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Master thesis

Association of maternal diet during early pregnancy and risk of gestational diabetes. The role of maternal metabolic profile and mental health: data from RHEA study, Crete.

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Heraklion, [February 2020]

Contents

List of abbreviations

GDM	Gestational Diabetes
ADA	American Diabetes Association
AHEI	Alternative Healthy Eating Index
ARFS	Australian Recommended Food Score
DASH	Dietary Approaches to Stop Hypertension
MedDiet	Mediterranean Diet
T2D	Type 2 Diabetes
IGT	Impaired Glucose Tolerance
OGTT	Oral Glucose Tolerance Test
PA	Physical Activity
CVD	Cardiovascular Diseases
IADPSG	International Association of Diabetes and Pregnancy Study Group
FFQ	Food Frequency Questionnaire
FAs	Fatty Acids
EPDS	Edinburgh Postnatal Depression Scale
OR	Odds Ratio
1H NMR	Proton Nuclear Magnetic Resonance

Περίληψη Μεταπτυχιακής Εργασίας

Τίτλος εργασίας: Συσχέτιση της διατροφής στην αρχή της εγκυμοσύνης με τον κίνδυνο ανάπτυξης διαβήτη κύησης. Ο ρόλος του μεταβολικού προφίλ και της ψυχικής υγείας της μητέρας: δεδομένα από τη μελέτη Ρέα, Κρήτη.

Της: Άννας Χαλκιαδάκη

Υπό τη επίβλεψη των: 1. Χρήστου Λιονή
2. Λήδα Χατζή
3. Μαρίνα Βαφειάδη
4. Κατερίνα Μαργετάκη
Ημερομηνία: Φεβρουάριος 2010

Εισαγωγή: Ο διαβήτης κύησης αποτελεί μια από τις κυριότερες διαταραχές κατά τη διάρκεια της εγκυμοσύνης προσβάλοντας πάνω από το 21% των γυναικών παγκοσμίως. Η διατροφή κατά διάρκεια της εγκυμοσύνης φαίνεται να παίζει σημαντικό ρόλο στην ανάπτυξη του διαβήτη κύησης.

Υπόθεση: Τα μη υγιεινά διατροφικά μοντέλα και τα συμπτώματα κατάθλιψης κατά τη διάρκεια της εγκυμοσύνης αυξάνουν τον κίνδυνο για διαβήτη κύησης μέσω τροποποίησης του μεταβολικού προφίλ της μητέρας.

Στόχος: Σκοπός της παρούσας έρευνας είναι η μελέτη της συσχέτισης της διατροφής στην αρχή της εγκυμοσύνης με τον κίνδυνο ανάπτυξης διαβήτη κύησης σε δείγμα γυναικών από τη μελέτη Ρέα. Επιπλέον, μελετήθηκε ο ρόλος του μεταβολικού προφίλ και η ψυχική υγεία της μητέρας.

Μέθοδος: Η παρούσα μελέτη αποτελεί μέρος της προοπτικής μελέτης μητέρας-παιδιού "Ρέα". Ερωτηματολόγια χρησιμοποιήθηκαν για τη συλογή δεδομένων σχετικά με τις διατροφικές συνήθειες και την ψυχική υγεία των γυναικών. Η διάγνωση του διαβήτη κύησης πραγματοποιήθηκε μέσω δοκιμασία ανοχής στη γλυκόζη κατά την $24^{η}$ -$28^{η}$ εβδομάδα κύησης. Η μέτρηση των μεταβολιτών στα ούρα πραγματοποιήθηκε με φασματομετρία 1H NHR (Proton nuclear magnetic resonance).

Αποτελέσματα: Δε βρέθηκε συσχέτιση μεταξύ των διατροφικών μοντέλων και του κινδύνου ανάπτυξης διαβήτη κύησης. Επίσης, δε βρέθηκε συσχέτιση μεταξύ του EPDS σκορ και του διαβήτη κύησης. Αυξημένη συμμόρφωση στο "Western type" διατροφικό μοντέλο συσχετίστηκε με μειώμενη πιθανότητα ανάπτυξης διαβήτη κύησης με την αλληλεπίδραση της γλυσίνης και λυσοφωσφατιδυλοχολίνη ακύλιο 18:0 (OR (95% CI) = 0.99 (0.99, 1.00) p=0.013). Αυξημένη συμμόρφωση στο "Healthy type" διατροφικό μοντέλο συσχετίστηκε με αυξημένη πιθανότητα ανάπτυξης διαβήτη κύησης με την αλληλεπίδραση της γλυσίνης και λυσοφωσφατιδυλοχολίνη ακύλιο 18:0 (OR (95% CI) = 1.003 (1.00, 1.005) p=0.036) (OR (95% CI) = 0.99 (0.99, 1.00) p=0.030).

Συμπεράσματα: Δε βρέθηκε συσχέτιση μεταξύ της διατροφής και της ψυχικής υγείας της μητέρας κατά τη διάρκεια της εγκυμοσύνης με τον κίνδυνο ανάπτυξης

διαβήτη κύσησης. Βρέθηκε αρνητική συσχέτιση μεταξύ του διατροφρικού μοντέλου "Western type" και της ισολευκίνης, της αλανίνης, της λυσίνης και της βαλίνης. Επιπλέον, βρέθηκε αρνητική συσχέτιση μεταξύ της Μεσογειακής διατροφής και του LysoPC a C18:1. Θετική συσχέτιση βρέθηκε μεταξύ του διατροφικού μοντέλου "Healthy type" και της αλανίνης, της ισολευκίνης, της βαλίνης και του LysoPC a C18:1. Τα αυξημένα επίπεδα γλυσίνης και LysoPCaC 18:0 συσχετίστηκαν με αυξημένο κίνδυνο ανάπτυξης διαβήτη κύησης.

Λέξεις κλειδιά: μελέτη PEA, διαβήτης κύησης, διατροφική αξιολόγηση, εγκυμοσύνη, μεταβολικό προφίλ, ψυχική υγεία

Abstract

Title: Association of maternal diet during early pregnancy and risk of gestational diabetes. The role of maternal metabolic profile and mental health: data from RHEA study, Crete.

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Introduction: GDM is among the most common medical disorders of the perinatal period affecting up to 21% of women globally. Maternal diet seems to play a significant role in the development of the GDM.

Hypothesis: Unhealthy eating patterns and depression symptoms during pregnancy increase the risk of GDM by the modification of maternal metabolic profile.

Aim: To examine the associations between maternal diet during pregnancy and the risk of developing gestational diabetes mellitus in a sample of women from the "Rhea" mother-child cohort. In addition, the role of maternal metabolic profile and depression symptoms will be examined.

Methods: The present study is part of the prospective "Rhea" mother-child cohort. Questionnaires were used to collect information about maternal dietary habits and mental health. Women were screened for GDM by the 100-g 3-h oral glucose tolerance test (OGTT) at weeks 24–28 of gestation. Urinary metabolites were measured using Proton nuclear magnetic resonance (1H NHR) spectrometry.

Results: It was found no significant association between any dietary pattern (Western type, Heathy type and MedDiet) and GDM, even after adjusting for potential confounders. Also, no significant association was found between EPDS score and GDM, even after adjusting for potential confounders. Higher compliance to Western type dietary pattern was associated with a reduction in the likelihood of GDM by the interaction of glycine and lysoPC a C18:0 (OR (95% CI) = 0.99 (0.99, 1.00) p=0.013). Higher compliance to Healthy type dietary pattern was associated with a higher likelihood of GDM by the interaction of glycine and lysoPC a C18:0 (OR (95% CI) = 1.003 (1.00, 1.005) p=0.036). Higher compliance to MedDiet was associated with a reduction in the likelihood of GDM by the interaction of glycine and lysoPC a C18:0 (OR (95% CI) = 0.99 (0.99, 1.00) p=0.030).

Conclusion: Maternal dietary patterns (Western type, Heathy type and MedDiet) and maternal mental health were not associated with the risk of GDM development in the current study. A negative association was observed between the Western type diet and isoleucine, alanine, leucine and valine. In addition, a negative association was observed between the MedDiet and LysoPC a C18:1. A positive association was observed between the Healthy type diet and alanine, isoleucine, leucine, valine and LysoPC a C18:1. Higher levels of glycine and LysoPCaC 18:0 were associated with a higher risk of GDM.

Key words: RHEA study, gestational diabetes, dietary assessment, pregnancy, metabolic profile, mental health

Introduction

According to the American Diabetes Association (ADA), Gestational Diabetes Mellitus (GDM) is defined as "diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation" (ADA, 2018). For both women and their offspring GDM has been related to short- and long-term adverse health outcomes, including development of diabetes type 2 and metabolic syndrome (Ashwal and Hod, 2015). However, the etiology and pathogenesis of GDM still remains unclear (Chen et al., 2018).

Food and dietary factors have been reported to affect glucose homeostasis and diet may also be associated with GDM risk factors (Donazar-Ezcurra, López-del Burgo and Bes-Rastrollo, 2017). The majority of previous studies have focused on the role of specific food items (Chen et al., 2009), or nutrients (Bo et al., 2001) in the development of GDM. However, due to the interactions and synergistic effects of nutrients (Hu, 2012), studying dietary patterns offers a comprehensive method for investigating the relationship between diet and disease risk (Binyou, Terry and Jinlin, 2007).

