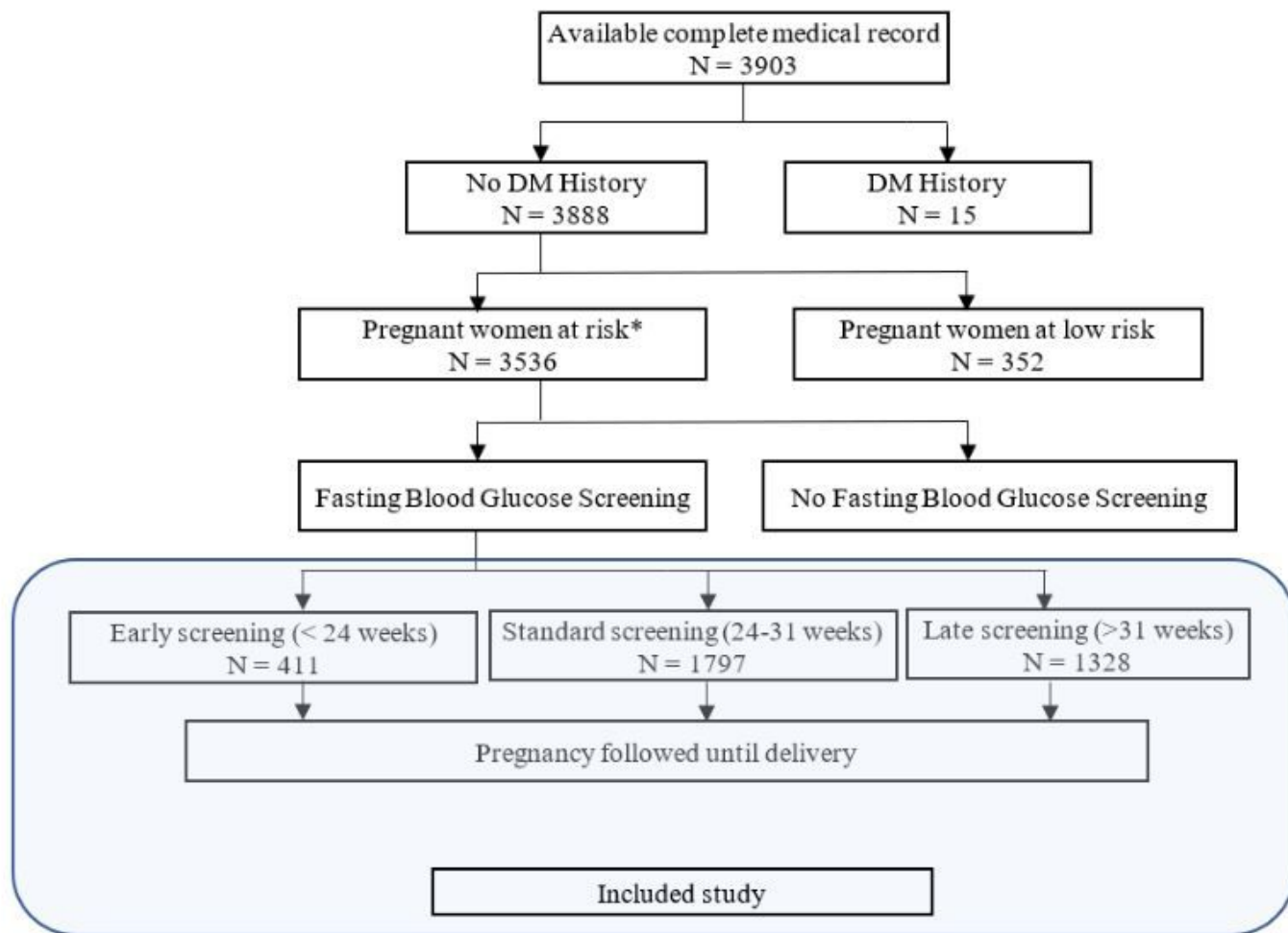


Figure 1



