MATERNAL CARDIOMETABOLIC HEALTH AND FETAL DEVELOPMENT: INSIGHTS FROM PRENATAL TO POSTNATAL LIFE

Ehsan Motevalizadeh

UNIVERSITAT ROVIRA i VIRGILI

Maternal Cardiometabolic Health and Fetal Development: Insights from Prenatal to Postnatal Life

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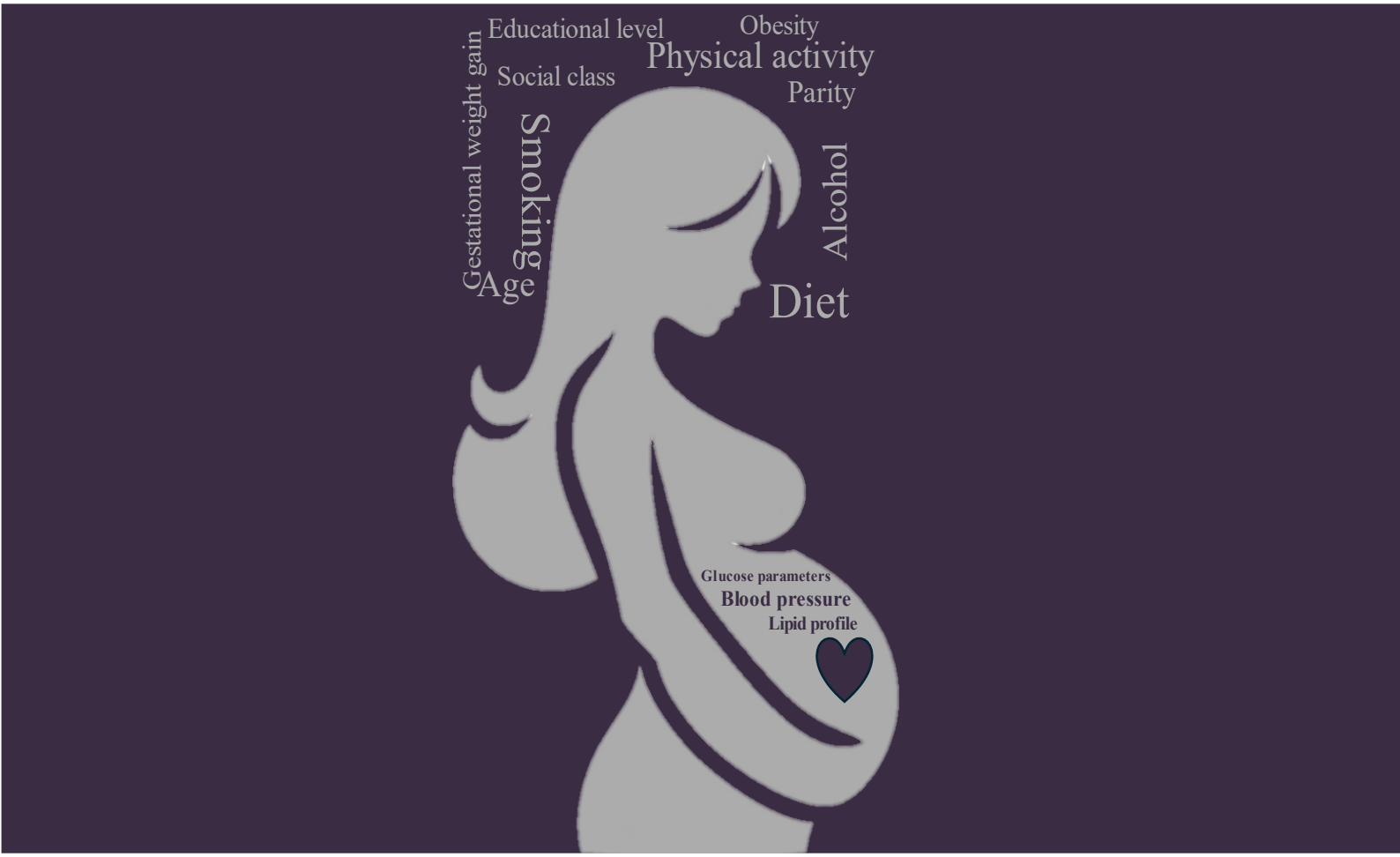

DOCTORAL THESIS

2024

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DOCTORAL THESIS

Thesis supervised by Dr. Victoria Arija Val,

and Dr. Andrés Díaz López

UNIVERSITAT ROVIRA i VIRGILI
Public Health and Nutritional Epidemiology Unit
Department of Basic Medical Sciences
Rovira i Virgili University
Reus, Tarragona
2024

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I STATE:
That the present study, entitled "**Maternal Cardiometabolic Health and Fetal Development: Insights from Prenatal to Postnatal Life**", presented by Mr. Ehsan Motevalizadeh for the award of the degree of Doctor, has been carried out under my supervision at the Department of Basic Medical Sciences of this university.

