scientific reports



OPEN Maternal mental health and gestational weight gain in a Brazilian Cohort

Dayana Rodrigues Farias²², Thais Rangel Bousquet Carrilho, Nathalia C. Freitas-Costa, Mônica Araújo Batalha, Mylena Gonzalez & Gilberto Kac

Depression and anxiety are common during pregnancy, but little is known about the influence of these disorders on gestational weight gain (GWG). Data from a prospective cohort of pregnant women followed in a public healthcare center in Rio de Janeiro, Brazil, were used to evaluate the association of depression, anxiety, and suicide risk with GWG. GWG was evaluated at 5-13, 20-26, 30–36, and 37–42 weeks, and GWG adequacy was determined. Statistical analyses included linear mixed-effect models and Poisson regression. We evaluated 206 women, in which 15% (n = 31) presented major depressive disorder, 19.4% (n = 34) suicide risk and 10% (n = 21) generalized anxiety disorder at baseline. Women with depression at the first trimester, persistent depressive symptoms, and anxiety symptoms at the second trimester presented significantly lower rates of GWG per week compared to those without depression or anxiety, respectively. Persistent depressive symptoms represented a 2.40 (95% CI 1.20; 4.81; p = 0.013) increase in the risk of insufficient GWG. There was no significant association between generalized anxiety disorder or suicide risk with GWG. The presence of depression, depressive symptoms, and anxiety during pregnancy were associated with lower GWG rates. Persistent depressive symptoms during pregnancy were directly associated with insufficient GWG.

Mental health disorders such as depression and anxiety are common during pregnancy^{1,2}. The prevalence of depression and anxiety vary widely depending on the pregnancy period and country and has been reported to be between 7 and 22% worldwide³⁻⁷. In low- and middle-income countries, this prevalence can be higher^{8,9}. Studies during pregnancy conducted in Brazil revealed prevalence around 14% to 20% for depression¹⁰⁻¹² and 19% to 40% for anxiety 1^{3-15} . The prevalence of suicide intention or suicide ideation varies from 5 to $14\%^{16,17}$ worldwide, and Brazilian studies reported values between 1818 and 23%19 during pregnancy.

These mental health disorders are a significant public health concern and may have short- and long-term impacts on the mother's and offspring's life²⁰⁻²³. A systematic review revealed that depressive symptoms during pregnancy were associated with preterm birth and low birth weight²⁴. Maternal mental health may modify appetite²⁵, dietary quality^{26,27}, and physical activity^{28,29}, which can also contribute to weight changes, and more specifically, lead to inadequate gestational weight gain (GWG)^{6,30-32}.

GWG is an important and potentially modifiable risk factor for several maternal and child health outcomes^{33,34}. Maternal weight gain trajectory was associated with increased risk of small-for-gestational-age (SGA) birth³⁵ and offspring obesity³⁶. GWG above or below the American Institute of Medicine (IOM) guidelines³⁴ is also related to gestational diabetes, hypertensive disorders, postpartum weight retention, and SGA birth and large for gestational age (LGA) and preterm infants^{34,37,38}.

Maternal mental health status during pregnancy may play a role in the determination of GWG. Two systematic reviews have evaluated the relationship between maternal psychological distress, including depression and anxiety, and GWG. However, the results are still inconclusive^{31,39}. In addition, the effect of these disorders on GWG trajectories remains unclear, especially in low and middle-income countries, where the prevalence of those disorders has increased substantially^{8,9}. Thus, this study aimed to estimate the association between depression, anxiety, and suicide risk with GWG trajectories and GWG adequacy among Brazilian women.

Nutritional Epidemiology Observatory, Department of Social and Applied Nutrition, Josué de Castro Institute of Nutrition, Federal University of Rio de Janeiro, Avenida Carlos Chagas Filho, 373, CCS, Bloco J, 2º andar, sala 29. Cidade Universitária – Ilha do Fundão, Rio de Janeiro, RJ 21941-902, Brazil. 🖾 email: dayana.farias@nutricao.ufrj.br

Results

The study had 8.2% of losses to follow-up, and we did not find significant differences in sociodemographic, obstetric, and anthropometric characteristic or mental health status at the study baseline between women who completed the follow-up (n = 189) and those who were lost (n = 17) (Supplemental Table 1).

Fifteen percent (n = 31) of the women had major depressive disorder, 19.4% (n = 34) suicide risk, and 10% (n = 21) generalized anxiety disorder at the study baseline. The prevalence of depressive symptoms decreased from 34.6% in the first trimester to 20.9% in the third trimester, and 9.1% (n = 16) presented persistent depressive symptoms during pregnancy. Most women presented GWG above the IOM guidelines at the third trimester (53.7%, n = 94), and 19.7% (n = 38) presented GWG below it (Table 1).

Women with first-trimester depression presented a significantly lower mean of total GWG compared to women without depression (10.9 (SD = 4.9) vs. 13.5 (SD = 5.6); p = 0.028]. The presence of depressive symptoms at second (11.1 (SD = 5.7) vs. 13.8 (SD = 5.4); p = 0.010] and third [11.2 (SD = 5.1) vs. 13.6 (SD = 5.6); p = 0.014] trimester and persistent depressive symptoms during pregnancy [8.6 (SD = 4.9) vs. 13.6 (5.4); p < 0.001] were associated with lower means of total GWG. It was observed a higher proportion of insufficient GWG in women with persistent depressive symptoms than adequate or excessive gestational weight gain [18.7% vs. 16.3% and 2.3%; p = 0.002, respectively]. Women classified as having anxiety symptoms at the second trimester presented significant lower means of total GWG [12.0 (SD = 5.4) vs. 14.0 (SD = 5.6); p = 0.015] and a higher proportion of insufficient GWG, compared to those with adequate or excessive GWG (58.8% vs. 42.9% and 34.7%; p = 0.049, respectively) (Table 1).

We observed a significant difference in GWG trajectory in women with depression in the first trimester compared with those without depression diagnostic, in which depressive women presented a lower rate of GWG per gestational week and a significant lower mean of cumulative GWG in the third trimester (Table 2 and Fig. 1A). Women with persistent depressive symptoms during pregnancy presented a lower rate of GWG per gestational week and a significantly lower mean of cumulative GWG in the second and third trimester, compared to those without persistent depressive symptoms (Table 2 and Fig. 1B). We observed a similar association between second-trimester state anxiety and GWG. Still, we did not observe significant differences in mean cumulative GWG between women with and without second-trimester state anxiety symptoms (Table 2 and Fig. 1C). Those associations were not attenuated by the adjustment for the minimal set of confounders (Table 2 and Fig. 1A–C). It was also observed that persistent depressive symptoms represented a 2.40 (95% CI 1.20; 4.81; p=0.013) increase in the risk of insufficient GWG (Table 3).