In recent years, many studies have been conducted to explore the association between maternal diet and the risk of GDM development. More specific, greater adherence to Mediterranean Diet (Karamanos et al., 2014) and high intake of polyunsaturated fat seems to be protective (Bo et al., 2001), while Western diet compliance (Zhang et al., 2006) and high intake of carbohydrate foods and saturated fats have been reported to increase the risk of GDM (Bo et al., 2001). Moreover, the role of maternal metabolic profile on GDM development also has been explored. Metabolomics are increasingly being employed as a biomarker discovery tool in epidemiology (McCabe and Perng, 2017). They have the advantage of capturing disease-relevant metabolic changes and identifying novel biomarkers of disease processes (Connor et al., 2010). Furthermore, metabolomics may increase our ability to identify early predictors of GDM or classify the risk of subsequent cardiovascular diseases among women (Chen et al., 2018). According to studies, amino acids, carbohydrate, ketones were found to be significantly increased in women with DGM (Scholtens et al., 2013).

It is considered that women are resistant to depression during pregnancy. However, antenatal depression affects at least 20% of women and has many impacts on both maternal (higher anxiety, greater obstetric complications and increased risk of postpartum depression) and fetal health (preterm birth sudden infant death syndrome) (Byrn and Penckofer, 2013). Research on the link between pregnancy depression and GDM is limited and conflicting indicating a significant association between depression and GDM (Bowers et al., 2013). However, the mechanisms underlying the development of the disease need further investigation.

Definition of GDM

Among the most common metabolic disorders and medical problems known during pregnancy is gestational diabetes mellitus (GDM) (Akhondan et al., 2012). Gestational diabetes mellitus (GDM) is a form of hyperglycaemia that is first recognized during pregnancy (Law and Zhang, 2017). For over 30 years, GDM has been defined as "carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy" (Harlev and Wiznitzer, 2010). The American Diabetes Association (ADA) defines GDM as diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation (ADA, 2017).

Pathogenesis and pathophysiology of GDM

Normal pregnancy, especially the third trimester, is characterized by elevated metabolic stresses on maternal lipid and glucose homeostasis, which includes insulin resistance and hyperinsulinemia (Buchanan and Xiang, 2005; Catalano et al., 1993). Also, normal pregnancy is accompanied by a 40% to 50% reduction in insulin sensitivity and a 200% to 250% increase in insulin secretion by the pancreatic β cells in order to maintain maternal euglycemia (Catalano et al., 1999). Pregnancy itself is also characterized by an altered inflammatory profile compared to the non-pregnant state, and excessive inflammation has been associated with a variety of adverse perinatal outcomes, including preterm delivery, gestational hypertension, and gestational diabetes (Christian and Porter, 2014).

Although the precise underlying mechanisms are yet to be identified, insulin resistance and inadequate insulin secretion to compensate for it play a central role in the pathophysiology of GDM (Kim and Ferrara, 2010; Buchanan and Xiang, 2005). Women who develop GDM are thought to have a compromised capacity to adapt to the increased insulin resistance characteristic of late pregnancy, primarily during the third trimester (Kim and Ferrara, 2010). Pregnancy-related metabolic challenges unmask a predisposition to glucose metabolic disorders in some women (Buchanan and Xiang, 2005; Knopp et al., 1982). Most women with GDM have β- cell dysfunction against a background of chronic insulin resistance to which the insulin resistance of pregnancy is partially additive (Buchanan and Xiang, 2005). Factors that contribute to insulin resistance or relative insulin deficiency both before and during pregnancy may have a deleterious effect during pregnancy and may be risk factors for GDM (Kim and Ferrara, 2010). The symptoms of GDM tend to occur from the 24th week of gestation. Overt symptoms of hyperglycemia during pregnancy are rare and difficult to distinguish from normal pregnancy symptoms but may include increased thirst and frequent urination (ADA, 2017).

Epidemiology of GDM

Worldwide

Although GDM has been recognized as one of the most common pregnancy complications, its epidemiology has not been well investigated due to lack of global consensus on the diagnosis of GDM. Globally, the prevalence of GDM ranged from 1.0 to 14.2 % of all pregnancies depending on diagnostic criteria and the study population.

As shown in Table 1, the Southeast Asia region consistently reported the highest GDM prevalence with a median of 5.4 % (range of 3–14.2 %), followed by Eastern Mediterranean countries with a median of 4.75 % (range of 1.9–13.7 %). America, Africa, and Western Pacific appeared to have similar GDM prevalence with a median of 3.7 % across the three regions. Europe had the lowest GDM prevalence among all the WHO regions. The low prevalence was evident across all European countries (range 1.2–3.1 %) except for Italy.

A recent study using data from the Pregnancy Risk Assessment Monitoring System (PRAMS) reported that the GDM prevalence (included 21 states that participated in PRAMS from 2007–2010) was 8.1 % in 2007–2008 and 8.5 % in 2009–2010 [22]. Another study using the Agency for Healthcare Research and Quality's (AHRQ) National and State Inpatient Database (included 12 states) found that the GDM prevalence increased from 3.71 % in 2000 to 5.77 % in 2010 among all hospital deliveries (Bardenheier et al., 2015).

Table 1. Worldwide prevalence of GDM

WHO region	Country	Year(s) of survey	GDM prevalence %	Sample size	Hospital or population setting	Diagnostic criteria
Africa	Ethiopia	1999*	3.7	890	Population—Tigray	WHO (1985)
Americas	Brazil	1991–1995	7.6	5004	Population—multi-city	WHO (1999)
	Canada	2000–2004	3.7	71,527	Population—Manitoba	NDDG
	USA	2005	3.9	126,8502	National population	ADA (2004)
Europe	Denmark	1999–2000	2.4	5235	Population—multi-city	WHO (1999)
	Finland	1996–1998	2.8	523	Population—Helsinki	C & C
	Ireland	2000	2.7	1889	Hospital—Dublin	NDDG
	Italy	2006	22.3	1103	Population—Sardinia	C & C
		1995–2001	8.7	3950	Population—Pisa	C & C
	Netherlands	1992–1997	2.0	1640	Population—Amsterdam-East	WHO (1985)
	Sweden	1991–1999	2.5	12,382	Population—Lund Malmo	WHO (1985)
		1994–1996	1.7	3616	Population—multi-city	WHO (1985)
	Switzerland	2000–2002	2.7	5788	Hospital—Lausanne	NDDG
	Turkey	1995–2004	3.1	3548	Hospital—Osmangazi	C & C
		2003*	1.2	807	Population—Trabzon City	C & C
	UK	1984–1988	1.5	11,205	Hospital—London	O & M
Eastern Mediterranean	Bahrain	2001–2002	13.5	10,495	Population—Salamanca	C & C
	Iran	2007*	4.7	2416	Hospital—Tehran	C & C
	Saudi Arabia	1988*	1.9	1088	Hospital—Riyadh	WHO (1985)
South East Asia	China	1996 *	3.0	713	Population—multi-city	WHO (1985)
		1990–1994	14.2	942	Hospital—Hong Kong	WHO (1999)
	India	1999–2002	3.8	10,00	Population—Srinagar/Kashmir	C & C
	Japan	1999–2001	2.9	749	Population—Mie	ADA (2004)
	Malaysia	2006	11.3	1600	Hospital	WHO (1999)
	Pakistan	2003–2004	8.5	633	Hospital—Karachi	ADA (2004)
	Sri Lanka	1997	5.5	721	Population	WHO (1985)
	Thailand	2001	5.3	1200	Hospital—Bangkok	NDDG
Western Pacific	Australia	1996*	6.7	3817	Hospital—Camperdown	C & C
		1996	3.6	60,600	Population—Victoria	NDDG
	New Zealand	1994–1995	2.6	4885	Hospital—South Auckland	C & C

(Chen et al., 2016)

Europe

The reported prevalence of GDM in Europe varies considerably, and in certain populations is reported to occur in more than 20% of pregnancies (Jelsma et al., 2013; Buckley et al., 2012). Unfortunately, accurate prevalence estimates in Europe are lacking due to highly inconsistent screening and diagnostic criteria both in high-risk women and the general pregnant population (Benhalima et al., 2015). This makes pan- European surveys of GDM very difficult and limits the effects of large-scale GDM prevention and treatment strategies (Egan et al., 2017).

According to DALI trial, a prospective, multicentre RCT which enrolled 1023 pregnant women between January 2012 and February 2014 from 11 centres in nine European countries (UK, Ireland, Austria, the Netherlands, Belgium, Denmark, Italy, Spain and Poland), 395 women were diagnosed with GDM at some time during pregnancy. There was a high prevalence of GDM in early pregnancy (<20 weeks' gestation), with 242 women (24%) from the overall population of 1023 diagnosed at this point. Also, there was a spread in the prevalence of GDM in early pregnancy, from a low of 10–11% in the UK and Ireland to a high of 43% in Denmark. A total of 672 women were retested at mid gestation (24–26 weeks), and 94 (14%) had developed GDM despite the interventions of the trial. Once again, there was a spread in prevalence from a low of 8% in Ireland to a high of 21%in Italy. Finally, 476 women who were previously categorised as having NGT (without GDM at the OGTT at 24–26 weeks) completed the final OGTT at 35–37 weeks' gestation, of whom 59 (13%) had developed GDM despite diet and lifestyle interventions. There was a spread in prevalence from a low of 9% in Italy to a high of 16% in Belgium. The lowest overall prevalence was in the UK (24%) and the highest prevalence was in Denmark (52%).