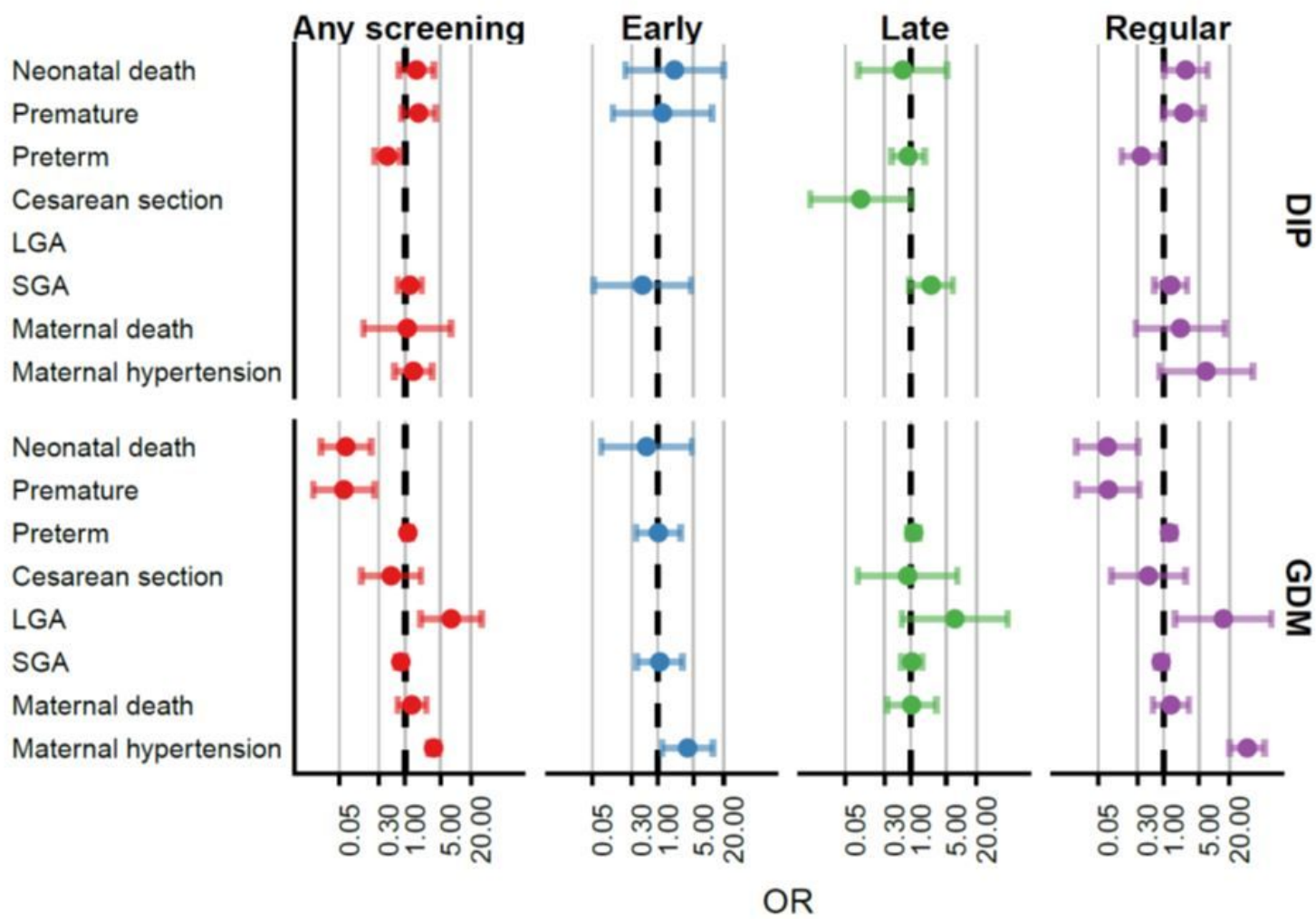


Figure 2

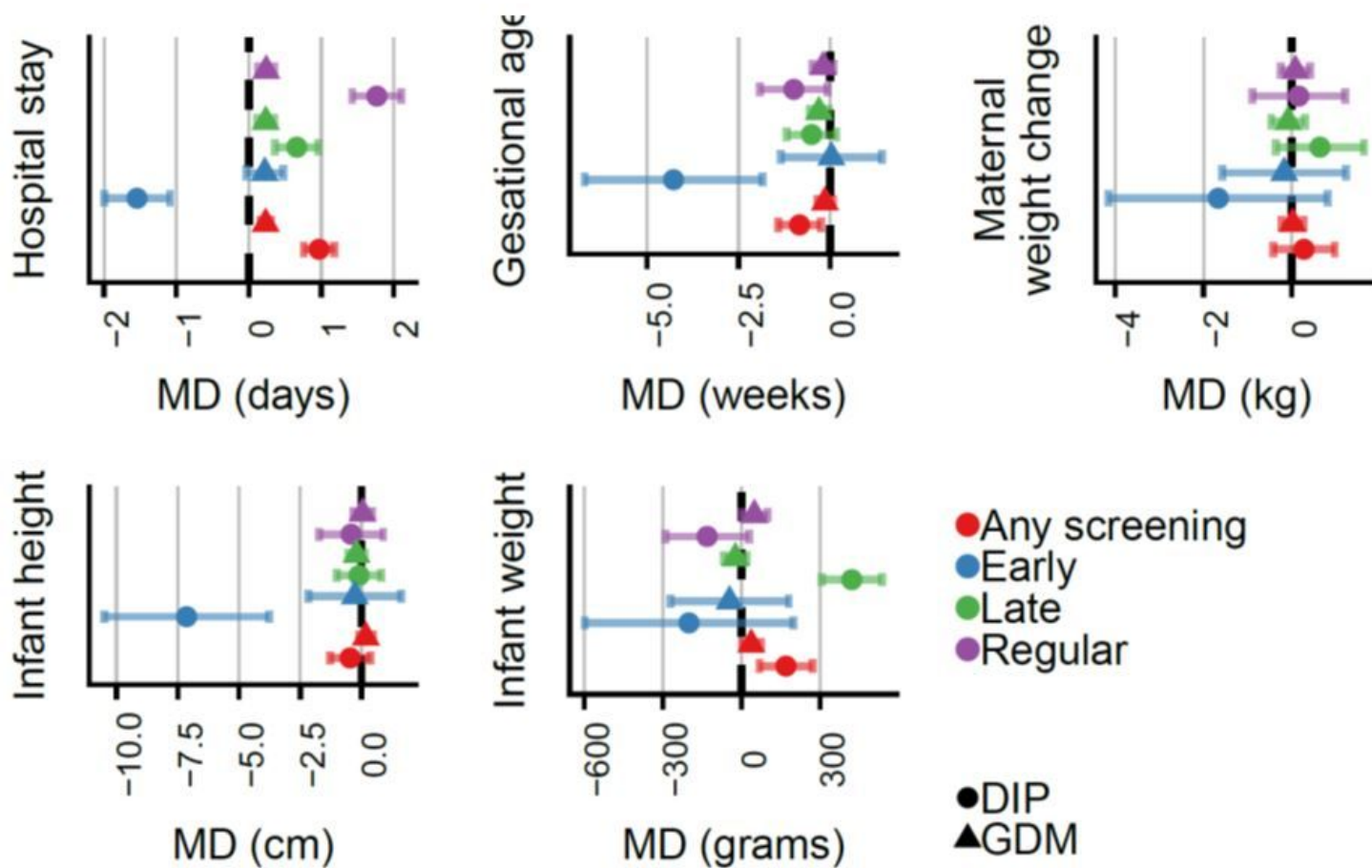


Figure 3

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