We did not observe a statistically significant association between generalized anxiety disorder or suicide risk with mean, trajectory (data not shown in tables), or adequacy of GWG in crude or adjusted models (Table 3).

Discussion

The study main finding was that women with persistent depressive symptoms during pregnancy presented a 0.1 kg/week lower rate of GWG throughout pregnancy and a 140% higher risk of insufficient GWG than women without persistent symptoms. The presence of major depressive disorder in the first trimester and second-trimester anxiety symptoms was also associated with a 0.08 kg/week and a 0.06 kg/week lower rate of GWG, respectively.

To the best of our knowledge, this is the first study that evaluated the association of maternal mental health prospectively measured in different time points during pregnancy, i.e., at the three pregnancy trimesters and GWG trajectories. The main strengths of this study are the longitudinal design that made it possible to evaluate GWG trajectories and repeated measures of maternal mental health during pregnancy. We also stand out using different methods (a diagnostic interview and screening scales) to evaluate maternal mental health. Furthermore, the use of LME models allowed women to include at least one measure of exposure and outcome during pregnancy. Thus women with missing data were not completely excluded from the analysis.

In contrast, the current study has limitations that are worth mentioning. First, like most longitudinal studies, the losses of follow-up (8.2%) reduced our sample size across time. However, we did not find significant differences between those who completed the study and the follow-up losses. We used self-reported pre-pregnancy weight to calculate GWG, which could introduce bias to our analyses. Nevertheless, studies have shown that women report pre-pregnancy weight accurately. The pre-pregnancy BMI classification with self-reported or first-trimester measured weight presents high agreement, especially in Brazil^{40–43}.

We found that persistent depressive symptoms were associated with lower GWG during pregnancy and increased risk of insufficient total GWG. The diagnosis of depression in the first trimester was also associated with lower GWG. Badon et al.⁶ evaluated 79,506 women from Northern California (USA), and found a U-shape association, in which maternal depression at any time 6 months prior to pregnancy was associated with 11% greater risk of GWG rate below the IOM guideline and 3% greater risk of GWG rate above the IOM guideline. The early pregnancy onset depression (up to 20 gestational weeks) was associated with a 4% higher risk of excessive GWG than non-depressed women. However, different studies did not find significant associations or found it in a different direction. Molyneaux et al.³ evaluated 13,314 pregnant women from the Avon Longitudinal Study of Parents and Children (UK) and did not find significant associations between persistent depressive symptoms (measured using EPDS at 18 and 32 weeks) with either inadequate or excessive GWG. Dolin, et al.⁴⁴ evaluated 508 low-income Hispanic women and did not find significant associations between second-trimester depressive symptoms and total GWG. Braig, et al.⁴⁵ used data from a birth cohort study in Ulm, Germany, to associate maternal depressive symptoms and GWG in 718 women. The authors did not find significant associations between depressive symptoms and GWG adequacy or GWG trajectories. Matthews et al.³² conducted a cross-sectional study with 1073 USA pregnant women and found a positive association between depressive symptoms and GWG at the second trimester. Hence, it is possible to observe no consensus about the association between maternal depression or depressive symptoms and GWG. The studies used different methodological

