Causation between Gestational Diabetes Mellitus(GDM) and Pregnancy Induced Hypertension(PIH): A Statistic Case Study in Harbin, China

Dan DIAO
Red cross central hospital
DIAO Fang
Red cross central hospital
XIAO Bin
Red cross central hospital
Ning LIU
Red cross central hospital
Fengjuan LI
Red cross central hospital
YANG Xu (civileng@hit.edu.cn)
Harbin Institute of Technology

Research Article

Keywords: gestational diabetes mellitus(GDM), pregnancy induced hypertension (PIH),

Posted Date: July 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-761408/v1

Causation between Gestational Diabetes mellitus(GDM) and Pregnancy induced Hypertension(PIH): A Statistic Case Study in Harbin, China

DIAO Dan[2], DIAO Fang[2], XIAO Bin[2], LIU Ning[2], LI Fengjuan[2], and YANG Xu[1,*]

[1]School of Civil Engineering, Harbin Institute of Technology, Harbin 150090, China
[2]Red cross central hospital, Harbin 150001, China
[*]corresponding author: yangxu_civileng@hit.edu.cn

ABSTRACT

Both gestational diabetes mellitus(GDM) and pregnancy induced hypertension (PIH) would influence the gestation significantly. However, the causation between these two symptoms remains speculative. 16,404 pregnant women were identified in Harbin, China in this study. We investigated the evaluate the causal effect of GMD on PIH based on the statistic inference theory. The statistical results indicated that GDM might cause PIH. Also, this case study demonstrated that the decrease temperature might also cause hypertension during pregnancy, and the prevalence rate of GDM increased with age. However, the prevalence of diabetes did not show a remarkable difference in varied areas and ages. This study could provide some essential information that will help to investigate the mechanism for GDM and PIH.

Introduction

Both gestational diabetes mellitus(GDM) and pregnancy induced hypertension (PIH) would influence the gestation significantly. However, the causation between these two symptoms remains speculative.

It has been demonstrated that the individuals with diabetes mellitus (including Type 1 and 2 diabetes mellitus) would be more likely diagnosed with hypertension than nondiabetics[1] The aortic arteriosclerosis of diabetics would accelerate remarkably[2], and their arterial compliance and elasticity decreased, which would directly cause systolic pressure increase[3]. Meanwhile, the damage of peripheral nerve caused by diabetes might induce microvascular dysfunction, which would also lead to an increase in systolic pressure[4–6].

All these discussions mentioned above were based on the influence of insulin resistance[7,8]. In the early stage of insulin resistance, hyperinsulinemia would cause reabsorption of sodium by kidney tubules, which cause sympathetic activity frequently[9]. Then, the increased vasoconstriction led to the smooth muscle of small artery proliferation and anastomotic stenosis. The intracellular calcium concentration increased, the sensitivity of the vasopressor increased. Finally, hypertension would be observed[10].

Otherwise, the mechanism of GDM is different from the other types of diabetes. GDM is a conditiondefined as any degree of glucose intolerance that starts or is first recognized during pregnancy, and it is characterized by recent hyperglycemia as a consequence of an association between insulin resistance and adequate insulin secretion[11,12]. The influence of GDM on hypertension or PIH has remained unclear.

In this study, we attempt to investigate the evaluate the causal effect of GMD on PIH based on the statistic inference theory. 16,404 pregnant women were included in this study. By implementing the method of causal effect for epidemiological research[13], the statistical results demonstrated that GDM might cause PIH. This study could provide some essential information that will help to investigate the mechanism for GDM and PIH.

Methods

Average causal effect analysis

Denote a dichotomous index A of exposure physical examination (positive or negative), and the other dichotomous outcome variable Y (positive or negative). In this study, the variables A (exposure) and Y(outcome) would be both considered as random variables. Let $Y^{A=1}$ be the outcome variable that would be observed with positive A, and $Y^{A=0}$ the outcome variable that would have been observed with negative A. $Y^{A=1}$ and $Y^{A=0}$ were also considered as random variables. In order to gain an average causal effect in a population of individuals, three sorts of information would be studied and compared: an outcome of interest the actions $A=1$ and $A=0$ to be compared, and a population of individuals whose outcomes $Y^{A=0}$ and $Y^{A=1}$.

A formal definition of the average causal effect in the population could be given[13] : an average causal effect of index A on outcome Y is present if $Pr[Y^{A=1}=1] \neq Pr[Y^{A=0}=1]$ in the population of interest. Comparatively, in the case that $Pr[Y^{A=1}=1] = Pr[Y^{A=0}=1]$, a null hypothesis of no average causal effect could be demonstrated true. When there is no causal effect for any individual in the population, i.e., $Y^{A=1} = Y^{A=0}$ for all individuals, it could be noted that a sharp causal null hypothesis is true.