Table 2. GDM prevalence in Europe according to gestation period and country

Country	Participants enrolled, *n*	Participants with GDM, *n* (%)			GDM total, *n* (%)
		Early pregnancy	Mid pregnancy	Late pregnancy	
Denmark	217	93/217 (43)	11/106 (10)	8/77 (10)	112/217 (52)
Belgium	101	21/101 (21)	12/75 (16)	10/61 (16)	43/101 (43)
Spain	99	25/99 (25)	10/65 (15)	6/46 (13)	41/99 (41)
Netherlands	80	27/80 (34)	4/44 (9)	1/18 (5)	32/81 (41)
Poland	91	17/91 (19)	12/68 (18)	7/47 (15)	36/91 (40)
Austria	110	22/110 (20)	12/72 (17)	6/45 (13)	40/110 (36)
Italy	116	16/116 (14)	18/85 (21)	5/54 (9)	39/116 (34)
Ireland	84	9/84 (11)	5/63 (8)	7/47 (15)	21/84 (25)
UK	125	12/125 (10)	10/94 (11)	9/74 (12)	31/125 (24)
TOTAL	1023	242/1023 (24)	94/672 (14)	59/476 (13)	395/1023 (39)

(Egan et al., 2017)

Greece

In the literature, only a few epidemiological data are available on GDM in the Greek population. According to a Greek cohort study by Varela and colleagues, in 2017 the prevalence of GDM in Greece was 14,5% (Varela et al., 2017). Another study reported that GDM prevalence differed significantly by season: winter = 28.1%, summer = 39.2%, spring = 32.4% and autumn = 32.4% ($P < 0.0001$) suggesting that GDM prevalence in Greece presents seasonal variation, with higher risk during summer due to post glucose load level variations (Vasileiou et al., 2018).

Risk factors for GDM

Well-recognized risk factors for GDM include advanced maternal age, a family history of type 2 diabetes, and a history of GDM (Ben-Haroush, Yogev and Hod, 2004; Berkowitz et al., 1992). The risk of GDM increases significantly and progressively in overweight, obese, and morbidly obese women. Cigarette smoking has not been consistently identified as a risk factor for GDM (Ben-Haroush, Yogev and Hod, 2004; Berkowitz et al., 1992). Asian, Hispanic, and Native American women, as compared with non-Hispanic white women, have an increased risk of GDM (Savitz et al., 2008; Ben-Haroush, Yogev and Hod, 2004; Berkowitz et al., 1992). African American women have been reported to have an increased risk of GDM, as compared with non-Hispanic whites, by some (Dooley et al., 1991; Solomon, Willett and Carey, 1997) although not all (Savitz et al., 2008; Berkowitz et al., 1992), investigators. Other reported risk factors include short maternal stature (Yang et al., 2002; Branchtein et al., 2000), polycystic ovary disease, previous stillbirth, high blood pressure during pregnancy, and multiple pregnancies (Ben-Haroush, Yogev and Hod, 2004). Also, among the factors that enhance the risk of diabetes in pregnant women are history of diabetes during previous pregnancies, excretion of glucose in urine, obesity, history of infantile death, history of giving birth to macrocosmic infant or any abnormality (Almasi and Salehiniya, 2014). Research in the past decade has identified a few lifestyle factors that are associated with GDM risk, including a Western dietary pattern, high consumption of red meat and sugary drinks, low consumption of dietary fiber, low glycemic index diet, and physical inactivity before pregnancy (Zhang and Ning, 2011).

Health outcomes in women with GDM and their offspring

Gestational diabetes increases the risk of complications for both mother and child during pregnancy, childbirth and beyond (Chen et al., 2016). Although most women with GDM regain normal glucose tolerance after delivery, many of them are featured with metabolic disorders in postpartum and later life. Women with GDM are at increased risk of developing impaired glucose tolerance (IGT) and T2D in their later life. On average, the risk of development of T2D is 7.4 times greater in GDM women than non-GDM women (Bellamy et al., 2009) and 2.6% to 70% will develop diabetes

mellitus 28 years later (Kim, Newton and Knopp, 2002). Moreover, recent data have indicated that women with a history of GDM might be at an increased risk of cardiovascular diseases (CVD) independent of T2D or obesity. Several studies have reported an association between GDM and CVD risk factors, including obesity, high blood pressure, abnormal plasma lipid levels, metabolic disorder, inflammation, and endothelial dysfunction (Tobias et al., 2011; Di Cianni et al., 2007). In addition, other nontraditional CVD risk biomarkers, such as higher level of C-reactive protein (CRP), E-selectin, fibrinogen, plasminogen activator inhibitor (PAI)-1, and lower circulation level of adiponectin, have been fund in women with a history of GDM (Di Cianni et al., 2007; Bo et al., 2007). Moreover, recent studies have directly linked a history of GDM with a CVD clinical event. A US study reported that among women with a family history of T2D, those with GDM were more likely to have a CVD event (odds ratio (OR)= 1.85; p=0.005), independent of T2D (Carr et al., 2006). The higher risk of development of CVD among women with a history of GDM was also reported by a larger study in Canada with a median follow-up of 11.5 years (Shah, Retnakaran and Booth, 2008). A recent publication from CARDIA (The Coronary Artery Risk Development in Young Adults) study found that the history of GDM was associated with atherosclerosis (measured by common carotid intima-media thickness), independent of prepregnancy obesity (Gunderson et al., 2014). In addition, pregnant women complicated with GDM tend to have increased risk of miscarriage, hypertensive disorders, macrosomia, cesarean delivery and postpartum hemorrhage (Kim, Newton and Knopp, 2002).

Excessive fetal growth and its consequences are the main concerns of GDM (Metzger et al., 2007). Consequences of excessive fetal growth include birth trauma, maternal morbidity from operative delivery, and possible lifelong increased risks of glucose intolerance and obesity in the offspring. The cesarean delivery rate is increased in patients with GDM, in part to avoid birth trauma and to avoid another potential morbidity of shoulder dystocia and newborn asphyxia, both associated with large-for-gestational-age newborns (Henriksen, 2008; Gottlieb and Galan, 2007). Other neonatal morbidities that potentially occur more frequently in infants of women with GDM include hypoglycemia, hyperbilirubinemia, hypocalcemia, erythremia, and poor feeding (Metzger et al., 2007). The offspring of these women are associated with large for gestational age, premature birth, neonatal respiratory distress syndrome, hypoglycemia, and also impaired glucose metabolism in early age (Kampmann, 2015). Several studies reported that children of women with GDM are more likely to be obese and have impaired glucose tolerance and diabetes in childhood and early adulthood (Fraser et al., 2007; ADA, 2004).

Maternal diet during pregnancy and risk of GDM

In the recent decade, more attention has been paid to nutritional issues and their relationship with different diseases regarding epidemiology of nutrition (Ehrampoush et al., 2016; Esmaillzadeh, Azadbakht and Kimiagar, 2007). Dietary patterns reflect the dietary habits of people, through which the manner of food and nutrient consumption is specified and provided for the person (Rashidkhani et al., 2009). In

most studies, specifically the effect of micro-nutrients or certain types of foods has been examined in pregnant women with GDM (Khosrowbeygi and Ahmadvand, 2017; Ramezani et al., 2017; Bao et al., 2014). Only a limited number of studies have dealt with the relationship between dietary patterns and GDM (Schoenaker et al., 2015; Shin, Lee and Song, 2015; Tobias et al., 2012). Analyses of overall food patterns account for any interactions or synergistic effects among individual foods or nutrients (Hu, 2002). The role of dietary patterns during pregnancy in relation to GDM risk is still uncertain (Shin, Lee and Song, 2015).

Four studies reported the Mediterranean Diet (MedDiet) as a protective dietary pattern against GDM, reaching statistical significance. The protectiveness is ranged from 15-38% (Karamanos et al., 2013; Tobias et al., 2012). Although women with better MedDiet compliance had lower incidence of GDM than those with lower compliance, Karamanos and colleagues reported that GDM incidence greatly differed when comparing ADA and IADPSG diagnostic criteria between the compliant groups (8% vs. 24%, respectively) (Karamanos et al., 2013). Adherence to a diet with a high Alternative Healthy Eating Index (AHEI) 2010 score was associated with a reduced risk of GDM by 19% (Zhang et al., 2014) or 46% (Tobias et al., 2012). When additional lifestyle factors were taken into account such as regular PA, normal BMI, non-smoker, the association with risk reduction was 83% (Zhang et al., 2014). Similarly to the AHEI scoring system, some studies used an Australian Recommended Food Score (ARFS) (Gresham et al., 2016) or Dietary Approaches to Stop Hypertension (DASH) score (Tobias et al., 2012). A high ARFS was not associated with GDM risk (Gresham et al., 2016), whereas a greater DASH diet compliance was associated with a 34% GDM risk reduction (Tobias et al., 2012).