Reus, 28 th of June 2024

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To my cherished love and my family,

for

constant support,

encouragement,

endless love,

trust...

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I am profoundly fortunate to have such incredible parents and brothers who have imbued my life with boundless luck and joy. I pledge to reciprocate their trust and belief by striving to become a better son and brother.

ABBREVIATIONS

BMI	Body Mass Index
BP	Blood Pressure
CCR	Cluster Cardiometabolic Risk
CIs	Confidence Intervals
DBP	Diastolic Blood Pressure
DOHaD	Developmental Origins of Health and Disease
ECLIPSES	Ensayo CLInico Para Suplementar con hierro a EmbarazadaS
FFQ	Food Frequency Questionnaire
GDM	Gestational Diabetes Mellitus
GWG	Gestational Weight Gain
HC	Head Circumference
HDL-c	High-Density Lipoprotein-cholesterol
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
IPAQ-S	International Physical Activity Questionnaire-Short version
IQR	Inter Quartile Range
IR	Insulin Resistance
LDL-c	Low-Density Lipoprotein-cholesterol
LGA	Large-for-Gestational-Age
ORs	Odds Ratios
OWO	Overweight or Obesity
PA	Physical Activity
RBC folate	Red-blood-cell folate
rMED	relative Mediterranean Diet
RR	Relative Risk
SBP	Systolic Blood Pressure
SD	Standard Deviation
SES	Socioeconomic status
SGA	Small-for-Gestational-Age
SPSS	Statistical Package of Social Sciences
T1	First trimester
T3	Third trimester
TC	Total cholesterol
TG	Triglycerides
β	β coefficients

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ABSTRACT

English

Previous research on maternal lifestyle behaviors and cardiometabolic risk during pregnancy has predominantly focused on individual risk markers, as glucose and serum lipid concentrations, along with arterial blood pressure (BP) levels. However, few studies have examined a cluster cardiometabolic risk (CCR) score that integrates several factors. Additionally, there is a limited understanding of the relationship between parity and elevated early-pregnancy insulin resistance (IR), particularly regarding the influence of overweight and obesity on this association. Furthermore, the connections between maternal cardiometabolic markers and fetal growth remain poorly understood and warrant further investigation. This dissertation aims to explore the relationships between socio-demographic, lifestyle, and clinical factors and cardiometabolic risk markers during pregnancy. Additionally, evaluate the effect of variations in maternal cardiometabolic markers on infant size in a Mediterranean pregnant population. Glucose and serum lipid concentrations, along with arterial blood pressure (BP) levels, are recognized indicators of cardiometabolic risk.

The dissertation encompasses three pertinent articles, comprising prospective cohort studies, cross-sectional analyses, and longitudinal evaluations. Data collection entailed an extensive array of demographic, gynecological, anthropometric, lifestyle, dietary, and biochemical variables from a cohort of healthy pregnant women enrolled in the ECLIPSES study at 12 weeks of gestation during the first and third trimesters (T1 and T3). Statistical methodologies encompassed bivariate analyses, as well as multivariate-adjusted logistic and linear regressions models, aiming to elucidate the associations between prenatal maternal factors and maternal cardiometabolic markers, including glucose metabolism parameters, lipid profile, and BP during pregnancy, and the consequences of these changes in maternal cardiometabolic markers on fetal growth indicators such as birth weight and birth head circumference (HC).

The findings from the three articles in this dissertation collectively elucidate the intricate relationships between maternal health factors and pregnancy outcomes.

First-trimester CCR score exhibited a positive association with maternal overweight/obesity and a negative association with higher education levels and physical activity (PA). These relationships persisted into the T3, with overweight/obesity continuing

to influence CCR score. Conversely, insufficient Gestational Weight Gain (GWG) and higher social class were associated with lower CCR score.