Furthermore, to compute how many times the positive A, relative to negative A, increases the positive Y, the causal risk ratio(CRR) could be used, which is given by

$$CRR = \frac{Pr[Y^{A=1}=1]}{Pr[Y^{A=0}=1]} \tag{1}$$

The CRR equaling 1 could represent a causal null.

A causal odds ratio (COR) is defined by the distribution of the potential outcomes under each treatment, which is given by[14,15]

$$COR = \frac{Pr[Y^{A=1}=1]/Pr[Y^{A=1}=0]}{Pr[Y^{A=0}=1]/Pr[Y^{A=0}=0]} \tag{2}$$

In general, a larger COR indicates more significant causation.

Case study on pregnant women

Study sample

To identify cases, 16,404 pregnant women were included in an outpatient setting (hospital outpatient departments) in Harbin, China, between December 22, 2018 and December 28, 2020. We included all outpatients with a documented diagnosis of pregnancy during about two years to improve diagnostic validity. The date of the first-time pregnancy diagnosis during the study period was assigned as their index date. These pregnant women were aged between 14 and 50. The PIH samples discussed in this study did not include those diagnosed with eclampsia.

Also, the ages of these pregnant women and their first diagnosis date were considered which might influence the causation between GDM and PIH. These two factors would be studied and discussed as well.

Causation analysis

This case study was devised to analyze the causal effect of GDM on PIH. In this case, denote exposure variable, i.e., the GDM as A_A ($A_A = 1$ indicated the GDM was diagnosed). Denote outcome variable, i.e., the PIH as Y_A ($Y_A = 1$ indicated the PIH was diagnosed). Therefore, $Y_A^{A=1} = 1$ represented the patient had a diagnosed PIH with the GDM observed.

Relatively, aiming to analyze the causal effect of PIH on GDM, denote exposure variable, i.e., the PIH as A_B ($A_B = 1$ indicated the PIH was diagnosed). Denote outcome variable, i.e., the GDM as Y_B ($Y_B = 1$ indicated the GDM was diagnosed). Therefore, $Y_B^{A=1} = 1$ represented the patient had a diagnosed GDM with the PIH observed.

Statement

We confirmed that all methods were carried out in accordance with relevant guidelines and regulations. We confirmed that all experimental protocols were approved by the institutional and licensing committee in Red cross central hospital, Harbin, China. We confirmed that informed consent was obtained from all subjects and the legal guardians of the subjects who below 16 years of age.

Results

Of these 16,404 pregnant women, 2,540(15.48%) and 218(1.33%) were diagnosed with the GDM and PIH, respectively. Meanwhile, 114(0.69%) had both the GDM and PIH. More details could be found in Tab. 1 and 2. Fig. 1 and 2 represented the distribution of GDM and PIH by age, respectively. Fig. 3 represented the distribution of GDM and PIH by month. It should be noted there were very few patients aged less than 20 and more than 43. Therefore, estimates of the prevalence rate were imprecise, these data were neglected in the following studies and discussions.

According to Fig. 1, 2, and 3, it could be observed that the GDM affects 10-25% of pregnancies, and PIH affects 1-5%. Moreover, the prevalence rate of GDM increased with age. By contrast, it is not obvious how the patient's age influenced the PIH. In addition, the GDM and PIH were observed relatively less in June and July.

Furthermore, the CRR of GDM on PIH is 52.29%. The CRR of PIH on GDM is 4.49%. The causal odds ratio between GDM and PIH is 2.76. With respect to the difference in the number of pregnancies with varied ages, only the distribution by month was discussed. Fig. 4 represented the distribution of patients who had both GDM and PIH. The COR was also plotted in Fig. 4. The CRR curves were plotted in Fig. 5. It could be observed that the probability that the GDM affects PIH is between 22.73% and 83.33% and that the PIH affects GDM is 2.48-7.07%. The range of COR from 1.39 to 5.18 had been explored based on this study.

Discussion

It should be noted that both diabetes combined with pregnancy and GDM would cause blood glucose to increase in pregnancy[16]. The medical record provided by outpatient departments had discriminated against these two conditions. In this study, it could be considered that the patients diagnosed with GDM had normal blood glucose before the pregnancy. By the same logic, the patients diagnosed with PIH could be treated that had normal blood pressure before the pregnancy. Therefore, it could be said that the pregnancy caused the GDM and PIH to some degree. The increased blood glucose or diabetes caused by pregnancy could be considered as exposure, and the PIH as an outcome, or vice versa. Based on these assumptions, the following discussions could be drawn:

Firstly, the relationship between GDM and PIH would be discussed. The CRR of PIH on GDM indicated that the percentage of the patients who had both PIH and GDM among the patients diagnosed only GDM. A very small CRR of PIH on GDM could be observed from Fig. 5, which indicated that the PIH was not likely to cause GDM.