With respect to Prudent (high intake of fruits, tomatoes, cabbages, green leafy vegetables, dark yellow vegetables, legumes, other vegetables, poultry and fish) and Western diets **(**high intake of red meat, processed meat, refined grain products, snacks, sweets and deserts, French fries and pizza), there were some conflicting results. Whilst compliance to a Prudent or Western diet resulted in a negative and positive association with GDM risk respectively in one study (Zhang et al., 2006), a second study observed no such relationships (Radesky et al., 2008). Several possible biologically adverse effects of components in red and processed meats, such as saturated fatty acids and cholesterol, on insulin sensitivity have been proposed and might be relevant to the pathophysiology of GDM. Nitrites, frequently used as a preservative in processed meats, have been implicated in the development of diabetes. Nitrosamines can be formed by the interaction of amino compounds with nitrites present either in the stomach or within the food product. They have been linked to beta cell toxicity (Lijinsky, 1999). Another potential explanation is related to the toxic effects of AGEs, which can be formed in meat and high-fat products through heating and processing (Peppa et al., 2002). Moreover, a diet high in AGEs was found to promote inflammatory mediators that might be important in the genesis of diabetes, such as TNF-a and C-reactive protein (Vlassara et al., 2002). Both biomarkers have been positively associated with the risk of GDM or gestational hyperglycaemia (Bo et al., 2005; Wolf et al., 2003). In addition, it has been proposed that food-derived AGEs may interact with glycoxidation-related genes, in particular, the AGE receptor (AGER) gene, to determine risk of type 2 diabetes by activating the AGE receptor signal transduction pathway involved in the inflammatory response (Kaňková and

Šebeková, 2005). Haem iron in red meat might also contribute to the increased risk of GDM, because body iron overload has been postulated to promote insulin resistance and increase the risk of type 2 diabetes (Jiang et al., 2004).

Prior evidence suggests that women who develop GDM have prepregnancy b cell dysfunction and insulin resistance, compromising their ability to adapt to the metabolic challenges presented in pregnancy (Dahlquist, 2007; Lijinsky, 1999). Adherence to diets such as the MedDiet, DASH, and AHEI may reduce GDM risk by minimizing such susceptibilities in the time leading up to pregnancy. Common components between the dietary patterns include fruit and vegetables, minimal red and processed meats, and carbohydrate quality. Fruit and vegetables are rich in antioxidants and photochemicals, dietary fiber, and micronutrients such as magnesium and vitamin C. The combination of these might prevent metabolic deterioration by opposing free radicals and improving systemic oxidative stress (Dahlquist, 2007). Foods such as fruit and vegetables might also indirectly confer a benefit by replacing harmful foods in the diet. Red and processed meats are sources of saturated fat, heme iron, nitrosamines, and other constituents and have been associated with b cell damage, oxidative stress, and insulin resistance as well as incident GDM (Schulze et al., 2003). Whole grains are high in insoluble fiber (low in glycemic index), which blunts absorption of glucose and subsequent insulin requirements (Peppa et al., 2002).

Maternal metabolic profile in early pregnancy and development of DGM

Metabolomics is increasingly being employed as a biomarker discovery tool in epidemiology and medicine, including the studies of GDM (McCabe and Perng, 2017; Huynh, Xiong and Bentley-Lewis, 2014). They can provide a phenotypic fingerprint of a complex biological system (Nicholson, Lindon and Holmes, 1999) and measure thousands of metabolites or low-molecular-weight intermediates (molecular weight < 1000) directly from these systems. Metabolomics has the advantage of capturing disease-relevant metabolic changes and identifying novel biomarkers of disease processes (Connor et al., 2010). Since metabolites participate as substrates or products of metabolic pathways, the compositional changes of the metabolome directly reflect the physiological status, gene expression, and environmental stimuli to the biological system (Blow, 2008). These metabolites have been used in the early detection of diseases, measuring biological responses to treatments/interventions, identifying the underlying pathways between risk factors and diseases, and discovering novel biomarkers associated with certain health stages/conditions. Currently, highly sensitive and specific screening methods to predict GDM in early gestation are unavailable. Researchers have recently started applying metabolomics as a technology for concurrent monitoring of a large number of metabolites from biological specimens.

The most frequently instrumental methods that have been used in metabolomics analyses are liquid chromatography (LC), gas chromatography (GC) and capillary electrophoresis (CE), coupled to mass spectrometry (MS), and proton nuclear

magnetic resonance (1H NMR) spectroscopy (are the most frequently used instrumental methods in Metabolomics) (Liu and Locasale, 2017). A variety of biological specimens have been used in the studies of GDM including maternal blood (plasma or serum) (Gika and Theodoridis, 2011), urine, hair (He et al., 2015), breath gas (Halbritter et al., 2012), colostrums (Azulay Chertok et al., 2017) and fetal synthesis and secretion, such as amniotic fluid (Graça et al., 2012), placenta (Uhl et al., 2015; Roverso et al., 2015) and newborn's meconium (Peng et al., 2015). Blood (plasma or serum) is the most frequently specimens that have been used in the studies of GDM. Blood volume in the human body is under strict regulation and the variation among individuals is relatively small. It also provides a snapshot of a patient's metabolic status at the time of sampling (Gika and Theodoridis, 2011).

Studies on the metabolic profile of women in early pregnancy to predict risk of GDM have reported inconsistent findings. Five studies that analyzed blood samples (plasma or serum), collected before the diagnosis of GDM, reported significant increases in the following metabolites of women who later developed GDM compared to those who did not: itaconic acid, cis-aconitate acid, (Wang et al., 2015) anthranilic acid, alanine, glutamate, allantoin, serine (Sussulini, 2017), total fatty acids, myristic acid, palmitic acid, palmitoleic acid, eicosapentaenoic acids, (Watson, 2013) flavonoids (sesaminol 2-O-triglucoside, and tricin 7-neohesperidoside) (Madsen, Lundstedt and Trygg, 2010). Also, the same studies reported significant decreases in creatinine, (Sussulini, 2017) phospholipids (unsaturated), (2E)-14-hydroxytetradec-2-enoic acid or its isomer, (2E,13R)-13-hydroxytetradec-2-enoic acid, 2,15-dihydroxy-pentadecanoic acid (orits isomers), (7R,8S,9Z,12Z,15Z)-7,8-dihydroxy-9,12,15-octadecatrienoicacid, (Madsen, Lundstedt and Trygg, 2010) trimethylamine-N-oxide and betaine (Grootveld, 2015).

Four studies that analyzed urine samples, a significant increase was reported for women with GDM compared to controls in choline, N-methyl-nicotinamide (Grootveld, 2015; Krumsiek et al., 2012), glucose, xylose (Krumsiek et al., 2012), 3-hydroxyisovalerate, 2-hydroxyisobutyrate, and citrate and in one study a significant decreases of 4-hydroxyphenylacetate and hippurate were reported (Krumsiek et al., 2012).

Several possible mechanisms have been proposed about how the metabolic profile in early pregnancy affects the GDM development. Elevated maternal circulating total fatty acids (FAs) have been associated with increased insulin resistance and β-cell dysfunction, which contribute to the development of gestational diabetes mellitus (GDM) and increase risk of adverse perinatal outcomes, including preterm delivery (Bentley-Lewis et al., 2015). Plasma polyunsaturated or chemically modified phospholipids reduction in plasma is not clear yet, but the pathophysiology effects of these changes could be an unbalanced proportion of pro-inflammatory/ anti-inflammatory factors that might lead to low-grade inflammation. Specifically, the decrease of polyunsaturated lysoglycerophospholipids signified the alteration of a common enzymatic activity, possibly related to cPLA (cytosolic calcium-dependent phospholipase-A2 isoform), similar to what is observed in patients with IGT and type 2-diabetes (Chen et al., 2010). Itaconic acid has been associated with inflammation demonstrating a potential role of inflammation in early pregnancy, in the development of GDM. It is recognized that inflammation often accompanies GDM, however, there have been few studies of the role of inflammation in its development, prior to diagnosis (Shin, Lee and Song, 2015).

Aim of the study

The aim of this study is to examine the associations between maternal diet and depression symptoms during pregnancy with the risk of developing gestational diabetes mellitus in a sub-sample of women from the "Rhea" mother-child cohort. Also, the effect of maternal diet on the maternal metabolic profile and how metabolomics link the maternal diet and the risk of gestational diabetes will be examined.

Material and methods

Study Population

The current study is part of the prospective "Rhea" mother-child cohort. The Rhea project examines pregnant women and their children, at the prefecture of Heraklion, Crete. Pregnant women (Greek and immigrants) were recruited at the time of the first comprehensive ultrasound examination at around week 12 of gestation, from four antenatal clinics (two public and two private) in Heraklion city, within a 12-month period starting in February 2007. The sample size of the present study was 806 participants who meet the inclusion criteria. In particular, the study included women with singleton pregnancies; aged older than 16 years; with no prior history of diabetes and psychiatric disorder. Also, the study included women with complete maternal dietary and antenatal mental health data. Women who experienced spontaneous or induced abortions or gave birth to stillborn infants were excluded. The study was approved by the ethical committee of the University Hospital in Heraklion, Crete, Greece, and all participants provided written, informed consent after complete description of the study.