The results of the next study showed that parity, as a clinical prenatal maternal factor, was shown to significantly affect IR, a key cardiometabolic marker associated with unfavorable perinatal outcomes. Higher parity was associated with increased insulin levels and a higher Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index. Multiparous women, compared to nulliparous women, exhibited a greater relative risk of elevated IR (>75th percentile), which was further exacerbated by concurrent overweight/obesity.

Finally, it was found that changes in maternal cardiometabolic markers significantly influenced neonatal outcomes. Elevated first-trimester Triglycerides (TG) levels were positively associated with increased birthweight, and higher Low-Density Lipoprotein-cholesterol (LDL-c) levels were linked to a greater likelihood of infants being Large-for-Gestational-Age (LGA). Conversely, elevated BP was inversely associated with birthweight and HC, with higher BP in the T3 increasing the risk of Small-for-Gestational-Age (SGA) outcomes.

The synthesis of findings highlights the critical role of commencing pregnancy at an optimal weight and socioeconomic status (SES) to mitigate cardiovascular risk among Catalan women. Parity exacerbates early-pregnancy IR, especially in overweight or obese mothers. Moreover, maternal cardiometabolic markers significantly influence neonatal size. Thus, implementing comprehensive prenatal care strategies that integrate lifestyle modifications and metabolic monitoring is imperative for achieving optimal maternal and neonatal outcomes.

Castellano

La investigación previa sobre los comportamientos de estilo de vida materno y el riesgo cardiometabólico durante el embarazo se ha centrado predominantemente en marcadores de riesgo individuales como las concentraciones de glucosa y lípidos séricos, junto con los niveles de presión arterial (PA). Sin embargo, pocos estudios han examinado un puntaje de riesgo cardiometabólico agrupado que integre varios factores. Además, existe una comprensión limitada de la relación entre la paridad y la resistencia a la insulina en las primeras etapas del embarazo, y particularmente en lo que respecta a la influencia del sobrepeso y la obesidad en esta asociación. Además, la asociación entre los marcadores cardiometabólicos maternos y el crecimiento fetal siguen siendo poco comprendida y merecen una mayor investigación. Esta tesis tiene como objetivo explorar las relaciones entre los factores sociodemográficos, de estilo de vida y clínicos, y los marcadores de riesgo cardiometabólico durante el embarazo. Además, evaluar el efecto de las variaciones en los marcadores cardiometabólicos maternos sobre el tamaño del recién nacido en una población de embarazadas mediterráneas.

La tesis abarca tres trabajos originales de investigación, que comprenden estudios de cohortes prospectivos, análisis transversales y evaluaciones longitudinales. La recolección de datos incluyó una amplia gama de variables demográficas, ginecológicas, antropométricas, de estilo de vida, dietéticas y bioquímicas de una cohorte de mujeres embarazadas saludables inscritas en el estudio ECLIPSES a las 12 semanas de gestación durante el primer y el tercer trimestre. Las metodologías estadísticas incluyeron análisis bivariados, así como modelos ajustados de regresiones logísticas y lineales multivariados, con el objetivo de elucidar las asociaciones independientes entre factores maternos prenatales y marcadores cardiometabólicos maternos, incluidos parámetros del metabolismo glucosa, perfil lipídico y PA durante el embarazo, y las consecuencias de estos cambios en los marcadores cardiometabólicos maternos sobre indicadores de crecimiento como el peso y la circunferencia de la cabeza del recién nacido.

Los hallazgos de los tres artículos en esta disertación dilucidan colectivamente las complejas relaciones entre los factores de salud materna y los resultados del embarazo.

La puntuación de CCR en el primer trimestre mostró una asociación positiva con el sobrepeso/obesidad materna y una asociación negativa con el nivel de educación más alto y

la actividad física. Estas relaciones persistieron en el tercer trimestre, con el sobrepeso/obesidad siendo el mayor contribuyente al riesgo cardiometabólico materno. Por el contrario, una ganancia de peso gestacional insuficiente y una clase social más alta se asociaron con puntuaciones en el CCR más bajas.

Los resultados del siguiente estudio mostraron que la paridad, como un factor clínico prenatal materno, afectó significativamente la IR, un marcador cardiometabólico clave asociado con resultados perinatales desfavorables. Una mayor paridad se asoció con niveles elevados de insulina y un índice HOMA-IR más alto. Las mujeres multíparas, en comparación con las nulíparas, exhibieron un mayor riesgo relativo de IR elevada (>pecentil 75), el cual se exacerbó aún más por el sobrepeso/obesidad concurrente.