Relatively, the CRR of GDM on PIH, i.e., the percentage of the patients who had both PIH and GDM among the patients diagnosed only PIH, could be observed larger. It could be demonstrated that GDM might cause PIH. The causal odds ratio between GDM and PIH represented in Fig. 4 also provided evidence of this view.

Secondly, the influence of region on the symptom would be discussed. The studies during 2013–2018 showed that the overall prevalence of GDM was 10-20% according to the IADPSG criteria[17–19]. Several types of research represented that the overall prevalence of PIH was less than 1%[20,21]. In general, the prevalence of hypertension was higher in cold areas than others[22]. The statistical results induced in this case study identified in the northeast of China demonstrated that the decrease temperature might also cause hypertension during pregnancy. However, the prevalence of diabetes did not show a remarkable difference in varied areas.

Finally, the influence of age and month on GDM and PIH would be discussed. The age might be a notable factor on GDM[23]. Fig. 1 and the statistical results represented in Tab. 1 and 2 demonstrated that older maternal age was significantly associated with risk of GDM. Besides, the lower prevalence of PIH drawn in Fig. 3 also demonstrated the influence of temperature on hypertension during pregnancy.

References

1. Robbins, J. M., Webb, D. A. & Sciamanna, C. N. Cardiovascular comorbidities among public health clinic patients with diabetes: the urban diabetics study. *Bmc Public Heal.* **5**, 1–9 (2005).
2. Osorio-Yáñez, C. *et al.* Per-and polyfluoroalkyl substances and calcifications of the coronary and aortic arteries in adults with prediabetes: Results from the diabetes prevention program outcomes study. *Environ. Int.* **151**, 106446 (2021).
3. Song, X.-T., Fan, L., Yan, Z.-N. & Rui, Y.-F. Echocardiographic evaluation of the effect of poor blood glucose control on left ventricular function and ascending aorta elasticity. *J. Diabetes its Complicat.* **35**, 107943 (2021).
4. Ergun-Longmire, B. *et al.* Diabetes education in pediatrics: how to survive diabetes. *Disease-a-Month* 101153 (2021).
5. Verdecchia, P. & Angeli, F. Natural history of hypertension subtypes (2005).
6. Saladini, F. *et al.* Natural history of hypertension subtypes in young and middle-age adults. *Am. journal hypertension* **22**, 531–537 (2009).
7. Carresi, C. *et al.* The effect of natural antioxidants in the development of metabolic syndrome: Focus on bergamot polyphenolic fraction. *Nutrients* **12**, 1504 (2020).
8. Reaven, G. M. Relationships among insulin resistance, type 2 diabetes, essential hypertension, and cardiovascular disease: similarities and differences. *The J. Clin. Hypertens.* **13**, 238–243 (2011).
9. Deng, J. *et al.* An increase in alveolar fluid clearance induced by hyperinsulinemia in obese rats with lps-induced acute lung injury. *Respir. Physiol. & Neurobiol.* **279**, 103470 (2020).
10. Tsang, C. C. S. *et al.* Racial/ethnic disparities in measure calculations for part d star ratings among medicare beneficiaries with diabetes, hypertension, and/or hyperlipidemia. *Res. Soc. Adm. Pharm.* **17**, 1469–1477 (2021).
11. Buchanan, T. A., Xiang, A., Kjos, S. L. & Watanabe, R. What is gestational diabetes? *Diabetes care* **30**, S105–S111 (2007).
12. Andersson-Hall, U., Joelsson, L., Svedin, P., Mallard, C. & Holmäng, A. Growth-differentiation-factor 15 levels in obese and healthy pregnancies: Relation to insulin resistance and insulin secretory function. *Clin. Endocrinol.* (2021).

13. Hernán, M. A. A definition of causal effect for epidemiological research. *J. Epidemiol. & Community Heal.* **58**, 265–271 (2004).

14. Holland, P. W. Statistics and causal inference. *J. Am. statistical Assoc.* **81**, 945–960 (1986).

15. Loomba, S., de Figueiredo, A., Piatek, S. J., de Graaf, K. & Larson, H. J. Measuring the impact of covid-19 vaccine misinformation on vaccination intent in the uk and usa. *Nat. human behaviour* **5**, 337–348 (2021).

16. Chen, L.-W. *et al.* Combined analysis of gestational diabetes and maternal weight status from pre-pregnancy through post-delivery in future development of type 2 diabetes. *Sci. reports* **11**, 1–11 (2021).