		GWG adequ	ıacy ^a			GWG ^b (kg)	
		Adequate	Insufficient	Excessive			
Maternal characteristics	N (%)	n (%)	n (%)	n (%)	p ^c	Mean (SD)	p^{d}
	188	52 (27.7)	37 (19.7)	99 (52.6)	~	13.2 (5.5)	-
First-trimester major depressive disorder ^e							
No	163 (86.7)	44 (84.6)	30 (81.1)	89 (89.9)		13.5 (5.6)	
Yes	25 (13.3)	8 (15.4)	7 (18.9)	10 (10.1)	0.352	10.9 (4.9)	0.028
Generalized anxiety disorder	Generalized anxiety disorder ^e						
No	169 (89.9)	43 (82.7)	34 (91.9)	92 (92.9)		13.3 (5.7)	
Yes	19 (10.1)	9 (17.3)	3 (8.1)	7 (7.1)	0.126	12.1 (4.4)	0.400
Suicide risk ^e	. ,	. ,	. ,				
No	152 (80.6)	43 (82.7)	28 (75.7)	81 (81.8)		13.3 (5.5)	
Yes	34 (19.4)	9 (17.3)	9 (24.3)	18 (18.2)	0.666	12.5 (5.7)	0.420
First-trimester EPDS score	,						
<11	122 (65.6)	29 (55.8)	23 (63.9)	70 (71.4)		13.7 (5.3)	
>11	64 (34.4)	23 (44.2)	13 (36.1)	28 (28.6)	0.153	12.2 (5.7)	0.067
Second-trimester EPDS scor	e		()			(+)	
<11	138 (78.9)	36 (73.5)	23 (69.7)	79 (85.0)		13.8 (5.4)	
>11	37 (21.1)	13 (26 5)	10 (30 3)	14 (15.0)	0 101	111(57)	0.010
Third-trimester FPDS score	57 (21.1)	15 (20.5)	10 (50.5)	11(13.0)	0.101	11.1 (5.7)	0.010
	145 (78.4)	36 (69 2)	28 (75 7)	81 (84.4)		136(56)	
>11	40 (21.6)	16 (30.8)	9 (24.3)	15 (15.6)	0.092	11.2 (5.1)	0.014
Persistent depressive sympto	40 (21.0)	10 (30.0)) (24.5)	15 (15.0)	0.072	11.2 (5.1)	0.014
No	153 (90 5)	41 (83 7)	26 (81 3)	86 (97 7)		136(54)	
Ves	16 (9.5)	8 (16 3)	6 (187)	2 (2 3)	0.002	86(49)	< 0.001
Second trimester state anvie	tv score ^g	0 (10.5)	0(10.7)	2 (2.5)	0.002	0.0 (4.7)	< 0.001
< 40	104 (58 4)	28 (57 1)	14 (41 2)	62 (65 3)		14.0 (5.6)	
>40	74 (41.6)	20 (37.1)	20 (58.8)	33 (34.7)	0.049	12.0 (5.4)	0.015
Third trimester state anxiety	scoreg	21 (12.5)	20 (30.0)	55 (51.7)	0.019	12.0 (3.1)	0.015
< 40	98 (53.0)	20 (39 2)	21 (56.8)	57 (58 8)		134 (58)	
>40	90 (33.0) 87 (47.0)	31 (60.8)	16(43.2)	40 (41.2)	0.067	12.9 (5.5)	0.538
2 40	.f	51 (00.8)	10 (43.2)	40 (41.2)	0.007	12.9 (5.5)	0.558
No.	122 (70.1)	29 (60 4)	21 (61.8)	72 (78 3)		13 7 (5 9)	
Ves	52 (29 9)	19 (39.6)	13 (38 2)	20 (21 7)	0.045	11.9 (4.8)	0.050
Age (years)	52 (2).)	17 (37.0)	15 (50.2)	20 (21.7)	0.045	11.7 (4.0)	0.050
< 30	127 (67 6)	37 (71.2)	26 (70.3)	64 (64 6)		129 (56)	
> 30	61 (32 4)	15 (28.8)	11 (29.7)	35 (35 4)	0.666	12.9 (5.0)	0.383
Education (schooling years)	01 (32.4)	13 (20.0)	11 (29.7)	33 (33.4)	0.000	15.0 (5.4)	0.383
Education (schooling years)	59 (20 9)	16 (20.9)	14 (27.9)	20 (20 2)		12 9 (5 4)	
<8 >8	120 (60 2)	26 (60.2)	14 (37.6)	20 (20.3)	0.562	12.0 (3.4)	0.620
<0 Marital status	130 (09.2)	30 (09.2)	23 (02.2)	/1 (/1./)	0.302	13.3 (3.0)	0.030
Marital status	152 (90.9)	42 (90.9)	21 (02 0)	70 (70.8)		12 2 (5 5)	
Live with partner	152 (80.8)	42 (80.8)	51 (85.8)	79 (79.8)	0.971	13.2 (5.5)	0.692
Does not nive with partner	36 (19.2)	10 (19.2)	0 (10.2)	20 (20.2)	0.871	15.8 (5.9)	0.082
Parity (parturnions)	142 (76.1)	20 (75.0)	21 (02 0)	72 (72 7)		127(5()	
0.000 1	145 (70.1)	39 (75.0)	51 (85.8)	75 (75.7)	0.165	12.7 (5.6)	0.055
≥2 D :	45 (23.9)	13 (25.0)	6 (16.2)	26 (26.3)	0.165	14.5 (5.2)	0.055
Desire to be pregnant	76 (40.4)	24 (46 2)	16 (42.2)	26 (26 1)		12 4 (5 5)	
Ies	/0 (40.4)	24 (40.2)	10 (43.2)	50 (50.4)	0.470	12.4 (5.7)	0.155
INU	112 (59.6)	28 (53.8)	21 (56.8)	03 (63.6)	0.470	13.0 (5.4)	0.155
Pre-pregnancy BMI (kg/m ²)							
< 20	117 (62.2)	37 (71.2)	25 (07.6)	55 (55.6)		13.8 (5.0) a	
25-29.9	50 (26.6)	12 (23.1)	8 (21.6)	30 (30.3)	0.010	12.4 (6.0) a,b	
≥30	21 (11.2)	3 (5.8)	4 (10.8)	14 (14.1)	0.310	10.7 (6.4) b	0.024
Pre-pregnancy leisure time p	physical activ	ity	aa (a (= `		· · · · · ·	10 = (= -)	
No	140 (74.5)	38 (73.1)	32 (86.5)	/0 (70.7)		12.7 (5.6)	
Yes	48 (25.5)	14 (26.9)	5 (13.5)	29 (29.3)	0.165	14.5 (5.2)	0.055

Table 1. Mental health status, socioeconomic and demographic characteristics according to GWG adequacy at the third trimester. *GWG* gestational weight gain, *EPDS* Edinburgh Postnatal Depression Scale, *BMI* body mass index, *SD* standard deviation, *N* sample size. ^aGWG adequacy according to the Institute of Medicine (2009) guidelines for gestational week; ^bGWG measured at the third trimester [median 39 (IQR: 38; 40) gestational weeks]; ^cp-value refers to chi-squared test; ^dp-value refers to Student's *t* test or one-way ANOVA. ^eMental health status assessed using Mini-International Neuropsychiatric Interview. ^fPersistent depressive symptoms were classified as 'yes' if the women presented Edinburgh Postnatal Depression Scale score ≥ 11 at the three pregnancy trimesters. ^gState anxiety symptoms were measured using the Spielberger State-Trait Anxiety Inventory. ^fPersistent anxiety symptoms were classified as 'yes' if the women presented Spielberger State Anxiety Inventory score ≥ 40 at the second and third trimesters. The analyses were not adjusted.

procedures, such as scales to evaluate depressive symptoms and measurements taken at other time points during pregnancy and different study designs, making comparisons difficult. The study of Molyneaux, et al.³ had an elevated sample size, but the authors evaluated persistent depressive symptoms in a short time compared to our study. Braig, et al.⁴⁵ measured depressive symptoms retrospectively reported after birth, which could have introduced bias due to the women's memory and/or her current mental health status. Finally, although Matthews et al.³² evaluated trimester-specific associations during pregnancy, the cross-sectional design did not allow the authors to model the GWG trajectories.