Finalmente, se encontró que los cambios en los marcadores cardiometabólicos maternos influyeron significativamente en los resultados del neonato al nacer. Los niveles elevados de TG en el primer trimestre se asociaron positivamente con un mayor peso al nacer, y los niveles más altos de colesterol LDL (LDL-c) se vincularon con una mayor probabilidad de que los neonatos fueran grandes para la edad gestacional (LGA). Por el contrario, la PA elevada se asoció inversamente con el peso al nacer y la circunferencia de la cabeza (HC), con una PA más alta en el tercer trimestre, aumentando también el riesgo de pequeño para la edad gestacional (SGA).

La síntesis de los hallazgos destaca el papel crítico de comenzar el embarazo con un peso y un estatus socioeconómico óptimos para mitigar el riesgo cardiovascular entre las mujeres catalanas. La paridad exacerba la IR en las primeras etapas del embarazo, especialmente en madres con sobrepeso u obesidad. Asimismo, los marcadores cardiometabólicos maternos influyen significativamente en el tamaño del neonato. Por lo tanto, es imperativo implementar estrategias integrales de atención prenatal que integren modificaciones en el estilo de vida y la monitorización metabólica para lograr resultados óptimos tanto maternos como neonatales.

Català

La investigació existent fins al moment sobre els comportaments relacionats amb l'estil de vida de la mare i el risc cardiometabòlic durant l'embaràs s'ha centrat principalment en marcadors de risc individuals com la concentració de glucosa, de lípids sèrics o els nivells de pressió arterial (PA). Pocs estudis han examinat una puntuació de risc cardiometabòlic agrupada (CCR) que integri diferents factors. No obstant això, hi ha una comprensió limitada de la relació entre la paritat i la resistència a la insulina (IR) en les primeres etapes de l'embaràs, especialment pel que fa a la influència del sobrepès i l'obesitat en aquesta associació. A més a més, l'associació entre els marcadors cardiometabòlics materns i el creixement fetal continua sent poc compresa i requereix una investigació més profunda. Aquesta tesi té com a objectiu explorar les relacions entre els factors sociodemogràfics, d'estil de vida i clínics, i els marcadors de risc cardiometabòlic durant l'embaràs, i addicionalment, avaluar l'efecte de les variacions en els marcadors cardiometabòlics materns sobre la mida del nounat en una població de dones embarassades mediterrànies.

La tesi inclou tres treballs originals de recerca que comprenen estudis de cohort prospectius, anàlisis transversals i avaluacions longitudinals. Les dades recol·lectades inclouen una àmplia gamma de variables demogràfiques, ginecològiques, antropomètriques, d'estil de vida, dietètiques i bioquímiques d'una cohort de dones embarassades sanes inscrites a l'estudi ECLIPSES a les 12 setmanes de gestació durant el primer i el tercer trimestre. La metodologia estadística va incloure anàlisis bivariants, així com models ajustats de regressions logístiques i lineals multivariants amb l'objectiu d'esclarir les associacions independents entre els factors materns prenatals i els marcadors cardiometabòlics materns, incloent paràmetres del metabolisme de la glucosa, perfil lipídic i PA durant l'embaràs, i les conseqüències d'aquests canvis en els marcadors cardiometabòlics sobre indicadors de creixement com el pes i el perímetre cranial del nounat.

Les troballes d'aquests tres articles posen de manifest la complexa relació existent entre els factors de salut materna i els resultats de l'embaràs.

La puntuació CCR en el primer trimestre va mostrar una associació positiva amb el sobrepès/obesitat matern i una associació negativa amb el nivell educatiu més alts i l'activitat física. Aquestes relacions van persistir al tercer trimestre, sent el sobrepès/obesitat el major

contribuent de risc cardiometabòlic matern. Per altra banda, un guany insuficient de pes gestacional i un nivell social més elevat es van associar amb puntuacions CCR més baixes.

Els resultats de l'estudi següent van mostrar que la paritat, com a factor matern prenatal clínic, va afectar significativament la IR, un marcador cardiometabòlic clau relacionat amb resultats perinatals desfavorables. Una paritat més elevada es va associar amb nivells d'insulina i un índex HOMA-IR més elevats. Les dones multipares, en comparació amb les nulíparas, van presentar major risc relatiu (RR) de IR elevada (>percentil 75), el qual es va veure agreujat per l'obesitat/sobrepès concurrent.