17. Juan, J., Yang, H.-X., Su, R.-N. & Kapur, A. Diagnosis of gestational diabetes mellitus in china: perspective, progress and prospects. *Matern. Medicine* **1**, 31–37 (2019).

18. Wang, C. *et al.* Prevalence of gestational diabetes mellitus and its determinants among pregnant women in beijing. *The J. Matern. & Neonatal Medicine* 1–7 (2020).

19. Li, G. *et al.* Incidence and risk factors of gestational diabetes mellitus: a prospective cohort study in qingdao, china. *Front. Endocrinol.* **11** (2020).

20. Yuan, X., Wang, J., Gao, Y., Wang, H. & Yu, B. Impact of maternal thyroid hormone in late pregnancy on adverse birth outcomes: A retrospective cohort study in china. *Endocr. J.* **68**, 317–328 (2021).

21. Li, L. *et al.* Cooking fuel and the risk of pregnancy-induced hypertension in lanzhou, china: A birth cohort study. *Food Sci. Technol.* (2021).

22. Yu, B. *et al.* The association of outdoor temperature with blood pressure, and its influence on future cardio-cerebrovascular disease risk in cold areas. *J. hypertension* **38**, 1080–1089 (2020).

23. Yong, H. Y. *et al.* Independent and combined effects of age, body mass index and gestational weight gain on the risk of gestational diabetes mellitus. *Sci. reports* **10**, 1–8 (2020).

Author contributions statement

Conceptualization, YANG Xu; Data collection: XIAO Bin, LIU Ning, LI Fengjuan; Data analysis and interpretation: DIAO Dan, DIAO Fang.

Conflicts of Interest

The author declares that there are no conflicts of interest.