	Gestational weight gain ^a (kg, n=206)				
	Model 1		Model 2		
	β (95% CI) ^b	<i>p</i> -value ^c	β (95% CI) ^b	<i>p</i> -value ^c	
First trimester major depressive disorder (no/yes)	0.15 (- 1.43; 1.73)	0.854	- 0.04 (- 1.63; 1.55)	0.959	
Gestational weeks	- 0.48 (- 0.77; - 0.19)	0.001	- 0.46 (- 0.76; - 0.18)	0.002	
Quadratic gestational weeks	0.04 (0.02; 0.05)	< 0.001	0.04 (0.02; 0.05)	< 0.001	
Cubic gestational weeks	- 0.0005 (- 0.0007; - 0.0003)	< 0.001	- 0.0005 (- 0.0007; - 0.0003)	< 0.001	
Interaction term ^d			·		
Major depressive disorder#gestational weeks	- 0.08 (- 0.14; - 0.02)	0.008	- 0.08 (- 0.14; - 0.02)	0.015	
Persistent depressive symptoms (no/yes)	- 1.40 (- 3.42; 0.62)	0.173	- 1.27 (- 3.31; 0.76)	0.220	
Gestational weeks	- 0.54 (- 0.84; - 0.24)	< 0.001	- 0.54 (- 0.84; - 0.24)	< 0.001	
Quadratic gestational weeks	0.04 (0.03; 0.06)	< 0.001	0.04 (0.03; 0.06)	< 0.001	
Cubic gestational weeks	- 0.0005 (- 0.0007; - 0.0003)	< 0.001	- 0.0005 (- 0.0007; - 0.0003)	< 0.001	
Interaction term ^d					
Persistent depressive symptoms#gestational weeks	- 0.10 (- 0.17; - 0.02)	0.011	- 0.10 (- 0.17; - 0.02)	0.010	
Second-trimester anxiety symptoms (no/yes)	0.44 (- 0.76; 1.65)	0.474	0.37 (- 0.84; 1.58)	0.381	
Gestational weeks	- 0.47 (- 0.77; - 0.18)	0.002	- 0.46 (- 0.76; - 0.16)	0.002	
Quadratic gestational weeks	0.04 (0.02; 0.05)	< 0.001	0.04 (0.02; 0.05)	< 0.001	
Cubic gestational weeks	- 0.0005 (- 0.0007; - 0.0003)	< 0.001	- 0.0005 (- 0.0007; - 0.0003)	< 0.001	
Interaction term ^d					
State anxiety score #gestational weeks	- 0.07 (- 0.11; - 0.02)	0.005	- 0.06 (- 0.10; - 0.02)	0.006	

Table 2. Association between maternal mental health during pregnancy and gestational weight gain for women followed at a public health care center in Rio de Janeiro, Brazil, 2009–2012. Major depressive disorder was assessed using Mini-International Neuropsychiatric Interview. Persistent depressive symptoms were classified as 'yes' if the women presented Edinburgh Postnatal Depression Scale score \geq 11 at the three pregnancy trimesters. State anxiety symptoms were measured using the Spielberger State-Trait Anxiety Inventory. Model 1 was adjusted for linear, quadratic, and cubic gestational weeks; Model 2 was further adjusted for desire to be pregnant, education, marital status, pre-pregnancy leisure time physical activity, parity, and pre-pregnancy body mass index. ^aCumulative gestational weight gain; ^bLongitudinal linear regression coefficient and 95% confidence interval (CI); ^cp-value refers to maximum likelihood estimator; ^dThe interaction term between mental health status and gestational weeks tests whether there were different trajectories of gestational weight gain according to the categories of the mental health status variable.

We also found that women with anxiety symptoms measured at the second trimester presented lower rates of GWG during pregnancy compared to those without anxiety symptoms. However, anxiety symptoms were not associated with GWG below IOM guidelines. Vehmeijer, et al.⁴ used data from a population-based cohort of 3,393 pregnant women and found that those with anxiety symptoms had a 40% lower risk of excessive weight gain, but the symptoms were not associated with increased risk of insufficient GWG, a result in line with the current study. On the other hand, Braig, et al.⁴⁵, did not find significant associations between anxiety symptoms

and GWG trajectories during pregnancy in a sample of German women. The distinction between the results of Braig, et al.⁴⁵ and ours may be attributed to differences in the scale used to assess anxiety symptoms and the fact that in their study, anxiety was retrospectively reported after delivery. Although Vehmeijer et al.⁴ used a different scale to estimate anxiety symptoms, they also evaluated it at the second trimester of pregnancy.

The mechanisms underlying the association of depression and anxiety with inadequate GWG are complex, but there is increasing evidence on depression and anxiety on dietary intake. Women with depressive symptoms tend to present a lower intake of macronutrients (carbohydrates, proteins, and fats) and poor diet quality than those without symptoms^{46,47}. Anxiety has also been reported to affect dietary intake during pregnancy by increasing fat intake and decreasing micronutrient intake⁴⁸. A study conducted by Din, et al.⁴⁹ found that women with depression, anxiety, and stress consumed less variety of foods and had lower intakes of milk, meat, and fruit. Thus, we hypothesized that the association of depression and anxiety with insufficient GWG is mediated by inadequate dietary intake during pregnancy. The evaluation of this possible mediation path in future studies may explain the observed association between depression, anxiety, and GWG in this study.

In conclusion, we found that maternal depression and anxiety symptoms were associated with insufficient GWG. The evaluation of mental health is not part of the prenatal care routine in the Brazilian Unified Health System. Still, the results of the present study suggest that the evaluation of depressive and anxiety symptoms during pregnancy should be considered to screen women at risk of insufficient GWG. This is the first study evaluating the longitudinal association between maternal depressive and anxiety symptoms and GWG. Although our results point towards a clinically meaningful association, we highlight that one should keep in mind that these results still need to be confirmed by studies with larger sample sizes and different populations.

Methods

Study design and sample. We used data from a prospective cohort of apparently healthy pregnant women evaluated during routine prenatal care in a public healthcare center in Rio de Janeiro, Brazil. The enrollment occurred from November 2009 to October 2011, and the present study analyzed data of four gestational time points (5–13, 20–26, 30–36, and 37–42 weeks).

Women were invited to participate if they presented gestational age between 5–13 weeks, age between 20 and 40 years old, and were free of any infectious or chronic non-communicable diseases, except obesity. After enrollment, 299 (93%) pregnant women accepted to participate in the study. Women were excluded if they suffered miscarriages, presented chronic arterial hypertension or multiple gestations, were diagnosed with infectious or non-communicable diseases after the enrollment, abandoned prenatal care, or delivered a stillbirth. For this study, women without information in the mental health questionnaires (n = 7, 3.1%) or without weight/GWG information (n = 11, 4.9%) were also excluded. Thus, we evaluated 206 women in the baseline and 183 in the first, 185 in the second, and 189 in the third follow-up visit (Fig. 2).

Maternal mental health. Three main instruments were used during pregnancy to evaluate maternal mental health status at different time points: the Edinburgh Postnatal Depression Scale (EPDS), the Spielberger State-Trait Anxiety Inventory (STAI), and the Mini International Neuropsychiatric Interview (M.I.N.I) (Supplemental Table 2).

The EPDS was used in the three pregnancy trimesters (between 5–13, 20–26, and 30–36 gestational weeks) to evaluate depressive symptoms. This scale measures the occurrence of depressive symptoms and contains 10 items, with four response options. Each response can be scored from 0 to 3, and the total score varies from 0 to 30^{50} . In this study, a translated and validated version of the EDPS was used⁵¹, and values ≥ 11 were considered positive for depressive symptoms. Additionally, a variable named 'persistent depressive symptoms' was constructed, and women were classified as 'yes' if they presented EPDS score ≥ 11 at the three-time points.