Data collection

During recruitment face-to-face structured questionnaires together with self-administered questionnaires and medical records were used to obtain information on several dietary, socio-demographic, lifestyle characteristics and psychosocial exposures during pregnancy. Also, height, weight and blood pressure were measured and urine samples were collected from pregnant women.

Maternal dietary assessment

Information on maternal dietary habits were collected during mid-pregnancy (14th–18th week of gestation) using a validated, semi-quantitative food frequency questionnaire (FFQ) of 250 food items (Chatzi et al., 2017). These food items were aggregated into seventeen food groups ('cereals and cereal products', 'meat and meat products', 'fish and seafood', 'dairy products', 'eggs', 'vegetable–animal fats except olive oil', 'olive oil', 'potatoes and other starchy roots', 'pulses', 'vegetables', 'nuts', 'fruits', 'sweets and deserts', 'nonalcoholic beverages', 'alcoholic beverages', 'salty snacks' and 'miscellaneous'). For each food item, participants were asked about both frequency of consumption and average portion size. The frequency of consumption

was given per day, per week and/or per month, depending on the food item. Photographs were used to visualize small, medium and large portion sizes for each food item and respondents had to choose one out of three pictures. To estimate the intake of each food item in grams, portion sizes were multiplied by daily frequencies of intake. For complex items (such as mixed dishes), standard recipes were used as described in the Composition Tables of foods and Greek dishes by Antonia Trichopoulou, 3rd edition. Individual portion sizes and recipes were used to calculate daily energy intake on the basis of the UK food tables (McCance and Widdowson's The Composition of Foods, 6th summary edition). Two dietary patterns were identified, 'Western' and 'Healthy' dietary pattern. Western dietary pattern comprised mainly meat and meat products, potatoes, sugar and sweets, cereals, fats except olive oil, salty snacks, eggs, beverages and sauces, while the health dietary pattern comprised mainly vegetables, fruit, nuts, pulses, fish and seafood, olive oil and dairy products.

Adherence to the Mediterranean Diet during pregnancy was assessed using a scale applied in a large cohort study (European Prospective Investigation into Cancer and Nutrition; EPIC) in adults. For beneficial components (vegetables, legumes, fruits and nuts, cereals, fish and seafood, dairy products), women whose consumption was below the median were assigned a value of 0, and women whose consumption was at or above the median were assigned a value of 1. For components presumed to be detrimental (meat, including all types of meat), women whose consumption was below the median were assigned a value of 1, whereas women whose consumption was at or above the median were assigned a value of 0. The fat intake was calculated by using the ratio of daily consumption of monounsaturated lipids to saturated lipids (Trichopoulou et al., 2003). Because the index had been developed for adults and the present study population involved pregnant women, dairy products were presumed to be protective and not detrimental dietary compounds, and alcohol consumption was not included in the index. The total Mediterranean Diet score ranged from 0 (minimal adherence to the traditional MD) to 8 (maximal adherence) (Chatzi et al., 2008).

Maternal mental health assessment

Maternal depressive symptoms were assessed at 28–32 weeks of gestation using the Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden and Jagovsky, 1987).
The EPDS is a widely used 10-item self-reported questionnaire providing an indication of the severity of mother's mood during the past 7 days. Items are rated on a 4-point Likert scale ranging from 0 (not at all) to 3 (most of the time) and refers to depressed mood, anhedonia, guilt, anxiety, and suicidal ideation.

Diagnosis of GDM

Women were screened for GDM at weeks 24–28 of gestation, and were classified as having GDM in the index pregnancy if two or more of the four plasma glucose values obtained during the 100-g 3-h oral glucose tolerance test (OGTT) were abnormal, as per the criteria proposed by Carpenter and Coustan: FBG≥95 mg/dL; 1-h values ≥ 180 mg/dL; 2-h values ≥ 155 mg/dL; and 3-h values ≥ 140 mg/dL (Carpenter and Coustan, 1982).

Metabolomics analysis

Urine samples were collected during the third trimester of pregnancy (median 32 weeks of gestation). Urinary metabolites were measured using Proton nuclear magnetic resonance (1H NHR) spectrometry.

Statistical Analysis

Univariate associations were examined between GDM and maternal characteristics. T-test was used in the case of continuous variables with normal distribution, Mann-Whitney U-test for continuous variables with non-normal distribution and chi-square test for categorical variables. Correlation between maternal characteristics and EPDS score were examined using Spearman's correlation coefficient in the case of continuous variables and Mann-Whitney U-test in the case of categorical variables due to the lack of normality of EPDS score.

Logistic regression models were performed to explore the relationship between the dietary pattern and GDM, and EPDS score and GDM. Both were adjusted for potential confounding variables. Confounders were selected if they were simultaneously associated with at least one independent and one depended variable with p-value <0.05.

Linear and logistic regression models were used to examine the relationship between maternal diet and maternal metabolites, and maternal metabolites and GDM, respectively. Both were adjusted for potential confounding variables. Confounders were selected if they simultaneously associate with at least one independent and one depended variable with p-value <0.05. All statistical analyses were performed using SPSS version 21.

Results

Participants characteristics

Table 1 summarizes participant characteristics according to the GDM status. Of the 806 women included to the analysis, 9.2% (n=74) were diagnosed with GDM at the time of OGTT testing (24–28 weeks' gestation) and 90.8% (n=732) were healthy at the same time point. The mean age of women with GDM was 30.5 years (±4.4 years) and women who did not diagnosed with GDM was 29.4 years (±5 years) and most of them were Greek (90.5% and 91.6%, respectively) and physically inactive during pregnancy (95.9% and 92,9%, respectively). Close to half of both groups were multiparous at recruitment (54.1% and 50.5%, respectively) and have completed middle educational level (60.3% and 58.2%, respectively). Also, most of women with and without GDM did not smoke, neither in early pregnancy (60.3% and 65.1%, respectively) nor at 12^{th} weeks of gestation (56.4% and 67.2%, respectively). Women diagnosed with GDM had a significantly higher BMI before pregnancy (p=0.020) and at 12^{th} weeks of gestation (p=0.001) when compared with those not diagnosed with GDM. They were also less likely to have suffered from diabetes before pregnancy (p<0.001). On the contrary, significantly more healthy participants had normal blood pressure compared with women diagnosed with GDM (p<0.001).

Table 1. Maternal characteristics in relation to gestational diabetes mellitus (GDM)

	GDM n= 74 (9,2%) n (%)	**No GDM n= 732 (90,8%) n (%)**	**P-value**
Age (yrs) (mean ± SD)	74 (30.46 ± 4.4)	730 (29.36± 5)	0.07[a]
BMI before pregnancy (kg/m2) (median ± SD)	24.4 (17, 47)	23.3 (16, 47)	0.02*[b]
BMI at 12th weeks of gestation (kg/m2) median (min,max)	26.5 (19, 45.2)	24.2 (16.1, 66.9)	0.001*[b]
Weight gain during pregnancy (kg) (median ± SD)	12 (0, 30)	13.5 (-7, 42)	0.051[b]
Origin			
Other	7 (9.5)	61 (8.4)	0.75
Greek	67 (90.5)	666 (91.6)	
Educational level			
Low	16 (21.6)	147 (20.2)	0.67
Middle	40 (54.1)	368 (50.5)	
High	18 (24.3)	213 (29.3)	

Table 1. Continued

	GDM	No GDM	P-value
Diabetes before pregnancy			
No	55 (75.3)	685 (95)	<0.001*
Yes	18 (24.7)	36 (5)	
Gestational Hypertension			
No	68 (93.2)	689 (96.5)	0.16
Yes	6 (6.8)	25 (3.5)	
Parity			
Nulliparous	29 (39.7)	302 (41.8)	0.74
Multiparous	44 (60.3)	421 (58.2)	
PA during pregnancy			
No	71 (95.9)	679 (92.9)	0.32
Yes	3 (4.1.)	52 (7.1)	
Smoking status in early pregnancy			
Non smokers	44 (60.3)	464 (65.1)	0.53
Quit During pregnancy	12 (16.4)	121 (17)	
Smokers during pregnancy	17 (23.3)	128 (18)	
Smoking at 12^{th} weeks of gestation			
No	22 (56.4)	264 (67.2)	0.18
Yes	17 (43.6)	129 (32.8)	
Alcohol consumption at 12^{th} week of gestation			
No	58 (78.4)	508 (69.4)	0.11
Yes	16 (21.6)	224 (30.6)	

BMI: Body Mass Index; PA, Physical Activity. Chi-square (2-tailed) tests were conducted to compare group differences, unless otherwise specified. [a] T-test was conducted for continuous variables that follow a normal distribution. [b] Mann-Whitney U test was conducted for continuous variables that did not follow a normal distribution. * $p < 0.05$.