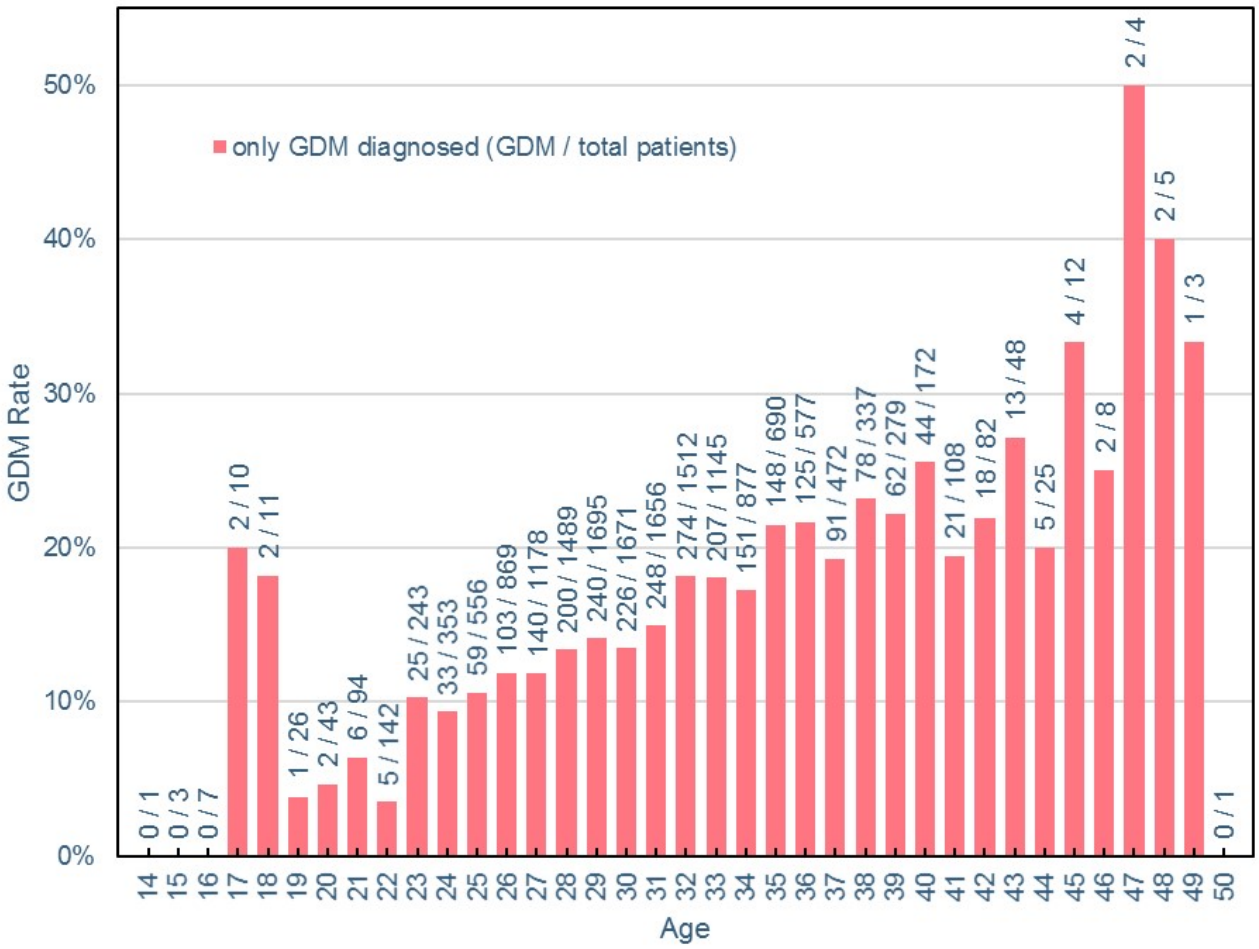

Figure 1. GDM rate distribution histogram with age

Table 1. Statistical results distributed by month

month	only GDM	only PIH	both GDM and PIH	neither GDM nor PIH	amount
Jan	245	17	9	1029	1311
Feb	248	19	9	1193	1480
Mar	247	19	15	1264	1554
Apr	271	24	11	1120	1436
May	202	18	8	1141	1381
Jun	202	12	5	1232	1458
Jul	196	12	10	1219	1447
Aug	198	17	14	1120	1360
Sept	194	14	9	1081	1307
Oct	170	22	5	1039	1245
Nov	183	18	9	958	1181
Dec	184	26	10	1013	1244
total	2540	218	114	13409	16389