The M.I.N.I. (version 5.0.0) was used to assess the presence of major psychiatric disorders, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. The M.I.N.I. is divided into 16 modules (A-P) with a series of questions related to several psychiatric disorders, such as major depressive episodes, generalized anxiety disorder, suicide risk, manic and hypomanic episodes, and obsessive–compulsive disorder. The complete version of the M.I.N.I was used to evaluate the occurrence of major depressive disorder (MDD), generalized anxiety disorder, and the current suicide risk at the first trimester of pregnancy.

Finally, anxiety symptoms were measured using STAI translated and adapted to be used in Brazil^{52,53} at the second (20–26 weeks) and third trimester (30–36 weeks). STAI consists of two distinct scales to measure state and trait anxiety. In the present study, only the state anxiety scale was used. State anxiety refers to a transitory emotional state concerning a specific period. The scale has 20 items with four response options, ranging from one (less anxious) to four (very anxious) points. The total score varies from 20 to 80 points, depending on the intensity of the symptoms. The women with score \geq 40 points were classified as having anxiety symptoms.

Gestational weight gain (outcomes). Maternal anthropometric data were collected according to the standardized protocol established by Lohman, et al.⁵⁴ at the four study visits. Weight (kg) was measured in each trimester on a digital scale (Filizzola PL 150; Filizzola Ltda, São Paulo, Brazil). To determine body mass index (BMI), duplicate measures of height (m) were taken with a portable stadiometer (Seca Ltda, Hamburg, Germany) at the first-trimester interview, and the average of the two measurements was used. Pre-pregnancy BMI (kg/m²) was calculated dividing the self-reported pre-pregnancy weight (kg) by the average height (in square meters) and classified according to the World Health Organization⁵⁵ cutoffs as underweight (<18.5 kg/m²), normal (≥ 18.5 and < 25.0 kg/m²), overweight (≥ 25.0 and < 30.0 kg/m²) and obesity (≥ 30 kg/m²).

GWG continuous and categorical were the outcomes of this study. Cumulative GWG was calculated based on the difference between the weight in each visit and self-reported pre-pregnancy weight. Total GWG was

Figure 1. Longitudinal prediction of gestational weight gain trajectory according to (**A**) first-trimester major depressive disorder status, (**B**) persistent depressive symptoms (PDS), and (**C**) Second-trimester state anxiety score. All the models were constructed using cumulative gestational weight gain and adjusted for linear, quadratic, and cubic gestational weeks, desire to be pregnant, education, marital status, pre-pregnancy leisure time physical activity, parity, and pre-pregnancy body mass index. (**A**) Number of observations: 749; Number of women: 206; Average of 3.6 observations per woman. Major depressive disorder status was assessed using Mini-International Neuropsychiatric Interview. (**B**) Number of observations: 645; Number of women: 165; Average of 3.9 observations per woman. Persistent depressive symptoms were classified as 'yes' if the women presented Edinburgh Postnatal Depression Scale score ≥ 11 at the three pregnancy trimesters. (**C**) Number of observations: 707; Number of state Anxiety Inventory.

classified in below (insufficient), within (adequate), and above (excessive) the IOM³⁴ guidelines for each BMI category (Table 4), but considering the woman gestational age at the last weight measurement (37–42 weeks). For example, the highest limit of the adequacy of a woman with a pre-pregnancy BMI between 18.5 and 25 kg/m² that had their last measure of weight at 38 weeks was calculated as 2 kg for the first trimester [13 weeks] + 0.5 kg/ week \times 25 weeks [38–13 weeks] = 14.5 kg. This way, we considered the gestational age when the last measurement of weight was obtained and to avoid possible misclassifications due to gestational ages different from 40 weeks⁵⁶. In this approach, we considered 0.5 kg of weight gain during the first trimester to calculate the lower limit and 2.0 kg of weight gain in the upper limit.

Co-variates. Maternal data such as age (years), education (schooling years), monthly per capita family income ($<1/\ge1$ minimum wage), marital status (live/does not live with a partner), parity (0 or $1/\ge2$ parturitions), desire to be pregnant (yes/no), and practice of pre-pregnancy leisure time physical activity (yes/no) were obtained from structured questionnaires administered by trained interviewers during the first-trimester visit.

Gestational age (GA) was calculated using the date from the first ultrasonography (US) performed prior to 24 weeks of gestation. In cases where the US was unavailable, the date of the last menstrual period was used (n = 14; 6.8%).

Ethics. The study protocol was approved by the Ethics Committee of Maternity Hospital of Federal University of Rio de Janeiro (protocol: 0023.0.361.000-08) and by the research ethics committee of the Municipal Secretary of Health of Rio de Janeiro city (protocol: 0139.0.314.000–09). All participants signed a term of consent, obtained freely and spontaneously after all necessary clarifications were provided. The study was carried out following the Declaration of Helsinki.

Statistical analysis. For continuous variables, we described the data using means and standard deviations (SD); for categorical, absolute (n) and relative frequencies (%) were used. We assessed the normality of continuous variables by using histograms and kurtosis and asymmetry measures.

We adjusted linear mixed models with random intercept and slope to evaluate the GWG trajectories during pregnancy according to maternal mental health, including GA as linear, quadratic, and cubic terms. We also tested the interaction between the mental health variables and GA. The coefficients (β) for each of those terms, 95% confidence intervals (CI), and p-values were estimated. For the GWG adequacy, Poisson models with robust variance were adjusted, and incidence rate ratios (IRR) and 95% CI were determined. Effect plots containing the adjusted longitudinal predictions were constructed to graphically represent the longitudinal trajectories of cumulative GWG according to first-trimester major depressive disorder status, persistent depressive symptoms, and anxiety symptoms.

All the multivariate models were adjusted considering the minimal but sufficient set of confounders. The adjustment was selected based on the construction of a directed acyclic graph (DAG), using the web application DAGgity⁵⁷ (Supplemental Figure 1), and considering the literature available on the exposure and outcomes studied. The minimal set of confounders to be included in the models was: desire to be pregnant, schooling years, marital status, pre-pregnancy leisure time physical activity, pre-pregnancy BMI, and parity. The multivariate models aim to evaluate the total effect of maternal mental health disorders on gestational weight gain. When estimating total effects, if one adjusts a model for a mediator, part of the effect of the exposure on the outcome could be not accounted for, and the total effect would be underestimated^{58,59}. Therefore, we did not adjust the models for possible mediators, such as dietary intake, nor considered them in the DAG.