Table 2. Maternal energy intake and food group consumption in relation to GDM

	GDM	NO GDM	p-value
	N (%)	N (%)	
Energy (kcals)	74	732	0.21
Energy			
<1000	4 (5.4)	32 (4.4)	0.77
1000-3999.99	67 (90.5)	679 (92.8)	
>40000	3 (4.1)	21 (2.9)	
Vegetables			
Below median	32 (43.2)	370 (50.5)	0.23
Above median	42 (56.8)	362 (49.5)	
Pulses			
Below median	36 (48.6)	348 (47.5)	0.86
Above median	38 (51.4)	384 (52.5)	
Cereal			
Below median	41 (55.4)	366 (50)	0.38
Above median	33 (44.6)	366 (50)	
Fish			
Below median	34 (45.9)	362 (49.5)	0.57
Above median	40 (54.1)	370 (50.5)	
Dairy			
Below median	37 (50)	362 (49.5)	0.929
Above median	37 (50)	370 (50.5)	
Meat			
Below median	39 (52.7)	366 (50)	0.66
Above median	35 (47.3)	366 (50)	
Fruits & Nuts			
Below median	45 (60.8)	361 (49.3)	0.059
Above median	29 (39.2)	371 (50.7)	
Fat ratio			
Below median	38 (51.4)	36 (48.6)	0.84
Above median	367 (50.1)	365 (49.9)	

GDM: Gestational Diabetes Mellitus. Chi-square (2-tailed) tests were conducted to compare group differences.

Both women with GDM and healthy women had no significant difference in energy and food groups intake (Table 2). Most of them had energy intake between 1000-3999.99kcals (90.5% and 92.8%, respectively). Close to half of the participants' food groups intake (vegetables, pulses, cereal, fish, dairy, meat, and fat ratio) was above median. Only healthy women had a trend towards higher intake of fruits and nuts comparing with women with GDM (p_{trend}=0.059) (Table 2).

Table 3. Odds ratios (95% confidence interval) for gestational diabetes mellitus (GDM) according to dietary pattern scores

	Odds Ratio (OR) (95% CI)	p-value
Western type		
Unadjusted model	1.02 (0.95- 1.09)	0.64
Model[1]	1.04 (0.97-1.12)	0.29
Model[2]	1.05 (0.97-1.13)	0.20
Model[3]	1.04 (0.96-1.13)	0.33
Healthy type		
Unadjusted model	1.02 (0.93-1.12)	0.63
Model[1]	1.04 (0.95-1.14)	0.38
Model[2]	1.04 (0.95- 1.14)	0.37
Model[3]	1.05 (0.95-1.15)	0.35
MedDiet Score (0-7)		
Unadjusted model	0.96 (0.83-1.11)	0.60
Model[1]	0.98 (0.84-1.14)	0.76
Model[2]	0.97 (0.83- 1.13)	0.69
Model[3]	0.98 (0.84-1.5)	0.81

CI: Confidence Interval,
Unadjusted model: Crude association between dietary patterns and GDM
Model[1]: Adjusted for maternal BMI at 12th week of gestation, maternal BMI before pregnancy, thyroid, 1st trimester antibiotics, 2nd trimester acetyl acid ($p \leq 0.05$)
Model[2]: Adjusted for model[1]+ maternal age, ($p \leq 0.1$);
Model[3]: Adjusted for model[2]+ maternal educational level, gestational hypertension, parity, alcohol consumption at 12th week of gestation, smoking at 12th week of gestation, ($p \leq 0.2$)

There was no significant association between any dietary pattern (Western type, Heathy type and MedDiet) and GDM, even after adjusting for potential confounders (Table 3).

Table 4 . Maternal characteristics in relation to maternal mental health

		EPDS score	
	n	**rho**	**p-value**
Maternal age	394	-0,091	0.07[a]
Weight gain during pregnancy	317	-0,051	0.37 [a]
Maternal BMI before pregnancy	393	0.078	0.12 [a]
Maternal BMI at 12th weeks of gestation	392	0.083	0.09 [a]
Gestational Hypertension			
No	372		0.53
Yes	17		
Alcohol consumption at 12th week			
No	282		0.46
Yes	113		
Smoking at 12th week of gestation			
No	150		0.04*
Yes	73		
Parity			
Nulliparous	169		0.47
Multiparous	221		
Physical activity during pregnancy			
No	358		0.017*
Yes	37		
Smoking status in early pregnancy			
Non smokers	238		0.05[b]
Quit During pregnancy	76		
Smokers during pregnancy	73		
Educational level			
Low	67		0.09
Middle	197		
High	264		

EPDS: Edinburg Postpartum Depression Scale. Mann- Whintey U test was conducted due to the lack of normality of EPDS score, unless otherwise specified. [a] Spearman's test was conducted for continuous variables. [b]Kruskal-Wallis test was conducted for qualitative variables with more than 2 categories. * $p < 0.05$.

There was no significant association between maternal age, weight gain during pregnancy, BMI before pregnancy and BMI at 12th week of gestation and EPDS score. Also, there was no significant difference between gestational hypertension, alcohol consumption at 12th week of gestation, parity and educational level and EPDS score. Significant difference was found only between EPDS score and smoking at 12th

week of gestation (p=0.043) and physical activity during pregnancy (p=0.017) (table 4).

Table 5. Association between prenatal EPDS score and GDM.

	Odds Ratio (OR) (95% CI)	p-value
EPDS score		
Unadjusted model	0.96 (0.89-1.03)	0.22
Model[1]	0.97 (0.89-1.06)	0.50
Model[2]	0.98 (0.89- 1.07)	0.70
Model[3]	0.95 (0.87-1.04)	0.28

CI: Confidence Interval, logistic regression analysis of dietary patterns and GDM
Unadjusted model: Crude association between EPDS score and GDM,
Model[1]: Adjusted for smoking at 12th week of gestation, diabetes before pregnancy ($p \leq 0.05$);
Model[2]: Adjusted for model[1] + maternal age (yrs), maternal BMI at 12th week, any drug at 2nd trimester($p \leq 0.1$);
Model[3]: Adjusted for model[2]+ maternal BMI before pregnancy, ($p \leq 20\%$)

There was no significant association between EPDS score and GDM, even after adjusting for potential confounders (table 5).

Table 6. Association between dietary patterns in pregnancy and maternal metabolites.

	Acetylcarnitine		Alanine		Glutamate		Glycine	
	b (95% CI)	**p-value**	**b (95% CI)**	**p-value**	**b (95% CI)**	**p-value**	**b (95% CI)**	**p-value**
Western type								
Unadjusted model	0.03 (-0.05, 0.12)	0.43	-4.50 (-10.80, 1.79)	0.16	-2.65 (-7.16, 1.85)	0.25	-1.69 (-6.17, 2.79)	0.46
Model[1]	0.05 (-0.08, 0.19)	0.42	-6.97 (-16.10, 2.16)	0.13	-2.96 (-10.33, 4.41)	0.43	-3.73 (-10.49, 3.04)	0.28
Model[2]	0.05 (-0.12, 0.22)	0.58	-16.38(-30.66,-2.11)	0.03*	-9.11 (-21.29, 3.06)	0.13	-7.33 (-18.07, 3.42)	0.18
Healthy type								
Unadjusted model	0.02 (-0.08, 0.13)	0.64	3.60 (-4.19, 11.39)	0.36	1.007 (-4.57, 6.59)	0.72	2.06 (-2.89, 8.01)	0.37
Model[1]	-0.11 (-0.32, 0.10)	0.31	10.27 (-4.19, 24.72)	0.16	3.69 (-7.97, 15.36)	0.53	8.63 (-2.08, 19.34)	0.12
Model[2]	-0.09 (-0.35, 0.18)	0.51	24.53 (2.50, 46.56)	0.03*	13.09 (-5.69, 31.88)	0.17	14.13 (-2.45, 30.70)	0.09
MedDiet Score								
Unadjusted model	0.09 (-0.07, 0.25)	0.26	8.29 (-3.71, 20.30)	0.17	3.46 (-5.14, 12.07)	0.43	2.98 (-5.55, 11.51)	0.49
Model[1]	0.18 (-0.05, 0.41)	0.13	-5.14 (-21.39, 11.11)	0.53	-1.54 (-14.66, 11.58)	0.82	-9.75 (-21.79, 2.29)	0.11
Model[2]	0.15 (-0.09, 0.38)	0.22	-9.74 (-29.76, 10.28)	0.33	-3.21 (-20.28, 13.86)	0.71	-6.03 (-21.09, 9.04)	0.42