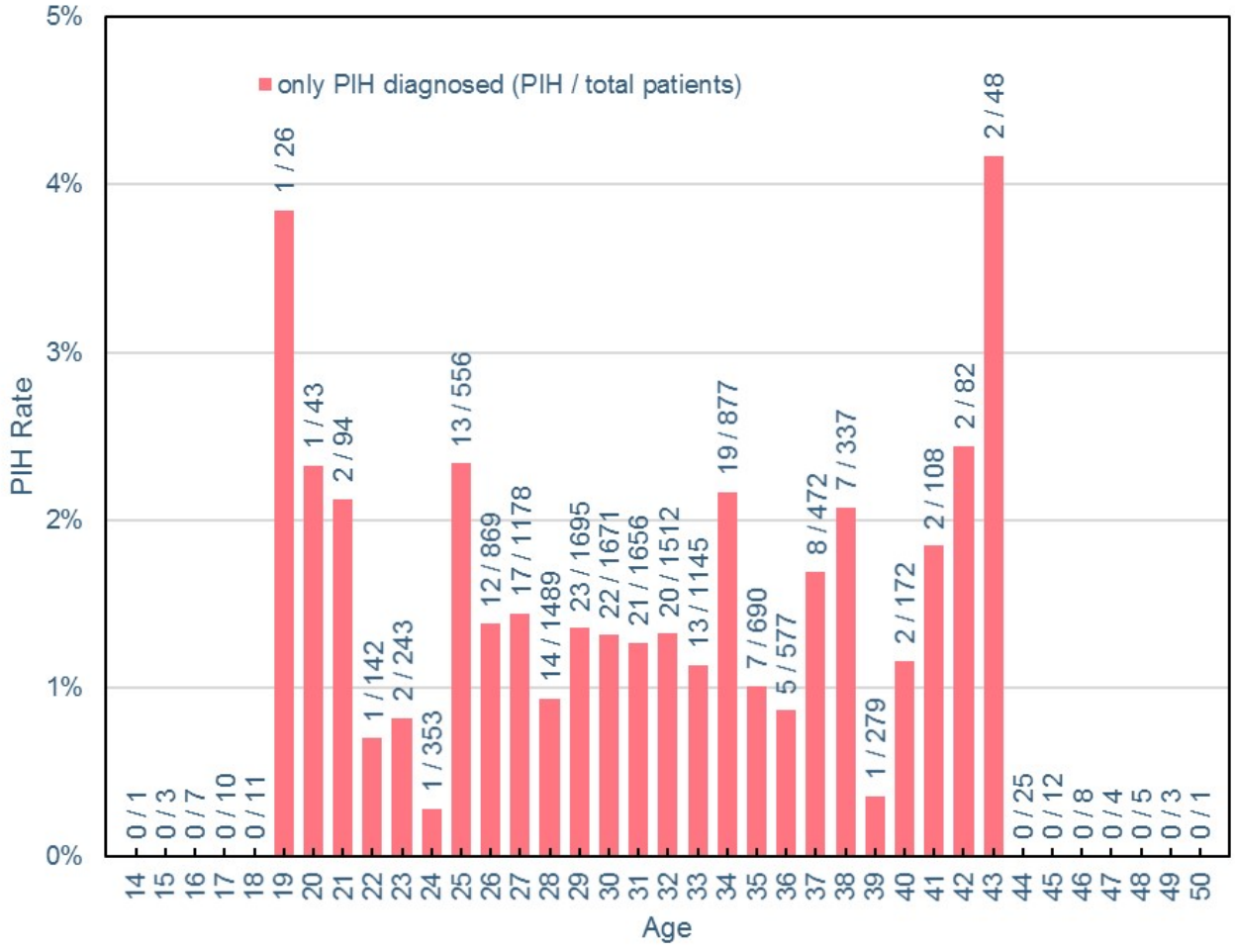

Figure 2. PIH rate distribution histogram with age

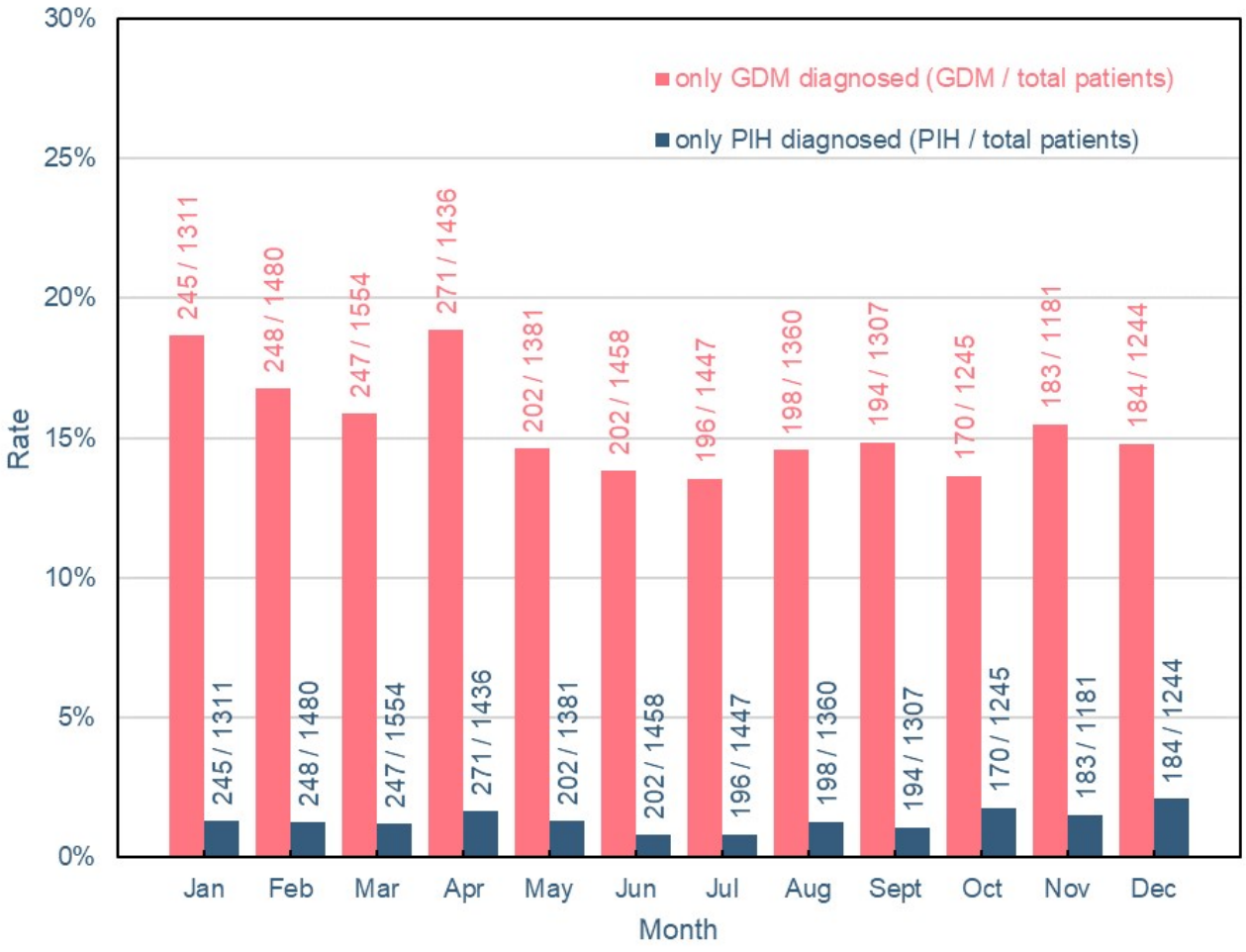

Figure 3. GDM and PIH rate distribution histogram with month