The associations between maternal mental health and GWG were considered statistically significant when p-value <0.05, except for the interaction terms, when a level of significance of 0.10 was used (commonly found in the literature when testing interactions). All the statistical analyses were conducted in Stata (version 15, Stata Corp., College Station, Texas, USA), and R version 3.6 (R Core Team, R Foundation for Statistical Computing Vienna, Austria, 2019) was used to construct the graphs.



	Insufficient gestational weight gain ^a				
	Model 1		Model 2		
	IRR (95% CI)	p-value ^b	IRR (95% CI)	p-value ^b	
First trimester major depressive disorder (no/yes)	1.52 (0.75; 3.09)	0.246	1.64 (0.80; 3.37)	0.172	
Persistent depressive symptoms (no/yes)	2.21 (1.07; 4.56)	0.032	2.40 (1.20; 4.81)	0.013	
Second trimester anxiety symptoms (no/yes)	1.70 (0.93; 3.10)	0.081	1.77 (0.97; 3.24)	0.064	
Third trimester anxiety symptoms (no/yes)	1.02 (0.55; 1.87)	0.939	1.01 (0.55; 1.86)	0.972	
Generalized anxiety disorder (no/yes)	0.78 (0.26; 2.32)	0.661	0.85 (0.29; 2.47)	0.762	
Suicide risk (no/yes)	1.36 (0.70; 2.62)	0.364	1.58 (0.81; 3.08)	0.175	

Table 3. Association between maternal mental health during pregnancy and insufficient gestational weight at the third trimester for women followed at a public health care center in Rio de Janeiro, Brazil, 2009–2012. Major depressive disorder, generalized anxiety disorder, and suicide risk were assessed using Mini-International Neuropsychiatric Interview. Persistently depressive symptoms were classified as yes if the women presented Edinburgh Postnatal Depression Scale score \geq 11 at the three pregnancy trimesters. State anxiety symptoms were measured using the Spielberger State-Trait Anxiety Inventory. Model 1 was not adjusted; Model 2 was adjusted for desire to be pregnant, education, marital status, pre-pregnancy leisure time physical activity, parity, and pre-pregnancy body mass index. *CI* confidence interval, *IRR* Incidence rate ratio. ^aGestational weight gain adequacy according to Institute of Medicine guidelines (adequate/excessive vs. insufficient weight gain); ^bp-value refers to Poisson regression.





Scientific Reports | (2021) 11:10787 |

	Rates of weight gain 2nd and 3rd trimester ^a	Total weight gain	
Prepregnancy BMI	Mean (range) in kg/week	Range in kg	
Underweight (<18.5 kg/m ²)	0.51 (0.44; 0.58)	12.5; 18,0	
Normal weight (18.5–24.9 kg/m ²	0.42 (0.35; 0.50)	11.5; 16.0	
Overweight (25.0–29.9 kg/m ²)	0.28 (0.23; 0.33)	7.0; 11.5	
Obese (≥ 30.0 kg/m ²)	0.22 (0.17; 0.27)	5.0; 9.0	

Table 4. Institute of Medicine guidelines for total and rate of weight gain during pregnancy, according to prepregnancy BMI. ^aConsidering a weight gain range of 0.5; 2 kg in the first trimester. Adapted from IOM³⁴.