Table 6. Continued

	Isoleucine		Leucine		Serine		Valine		Creatinine	
	b (95% CI)	**p-value**	**b (95% CI)**	**p-value**	**b (95% CI)**	**p-value**	**b (95% CI)**	**p-value**	**b (95% CI)**	**p-value**
Western type										
Unadjusted model	-1.59 (-3.17, -0.007)	0.049*	-3.48 (-9.11, 2.15)	0.22	-1.79 (-5.36, 1.77)	0.32	-3.54 (-7.28, 0.19)	0.063	-1.32 (-3.82, 1.18)	0.29
Model[1]	-2.35 (-4.51, -0.18)	0.03*	-8.93 (-18.08, 0.22)	0.06	-3.98 (-9.21, 1.29)	0.14	-5.62 (-10.75, -0.49)	0.032*	-2.62 (-6.81, 1.57)	0.22
Model[2]	-3.78 (-7.16, -0.40)	0.03*	-18.02 (-33.20, -2.83)	0.02*	-7.99 (-16.18, 0.19)	0.06	-12.14 (-20.23, -4.06)	0.004**	-5.55 (-12.53, 1.44)	0.12
Healthy type										
Unadjusted model	0.48 (-1.50, 2.46)	0.63	2.87 (-4.09, 9.82)	0.41	2.58 (-1.79, 6.96)	0.25	1.86 (-2.80, 6.52)	0.43	0.32 (-2.78, 3.42)	0.84
Model[1]	3.79 (0.37, 7.21)	0.03*	14.84 (0.36, 29.31)	0.045*	7.56 (-0.78, 15.89)	0.08	-8.88 (0.76, 17.01)	0.03*	4.52 (-2.11, 11.14)	0.18
Model[2]	5.89 (0.68, 11.10)	0.03*	29.21 (5.77, 52.64)	0.02*	11.76 (-0.86, 24.39)	0.08	19.39 (6.92, 31.87)	0.003**	8.55 (-2.23, 19.33)	0.12
MedDiet Score										
Unadjusted model	0.92 (-2.14, 3.98)	0.55	3.46 (-7.31, 14.23)	0.53	3.92 (-2.85, 10.69)	0.25	4.18 (-3.004, 11.37)	0.25	0.76 (-4.03, 5.55)	0.75
Model[1]	-3.71 (-7.57, 0.14)	0.06	-11.29 (-27.57, 4.99)	0.17	-5.85 (-15.22, 3.53)	0.22	-6.39 (-15.53, 2.74)	0.17	-4.75 (-12.19, 2.71)	0.21
Model[2]	-3.92 (-8.65, 0.82)	0.10	-8.80 (-30.09, -12.49)	0.41	-2.16 (-13.63, 9.31)	0.70	-7.02 (-18.36, 4.32)	0.22	-5.70 (-15.50, 4.10)	0.25

Table 6. Continued

	Taurine		LysoPC a C 18:0		LysoPC a C 18:1		LysoPC a C 18:2	
	b (95% CI)	**p-value**	**b (95% CI)**	**p-value**	**b (95% CI)**	**p-value**	**b (95% CI)**	**p-value**
Western type								
Unadjusted model	0.89 (-1.62, 3.39)	0.48	0.14 (-1.15, 1.43)	0.83	0.26 (-0.27, 0.83)	0.32	0.34 (-0.006, 0.69)	0.054
Model[1]	2.24 (-2.06, 6.54)	0.30	-0.66 (-1.59, 0.28)	0.17	-0.66 (-1.59, 0.28)	0.17	0.18 (-0.36, 0.73)	0.50
Model[2]	2.23 (-5.26, 9.72)	0.55	0.03 (-2.69, 2.75)	0.98	-0.81 (-1.85, 0.22)	0.12	-0.16 (-1.08, 0.76)	0.73
Healthy type								
Unadjusted model	1.19 (-1.90, 4.27)	0.45	0.78 (-0.81, 2.35)	0.34	0.83 (0.17, 1.49)	0.01*	0.25 (-0.18, 0.68)	0.26
Model[1]	-3.37 (-10.18, 3.44)	0.33	2.09 (-1.40, 5.59)	0.24	1.69 (0.25, 3.16)	0.03*	0.06 (-0.80, 0.92)	0.89
Model[2]	-0.48 (-12.04, 11.08)	0.93	1.88 (-2.31, 6.07)	0.37	2.48 (0.89, 4.08)	0.003**	0.49 (-0.93, 1.92)	0.49
MedDiet Score								
Unadjusted model	3.41 (-1.33, 8.15)	0.16	0.54 (-1.91, 2.99)	0.66	0.87 (-0.16, 1.91)	0.09	0.17 (-0.51, 0.84)	0.63
Model[1]	5.09 (-2.57, 12.75)	0.19	-0.99 (-4.93, 2.94)	0.24	-0.55 (-2.21, 1.12)	0.51	-0.17 (-0.79, 1.14)	0.73
Model[2]	7.53 (-2.97, 18.04)	0.16	1.29 (-5.09, 2.52)	0.49	-1.59(-3.05, -0.15)	0.03*	-0.39 (-1.69, 0.91)	0.54

CI: Confidence Interval, linear regression analysis of dietary patterns and GDM, Unadjusted model: Crude association between dietary patterns and Metabolomics, Model[1]: Adjusted for maternal age, maternal weight at 12th week of gestation, , maternal BMI before pregnancy, smoking at 30th week of gestation, maternal educational level, ($p \leq 0,01$); Model[2]: Adjusted for model[1]+ maternal weight before pregnancy, maternal BMI at 12th week of gestation, smoking at 12th, maternal educational level, any drug at 2st trimester, ($p \leq 0.05$);*$p<0.05$,**$p<0.01$

No association was observed between the three dietary patterns and the following metabolites: acetylcarnitine, glutamate, glycine, serine, creatinine, taurine and LysoPC a C18:0 (Table 6). Additionally, no association was observed between the MedDiet and alanine, isoleucine, valine, LysoPC a C18:1 and LysoPC a C18:2. The lack of the above associations remained even after adjusting for potential confounders.

The Western type diet demonstrates a negative association with isoleucine in an unadjusted model (1.59ppm reduction per SD increase in Western type diet score; 95% CI: -3.17, -0.007: p=0.049). This association became stronger after adjusting for confounding variables (3.78ppm reduction per SD increase in Western type diet score; 95% CI: -7.16, -0.04: p=0.03). Additionally, the Western type diet demonstrate a negative association with alanine and leucine after adjusting for confounding variables (16.38ppm and 18.02 reduction per SD increase in Western type score, respectively; 95% CI: -30.66, -2,11: p=0.03 and 95% CI: -33.2, -2.83: p=0.02, respectively). We found a negative association between Western type diet and valine after adjusting for confounding variables (5.62ppm reduction per SD increase in Western type diet score; 95% CI: -10.75, -0.49: p=0.032). This association became stronger after adjusting for cofounding variables in model^2 (12,14ppm reduction per SD increase in Western type diet score; 95% CI: -20.23, -4.06: p=0.004).
The Healthy type diet demonstrates a positive association with alanine and isoleucine after adjusting for confounding variables (24.53ppm and 5.89ppm increase per SD increase in Healthy type score, respectively; 95% CI: 2.5, -46.56: p=0.03 and 95% CI: 0.68, 11.01: p=0.03, respectively). It was found a positive association between Healthy type diet- leucine and Healthy type diet- valine after adjusting for confounding variables (14.84ppm and 8.88ppm increase per SD increase in Healthy type diet score, respectively; 95% CI: 0.36, 29.31: p=0.045 and 95% CI: 60.76, 17.01: p=0.03, respectively). This association became stronger after adjusting for cofounding variables in model^2 (29.21ppm and 19.39ppm increase per SD increase in Healthy type diet score, respectively; 95% CI: 5.77, 52.64: p=0.02 and 95% CI: 6.29, 31.87: p=0.003, respectively). A positive association was observed between the Healthy type diet and LysoPC a C18:1 in an undjusted model with a stronger association after adjusting for confounding variables (0.083ppm and 2.48ppm increase per SD increase in Healthy type diet score, respectively; 95% CI: 0.17, 1,49: p=0.01 and 95% CI: 0.89, 4.08: p=0.003, respectively).

The MedDiet demonstrates a negative association with LysoPC a C18:1 after adjusting for confounding variables (1.59ppm reduction per SD MedDiet score; 95% CI: -3.05, -0.15: p=0.03).

Table 7. Association between maternal metabolites and GDM

	GDM	
	OR (95% CI)	**p-value**
Acetylcarnitine		
Unadjusted model	0.88 (0.39, 1.97)	0.88
Model[1]	0.88 (0.39, 1.97)	0.76
Model[2]	0.71 (0.25, 1.99)	0.52
Alanine		
Unadjusted model	1.008 (0.99, 1.02)	0.24
Model[1]	1.008(0.99, 1.02)	0.22
Model[2]	1.02 (0.99, 1.04)	0.13
Glutamate		
Unadjusted model	1.006 (0.99, 1.020)	0.34
Model[1]	1.007 (0.99, 1.02)	0.29
Model[2]	1.02 (0.99, 1.04)	0.12
Glycine		
Unadjusted model	0.97 (0.94, 1.001)	0.06
Model[1]	0.97 (0.94, 1.000)	0.04*
Model[2]	0.95 (0.91, 0.99)	0.03*
Isoleucine		
Unadjusted model	0.94 (0.85, 1.05)	0.27
Model[1]	0.94 (0.85, 1.05)	0.26
Model[2]	0.92 (0.79, 1.08)	0.29
Leucine		
Unadjusted model	1.003 (0.99, 1.02)	0.66
Model[1]	1.002 (0.99, 1.02)	0.73
Model[2]	1.005 (0.99, 1.02)	0.62
Serine		
Unadjusted model	1.000 (0.97, 1.04)	0.98
Model[1]	1.001 (0.96, 1.04)	0.95
Model[2]	1.003 (0.96, 1.05)	0.91