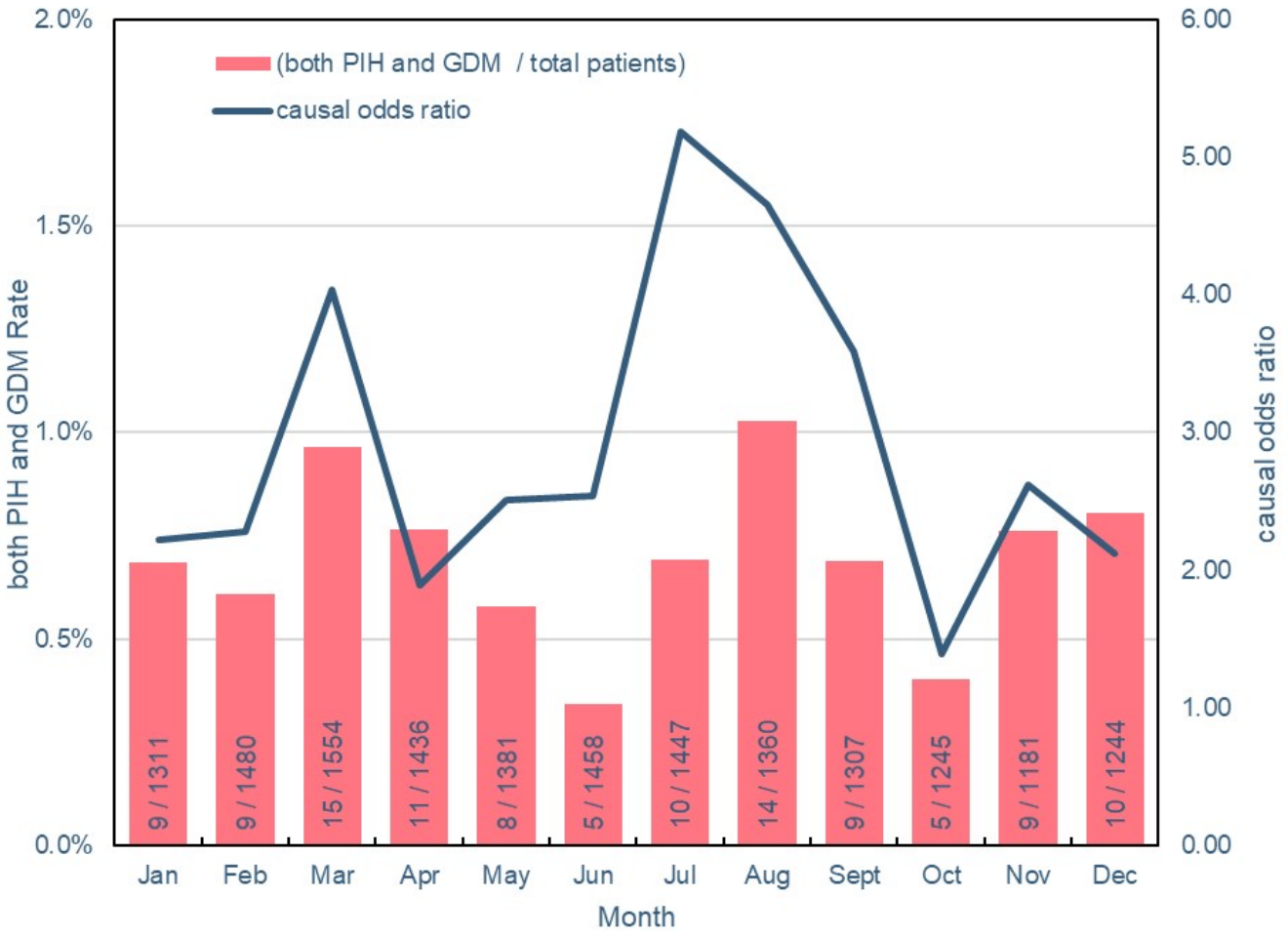

Figure 4. Both GDM and PIH rate distribution histogram with month and effect of month on causal odds ratio