Received: 20 January 2021; Accepted: 20 April 2021 Published online: 24 May 2021

References

- Ruiz, R. J. & Fullerton, J. T. The measurement of stress in pregnancy. Nurs. Health Sci. 1, 19–25. https://doi.org/10.1046/j.1442-2018.1999.00004.x (1999).
- Woods, S. M., Melville, J. L., Guo, Y., Fan, M. Y. & Gavin, A. Psychosocial stress during pregnancy. Am. J. Obstet. Gynecol. 202(61), e61-67. https://doi.org/10.1016/j.ajog.2009.07.041 (2010).
- Molyneaux, E., Poston, L., Khondoker, M. & Howard, L. M. Obesity, antenatal depression, diet and gestational weight gain in a population cohort study. Arch. Womens Ment. Health 19, 899–907. https://doi.org/10.1007/s00737-016-0635-3 (2016).
- Vehmeijer, F. O. L. et al. Psychological distress and weight gain in pregnancy: A population-based study. Int. J. Behav. Med. 27, 30–38. https://doi.org/10.1007/s12529-019-09832-0 (2020).
- Eichler, J., Schmidt, R., Hiemisch, A., Kiess, W. & Hilbert, A. Gestational weight gain, physical activity, sleep problems, substance use, and food intake as proximal risk factors of stress and depressive symptoms during pregnancy. *BMC Pregnancy Childbirth* 19, 175. https://doi.org/10.1186/s12884-019-2328-1 (2019).
- Badon, S. E., Hedderson, M. M., Hyde, R. J., Quesenberry, C. P. & Avalos, L. A. Pre- and early pregnancy onset depression and subsequent rate of gestational weight gain. J. Womens Health 28, 1237–1245. https://doi.org/10.1089/jwh.2018.7497 (2019).
- Heery, E., Kelleher, C. C., Wall, P. G. & McAuliffe, F. M. Prediction of gestational weight gain—A biopsychosocial model. *Public Health Nutr.* 18, 1488–1498. https://doi.org/10.1017/S1368980014001815 (2015).
- Bennett, H. A., Einarson, A., Taddio, A., Koren, G. & Einarson, T. R. Prevalence of depression during pregnancy: Systematic review. Obstet. Gynecol. 103, 698–709. https://doi.org/10.1097/01.AOG.0000116689.75396.5f (2004).
- Dennis, C. L., Falah-Hassani, K. & Shiri, R. Prevalence of antenatal and postnatal anxiety: Systematic review and meta-analysis. Br. J. Psychiatry 210, 315–323. https://doi.org/10.1192/bjp.bp.116.187179 (2017).
- Cunha Figueiredo, A. C. *et al.* Association between plasma concentrations of vitamin D metabolites and depressive symptoms throughout pregnancy in a prospective cohort of Brazilian women. *J. Psychiatr. Res.* 95, 1–8. https://doi.org/10.1016/j.jpsychires. 2017.07.009 (2017).
- Pereira, P. K., Lovisi, G. M., Pilowsky, D. L., Lima, L. A. & Legay, L. F. Depression during pregnancy: Prevalence and risk factors among women attending a public health clinic in Rio de Janeiro, Brazil. *Cad. Saude Publica* 25, 2725–2736 (2009).
- Silva, R. A. D. *et al.* Depression during pregnancy in the Brazilian public health care system. *Braz. J. Psychiatry* 32, 139–144 (2010).
 Verly-Miguel, M. V. *et al.* Serum docosahexaenoic acid (DHA) is inversely associated with anxiety disorders in early pregnancy. *J. Anxiety Disord.* 30, 34–40. https://doi.org/10.1016/j.janxdis.2014.12.002 (2015).
- Paskulin, J. T. A. et al. Association between dietary patterns and mental disorders in pregnant women in Southern Brazil. Braz. J. Psychiatry 39, 208–215 (2017).
- Silva, M. M. d. J., Nogueira, D. A., Clapis, M. J. & Leite, E. P. R. C. Anxiety in pregnancy: prevalence and associated factors. *Revista da Escola de Enfermaçem da USP* 51 (2017).
- Newport, D. J., Levey, L. C., Pennell, P. B., Ragan, K. & Stowe, Z. N. Suicidal ideation in pregnancy: Assessment and clinical implications. Arch. Womens Ment. Health 10, 181–187. https://doi.org/10.1007/s00737-007-0192-x (2007).
- Lindahl, V., Pearson, J. L. & Colpe, L. Prevalence of suicidality during pregnancy and the postpartum. Arch. Womens Ment. Health 8, 77–87. https://doi.org/10.1007/s00737-005-0080-1 (2005).
- Farias, D. R. *et al.* Prevalence of psychiatric disorders in the first trimester of pregnancy and factors associated with current suicide risk. *Psychiatry Res.* 210, 962–968. https://doi.org/10.1016/j.psychres.2013.08.053 (2013).
- Castro e Couto, T. et al. Suicidality among pregnant women in Brazil: Prevalence and risk factors. Arch. Womens Ment. Health 19, 343–348. https://doi.org/10.1007/s00737-015-0552-x (2016).
- Grigoriadis, S. et al. Maternal anxiety during pregnancy and the association with adverse perinatal outcomes: Systematic review and meta-analysis. J. Clin. Psychiatry https://doi.org/10.4088/JCP.17r12011 (2018).
- Grigoriadis, S. *et al.* The impact of maternal depression during pregnancy on perinatal outcomes: A systematic review and metaanalysis. *J. Clin. Psychiatry* 74, e321-341. https://doi.org/10.4088/JCP.12r07968 (2013).
- Rees, S., Channon, S. & Waters, C. S. The impact of maternal prenatal and postnatal anxiety on children's emotional problems: A systematic review. *Eur. Child Adolesc. Psychiatry* 28, 257–280. https://doi.org/10.1007/s00787-018-1173-5 (2019).
- Suri, R., Lin, A. S., Cohen, L. S. & Altshuler, L. L. Acute and long-term behavioral outcome of infants and children exposed in utero to either maternal depression or antidepressants: A review of the literature. J. Clin. Psychiatry 75, e1142-1152. https://doi. org/10.4088/JCP.13r08926 (2014).
- Accortt, E. E., Cheadle, A. C. & DunkelSchetter, C. Prenatal depression and adverse birth outcomes: An updated systematic review. *Matern. Child Health J.* 19, 1306–1337. https://doi.org/10.1007/s10995-014-1637-2 (2015).
- Maxwell, M. A. & Cole, D. A. Weight change and appetite disturbance as symptoms of adolescent depression: Toward an integrative biopsychosocial model. *Clin. Psychol. Rev.* 29, 260–273. https://doi.org/10.1016/j.cpr.2009.01.007 (2009).
- Beydoun, M. A. et al. Role of depressive symptoms in explaining socioeconomic status disparities in dietary quality and central adiposity among US adults: A structural equation modeling approach. Am. J. Clin. Nutr. 90, 1084–1095. https://doi.org/10.3945/ ajcn.2009.27782 (2009).
- Pagoto, S. L. et al. Association of depressive symptoms and lifestyle behaviors among Latinos at risk of type 2 diabetes. J. Am. Diet. Assoc. 109, 1246–1250. https://doi.org/10.1016/j.jada.2009.04.010 (2009).
- Wielopolski, J. et al. Physical activity and energy expenditure during depressive episodes of major depression. J. Affect. Disord. 174, 310–316. https://doi.org/10.1016/j.jad.2014.11.060 (2015).