Table 7. Continued

	GDM	
	OR (95% CI)	**p-value**
Valine		
Unadjusted model	1.04 (0.99, 1.1)	0.11
Model[1]	1.05 (0.99, 1.1)	0.09
Model[2]	1.05 (0.98, 1.13)	0.18
Creatinine		
Unadjusted model	0.99 (0.97, 1.01)	0.28
Model[1]	0.99 (0.97, 1.01)	0.66
Model[2]	0.99 (0.97, 1.02)	0.76
Taurine		
Unadjusted model	0.99 (0.97, 1.02)	0.67
Model[1]	0.99 (0.97, 1.02)	0.12
Model[2]	0.98 (0.95, 1.02)	0.34
LysoPC a C 18:0		
Unadjusted model	1.04 (0.99, 1.09)	0.17
Model[1]	1.04 (0.99, 1.09)	0.70
Model[2]	1.11 (1.01, 1.22)	0.03*
LysoPC a C 18:1		
Unadjusted model	0.99 (0.87, 1.12)	0.81
Model[1]	0.97 (0.85, 1.11)	0.29
Model[2]	0.82 (0.62, 1.06)	0.13
LysoPC a C18:2		
Unadjusted model	0.90 (0.77, 1.12)	0.34
Model[1]	0.89 (0.82, 1.11)	0.52
Model[2]	1.08 (0.84, 1.40)	0.55

CI: Confidence Interval, logistic regression analysis of maternal metabolites and GDM
Unadjusted model: Crude association between maternal metabolites and GDM,
Model[1]: Adjusted for maternal BMI at 12th week of gestation, ($p \leq 0.001$);
Model[2]: Adjusted for weight before and at 12th week of gestation, ($p \leq 0.05$); *$p < 0.05$

No association was observed between maternal metabolites and GDM status, except for glycine and LysoPC a C18:0 (Table 7). Specifically, in unadjusted model there was a trend towards higher levels of glycine being associated with a reduction in the risk of GDM (OR (95% CI) = 0.97 (0.94, 1.001) p=0.06). The association became stronger after adjusting for confounding variables in model[1] and model[2] (OR (95% CI) = 0.97 (0.94, 1.000) p=0.04), (OR (95% CI) = 0.95 (0.91, 0.99) p=0.03), respectively. Higher levels of LysoPCaC 18:0 were associated with a higher risk of GDM after adjusting for confounding variables in model[2] (OR (95% CI) = 1.11 (1.01, 1.22) p=0.03).

Table 8. Interaction of Glycine, LysoPC a C18:0 in the relation of maternal diet and GDM

	GDM	
	OR (95% CI)	**p-value**
Western type	0.99 (0.99, 1.000)	0.013
Healthy type	1.003 (1.00, 1.005)	0.036
MedDiet	0.99 (0.99, 1.000)	0.030

CI: Confidence Interval, logistic regression analysis of maternal metabolites and GDM

Higher compliance to Western type dietary pattern was associated with a reduction in the likelihood of GDM by the interaction of glycine and lysoPC a C18:0 (OR (95% CI) = 0.99 (0.99, 1.00) p=0.013). Higher compliance to Healthy type dietary pattern was associated with a higher likelihood of GDM by the interaction of glycine and lysoPC a C18:0 (OR (95% CI) = 1.003 (1.00, 1.005) p=0.036). Higher compliance to MedDiet was associated with a reduction in the likelihood of GDM by the interaction of glycine and lysoPC a C18:0 (OR (95% CI) = 0.99 (0.99, 1.00) p=0.030).

Discussion

In the current study no significant association was observed between the dietary patterns (Western type, Healthy type and MedDiet) and GDM, and EPDS score and GDM even after adjusting for potential confounders. Also, no association was observed between the three dietary patterns and the following metabolites, acetylcarnitine, glutamate, glycine, serine, creatinine, taurine and LysoPCaC18:0. Additionally, no association was observed between the MedDiet and alanine, isoleucine, valine, LysoPCaC18:1 and LysoPCaC18:2. Higher adherence to the Western type diet was associated with lower concentrations of isoleucine, alanine, leucine and valine. Additionally, higher adherence to the MedDiet was associated with lower concentration of LysoPCaC18:1. Higher adherence to the Healthy type diet demonstrates a positive association with alanine and isoleucine, leucine, valine, LysoPCaC18:1. Women with GDM had higher levels of glycine and lower levels of LysoPC a C18:0 compared to healthy pregnant women

Unlike prior research (Zareei et al., 2018; Schoenaker et al., 2015; Karamanos et al., 2013; Tobias et al., 2012) the present study found no significant association between the dietary patterns (Western type, Healthy type and MedDiet) and GDM, even after adjusting for potential confounders. Same results were reported by Mak et al. for Western and Healthy dietary pattern (Mak et al., 2018). Also, a case-control study conducted in Tehran reported a positive association between Western dietary pattern and risk of GDM, after adjustment for potential confounders but no significant association between healthy dietary pattern and risk of GDM. On the contrary, a large prospective cohort study reported a strong association between healthy dietary pattern and risk of GDM (Zhang et al., 2006).

Discrepancies between results of studies could be referring to differences in study design, sample size, food questionnaire, definition, and number of the food groups. Since dietary patterns reflect the culture, food preferences, and environmental factors (such as food availability), it can be expected that different dietary patterns are identified in different populations and time periods (Sedaghat et al., 2017).

No significant association was found between EPDS score and GDM, even after adjusting for potential confounders. Previous studies also support this finding (Katon et al., 2011; Mautner et al., 2009), including a prospective study conducted in Greek women reported the same results (Varela et al., 2017). Other studies found a significant association between antenatal depression and risk of GMD (Hinkle et al., 2016; Bowers et al., 2013; Backes Kozhimannil et al., 2009). There are several possible explanations for the results inconsistency among different studies. There are significant variations in the methodology and design of the studies, variability in sample size and methods of maternal depression assessment.

In this study no association was observed between the three dietary patterns and the following metabolites, acetylcarnitine, glutamate, glycine, serine, creatinine, taurine and LysoPCaC18:0. Additionally, no association was observed between the MedDiet and alanine, isoleucine, valine, LysoPCaC18:1 and LysoPCaC18:2. Higher adherence to the Western type diet was associated with lower concentrations of isoleucine, alanine, leucine and valine. Higher adherence to the MedDiet was associated with lower concentration of LysoPCaC18:1. Higher adherence to the Healthy type diet

demonstrates a positive association with alanine and isoleucine, leucine, valine, LysoPCaC18:1.

To our knowledge there are no previous studies about the effect of maternal dietary patterns on the metabolic profile of pregnant women. According to a randomised control trial a low glycaemic index diet was associated with higher concentrations of phospholipids (PL) and acylcarnitines (AC) in maternal blood of 25 women (Marchioro et al., 2019).

Women with GDM had higher levels of glycine and lower levels of LysoPC a C18:0 compared to healthy pregnant women. Inconsistent results were reported by 3 studies that analyzed urine samples collected after GDM diagnosis. Sachse et al. reported an increase in citrate (Sachse et al., 2012) while Lorenzo et al. in D-Phenylalanine (Lorenzo et al., 2015). Dudzik et al. found an increase in Phosphatidylethanolamines (38:6, 36:5), Phosphatidylcholines (38:1, 40:3), acetylcarnitine, linoleic acid, glycerol, 3- and 2-hydroxybutyrate and fumaric acid and a decrease in Glycerophospholipids (LPE with 16:0, 18:0, 18:2, 20:0, 20:1, 20:2, 22:4 and 22:6 chains), lysophosphatidylcholines (LPC with 16:0; 18:0, 18:1, 18:2, 18:3, 20:3, 20:4, 20:5 acyl chains), Lysophosphatidylinositol (LPI 20:4), Lysophosphatidylserine (LPS with 20:0), lysophosphatidic acid (LPA with 18:2), bile acids (trihydroxy-cholestanoyl taurine, taurolithocholic acid glucuronide), araquidonate and docosahexaenoic acid methyl esters, glycerophosphocholine, creatinine, pyruvic acid and amino acids (Dudzika et al., 2014).

According to literature, reduced glycine level in GDM may reflect on enhanced gluconeogenesis, glutathione synthesis or both (Sekhar et al., 2010). The higher levels of glycine observed in this study may be due to the small number of urine samples collected from pregnant women. Lysophosphatidylcholines (LPCs) have been found to induce glucose-induced insulin secretion from pancreatic β-cells (Ferrannini et al., 2012; Soga et al., 2005) and improve glycemia. in both normal and type 1 and 2 diabetic mice through an enhanced glucose uptake (Yea et al., 2009). Thus, the observed decrease of lysoglycerophospholipids in GDM may be associated with glucose intolerance through altered glucose metabolism and β-cell dysfunction.

The limitations of the current study included usage of food frequency questionnaire for collecting that nutritional data of the pregnant women. This questionnaire was completed based on the subjects' memory; this may have caused some error in reporting due to possible lack of understanding about the amount. Also, dietary intake was assessed at a single time point, even though the habitual diet of pregnant women may change over time. Urine metabolites were only measured in a small number of women at one occasion during pregnancy. Metabolomics data as a reflection of systemic metabolic processes, in general, need to be interpreted with caution as it may be influenced by phenotype and lifestyle factors. Finally, the study was only conducted on women living in Heraklion city and may limit the generalization of study results to the entire Iranian population.

Conclusion

Maternal dietary patterns (Western type, Heathy type and MedDiet) and maternal mental health were not associated with the risk of GDM development in the current study. A negative association was observed between the Western type diet and

isoleucine, alanine, leucine and valine. In addition, a negative association was observed between the MedDiet and LysoPC a C18:1. A positive association was observed between the Healthy type diet and alanine, isoleucine, leucine, valine and LysoPC a C18:1. Higher levels of glycine and LysoPCaC 18:0 were associated with a higher risk of GDM.

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