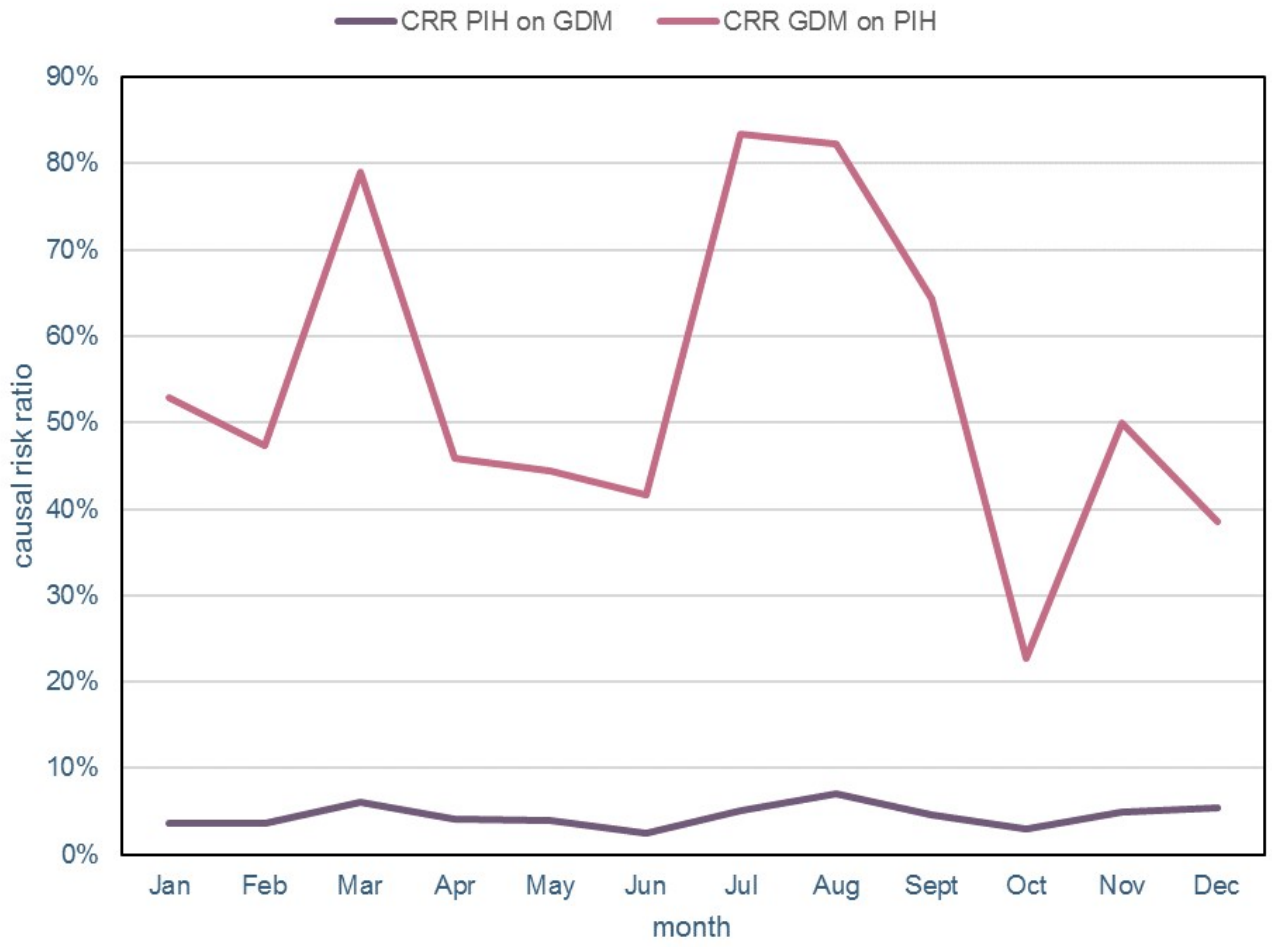

Figure 5. Effect of month on Causal risk ratio

Table 2. Statistical results distributed by age

age	only GDM	only PIH	both GDM and PIH	neither GDM nor PIH	amount
14	0	0	0	1	1
15	0	0	0	3	3
16	0	0	0	7	7
17	2	0	0	8	10
18	2	0	0	9	11
19	1	1	0	22	11
20	2	1	0	40	43
21	6	2	1	85	94
22	5	1	0	136	142
23	25	2	0	215	243
24	33	1	1	317	353
25	59	13	2	480	556
26	103	12	7	745	869
27	140	17	5	1015	1178
28	200	14	6	1266	1489
29	240	23	12	1409	1695
30	226	22	6	1407	1671
31	248	21	8	1365	1656
32	274	20	12	1198	1512
33	207	13	10	902	1145
34	151	19	6	690	877
35	148	7	7	520	690
36	125	5	9	434	577
37	91	8	5	360	472
38	78	7	3	245	337
39	62	1	4	204	279
40	44	2	3	114	172
41	21	2	2	82	108
42	18	2	2	60	82
43	13	2	1	31	48
44	5	0	2	17	25
45	4	0	0	8	12
46	2	0	0	6	8
47	2	0	0	2	4
48	2	0	0	3	5
49	1	0	0	2	3
50	0	0	0	1	1
total	2540	218	114	13409	16389