- Helgadottir, B., Forsell, Y. & Ekblom, O. Physical activity patterns of people affected by depressive and anxiety disorders as measured by accelerometers: A cross-sectional study. *PLoS ONE* 10, e0115894. https://doi.org/10.1371/journal.pone.0115894 (2015).
- Kapadia, M. Z. et al. Psychological antecedents of excess gestational weight gain: A systematic review. BMC Pregnancy Childbirth 15, 107. https://doi.org/10.1186/s12884-015-0535-y (2015).
- Hartley, E., McPhie, S., Skouteris, H., Fuller-Tyszkiewicz, M. & Hill, B. Psychosocial risk factors for excessive gestational weight gain: A systematic review. Women Birth 28, e99–e109. https://doi.org/10.1016/j.wombi.2015.04.004 (2015).
- Matthews, J., Huberty, J., Leiferman, J. & Buman, M. Psychosocial predictors of gestational weight gain and the role of mindfulness. *Midwifery* 56, 86–93. https://doi.org/10.1016/j.midw.2017.10.008 (2018).
- 33. Viswanathan, M. et al. Outcomes of maternal weight gain. Evidence report/technology assessment, 1-223 (2008).
- Rasmussen, K. M., Yaktine, A. L. & Institute of Medicine (U.S.). Committee to Reexamine IOM Pregnancy Weight Guidelines. Weight Gain During Pregnancy: Reexamining the Guidelines. (National Academies Press, 2009).
- Pugh, S. J. *et al.* Patterns of gestational weight gain and birthweight outcomes in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Fetal Growth Studies-Singletons: A prospective study. *Am. J. Obstet. Gynecol.* 217, 346. e341–346.e311. https://doi.org/10.1016/j.ajog.2017.05.013 (2017).
- Leonard, S. A., Rasmussen, K. M., King, J. C. & Abrams, B. Trajectories of maternal weight from before pregnancy through postpartum and associations with childhood obesity. *Am. J. Clin. Nutr.* 106, 1295–1301. https://doi.org/10.3945/ajcn.117.158683 (2017).
- Goldstein, R. F. et al. Association of gestational weight gain with maternal and infant outcomes: A systematic review and metaanalysis. JAMA 317, 2207–2225. https://doi.org/10.1001/jama.2017.3635 (2017).
- Nehring, I., Schmoll, S., Beyerlein, A., Hauner, H. & von Kries, R. Gestational weight gain and long-term postpartum weight retention: A meta-analysis. Am. J. Clin. Nutr. 94, 1225–1231. https://doi.org/10.3945/ajcn.111.015289 (2011).
- Kapadia, M. Z. et al. Psychological factors and trimester-specific gestational weight gain: A systematic review. J. Psychosom. Obstet. Gynaecol. 36, 15–22. https://doi.org/10.3109/0167482x.2014.993311 (2015).
- Holland, E., Moore Simas, T. A., Doyle Curiale, D. K., Liao, X. & Waring, M. E. Self-reported pre-pregnancy weight versus weight measured at first prenatal visit: Effects on categorization of pre-pregnancy body mass index. *Matern. Child Health J.* 17, 1872–1878. https://doi.org/10.1007/s10995-012-1210-9 (2013).
- Bannon, A. L. et al. Comparison of self-reported and measured pre-pregnancy weight: Implications for gestational weight gain counseling. Matern. Child Health J 21, 1469–1478. https://doi.org/10.1007/s10995-017-2266-3 (2017).
- Natamba, B. K., Sanchez, S. E., Gelaye, B. & Williams, M. A. Concordance between self-reported pre-pregnancy body mass index (BMI) and BMI measured at the first prenatal study contact. *BMC Pregnancy Childbirth* 16, 187. https://doi.org/10.1186/s12884-016-0983-z (2016).
- Rangel Bousquet Carrilho, T. et al. Agreement between self-reported pre-pregnancy weight and measured first-trimester weight in Brazilian women. BMC Pregnancy Childbirth 20, 734. https://doi.org/10.1186/s12884-020-03354-4 (2020).
- Dolin, C. D. et al. Predictors of gestational weight gain in a low-income hispanic population: Sociodemographic characteristics, health behaviors, and psychosocial stressors. Int. J. Environ. Res. Public Health https://doi.org/10.3390/ijerph17010352 (2020).
- Braig, S., Logan, C. A., Reister, F., Rothenbacher, D. & Genuneit, J. Psychosocial stress and longitudinally measured gestational weight gain throughout pregnancy: The Ulm SPATZ Health Study. Sci. Rep. 10, 1996. https://doi.org/10.1038/s41598-020-58808-8 (2020).
- Saeed, A., Raana, T., Saeed, A. M. & Humayun, A. Effect of antenatal depression on maternal dietary intake and neonatal outcome: A prospective cohort. Nutr. J. 15, 64. https://doi.org/10.1186/s12937-016-0184-7 (2016).
- Avalos, L. A. et al. Prenatal depression and diet quality during pregnancy. J. Acad. Nutr. Diet. 120, 972–984. https://doi.org/10. 1016/j.jand.2019.12.011 (2020).
- Hurley, K. M., Caulfield, L. E., Sacco, L. M., Costigan, K. A. & Dipietro, J. A. Psychosocial influences in dietary patterns during pregnancy. J. Am. Diet. Assoc. 105, 963–966. https://doi.org/10.1016/j.jada.2005.03.007 (2005).
- Din, Z. et al. Inadequate dietary intake in women with antenatal psychological distress: A population based study in Pakistan. J. Food Nutr. Res. https://doi.org/10.12691/jfnr-2-12-25 (2014).
- Cox, J. L., Holden, J. M. & Sagovsky, R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br. J. Psychiatry 150, 782–786. https://doi.org/10.1192/bjp.150.6.782 (1987).
- Santos, I. S. et al. Validation of the Edinburgh Postnatal Depression Scale (EPDS) in a sample of mothers from the 2004 Pelotas Birth Cohort Study. Cad. Saude Publica 23, 2577–2588 (2007).
- Biaggio, A. M. B., Natalício, L. & Spielberger, C. D. In Cross-Cultural Research on Anxiety (eds Spielberger, C. D. & Dias-Guerrero, R.) 29-40 (Hemisphere/Wiley, 1976).
- 53. Biaggio, A. M. B. & Natalício, L. Manual para o Inventário de Ansiedade Traço-Estado (IDATE). (Centro Editor de Psicologia Aplicada-CEPA, 1979).
- 54. Lohman, T. G., Roche, A. F. & Martorell, R. Anthropometric Standardization Reference Manual (Human Kinetics Books, 1988).
- WHO. Maternal anthropometry and pregnancy outcomes. A WHO Collaborative Study: Introduction. Bull. World Health Organ. 73(Suppl), 1–6 (1995).
- Hutcheon, J. A. et al. The bias in current measures of gestational weight gain. Paediatr. Perinat. Epidemiol. 26, 109–116. https:// doi.org/10.1111/j.1365-3016.2011.01254.x (2012).
- Textor, J., van der Zander, B., Gilthorpe, M. S., Liskiewicz, M. & Ellison, G. T. Robust causal inference using directed acyclic graphs: The R package "dagitty". Int. J. Epidemiol. 45, 1887–1894. https://doi.org/10.1093/ije/dyw341 (2016).
- MacKinnon, D. P., Krull, J. L. & Lockwood, C. M. Equivalence of the mediation, confounding and suppression effect. *Prev. Sci.* 1, 173–181. https://doi.org/10.1023/a:1026595011371 (2000).
- Suttorp, M. M., Siegerink, B., Jager, K. J., Zoccali, C. & Dekker, F. W. Graphical presentation of confounding in directed acyclic graphs. *Nephrol. Dial Transplant.* 30, 1418–1423. https://doi.org/10.1093/ndt/gfu325 (2015).

Acknowledgements

The study was funded by the National Council for Scientific and Technological Development (CNPq in the Portuguese acronym; grant number: 471196/2010-0) and the Carlos Chagas Filho Foundation for Research Support of Rio de Janeiro State (FAPERJ in the Portuguese acronym, grant number E-26/111.400/2010, E_14/2010).

Author contributions

D.R.F., T.R.B.C., and N.C.F.C. analyzed and interpreted the data and wrote the manuscript, with input from all authors. M.B., M.G. and G.K., contributed to the interpretation of the data and revision of the manuscript. G.K. coordinated the study and participated in all phases of analysis and interpretation of the data and writing of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/ 10.1038/s41598-021-90179-6.

Correspondence and requests for materials should be addressed to D.R.F.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2021