Finalment, es va trobar que els canvis en els marcadors cardiometabòlics materns influïren significativament en els resultats del nadó al nèixer. Els nivells elevats de triglicèrids (TG) del primer trimestre es van associar positivament amb un major pes al néixer, i els nivells més alts de colesterol LDL es van relacionar amb una major probabilitat que els nadons fossin grans per a l'edat gestacional. Tanmateix, la PA elevada es va associar inversament amb el pes al néixer i el perímetre cranial, amb una PA més elevada en el tercer trimestre, augmentant també el risc de nounats petits per a l'edat gestacional.

La síntesi de les troballes destaca el fet d'iniciar l'embaràs amb un pes i un nivell socioeconòmic òptims pot reduir el risc cardiovascular en les dones catalanes. La paritat augmenta la IR en les primeres etapes de l'embaràs, especialment en mares amb sobrepès o obesitat. Tanmateix, els marcadors cardiometabòlics materns influeixen significativament en la mida del nadó. Així doncs, implementar estratègies d'atenció prenatal que integrin modificacions en l'estil de vida i monitorització metabòlica és necessari per aconseguir resultats òptims tant per a la mare com per al nounat.

LIST OF FIGURES

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Introduction

This section provides summarized evidence on the physiological and metabolic changes observed during typical pregnancies, focusing on maternal health implications. It covers variations in body weight, gestational weight gain (GWG), cardiovascular markers (such as glucose and lipid metabolism and Blood pressure (BP)), and explores how sociodemographic factors, lifestyle choices (diet, physical activity (PA), smoking), and clinical characteristics (like obesity and GWG) influence metabolic alterations during pregnancy. Furthermore, it discusses the developmental origins of health and disease (DOHaD) theory and the importance of birth size measurements as indicators of fetal growth and long-term health outcomes. This comprehensive overview sets the context for understanding the complexities of maternal and fetal health during pregnancy. Finally, this section concludes with the research justification.

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INTRODUCTION

Pregnancy is a natural state involving multiple changes in the body systems of women, including metabolic, biochemical, physiological, hematological, and immunological alterations. In most women, these changes occur in normal conditions without any complications during pregnancy, returning to their non-pregnant state after delivery [1], with minimal residual effects. In certain circumstances, however, these changes may unmask or worsen a pre-existing condition or disease.

Pregnancy represents a continual and evolving anabolic process characterized by heightened metabolic demands. This physiological state necessitates increased nutritional intake to achieve two primary objectives: first, to sustain a consistent provision of essential metabolites critical for fetal growth and development, and second, to furnish the mother with adequate energy reserves and altered substrate requirements to accommodate the escalating physiological demands throughout pregnancy, labor, and lactation stages [2,3].

Overall, pregnancy is a pivotal and delicate phase in a woman's life, wherein her nutritional status, obstetric conditions, and lifestyle choices profoundly influence cardiometabolic changes, carrying substantial health implications for both mother and newborn in the short and long term. Nevertheless, our comprehension of the intricate metabolic adaptations during gestation remains incomplete, warranting further investigation. These adaptations vary depending on factors such as lifestyle behaviors, genetic characteristics, dietary intake, supplement use, and pre-pregnancy nutritional status [2].

1. Maternal physiological/metabolic changes during normal pregnancies

Physiology pregnancy

During pregnancy, extensive physiological adjustments occur across various organ systems to meet the demands of gestation and fetal development [4]. These adaptations involve the cardiovascular, respiratory, renal, digestive, and hematologic systems. Key changes include increased plasma volume, weight gain, and alterations in fat distribution, primarily affecting cardiovascular, renal, and digestive functions. The expanded plasma volume and weight gain necessitate modifications in cardiac output and vascular resistance to satisfy the metabolic requirements of both the mother and the developing fetus [5].

Additionally, placental function and fetal gender introduce complexity to these adaptations, potentially influencing maternal physiological responses. A critical aspect of pregnancy physiology involves the establishment of the maternal-fetal circulation interface, which facilitates the transfer of bioactive molecules such as steroid hormones, micronutrients, and nucleic acids between the maternal and fetal systems. The levels of these substances fluctuate throughout pregnancy, and disruptions can contribute to conditions like hypertension and gestational diabetes, posing significant health risks to the mother [6–8].

Moreover, pregnancy induces notable metabolic changes that affect nutrient utilization and energy expenditure, underscoring the dynamic interplay between maternal physiology and fetal development. The prominent maternal physiological changes that occur during a normal versus a complicated pregnancy are summarized in **Figure 1**.

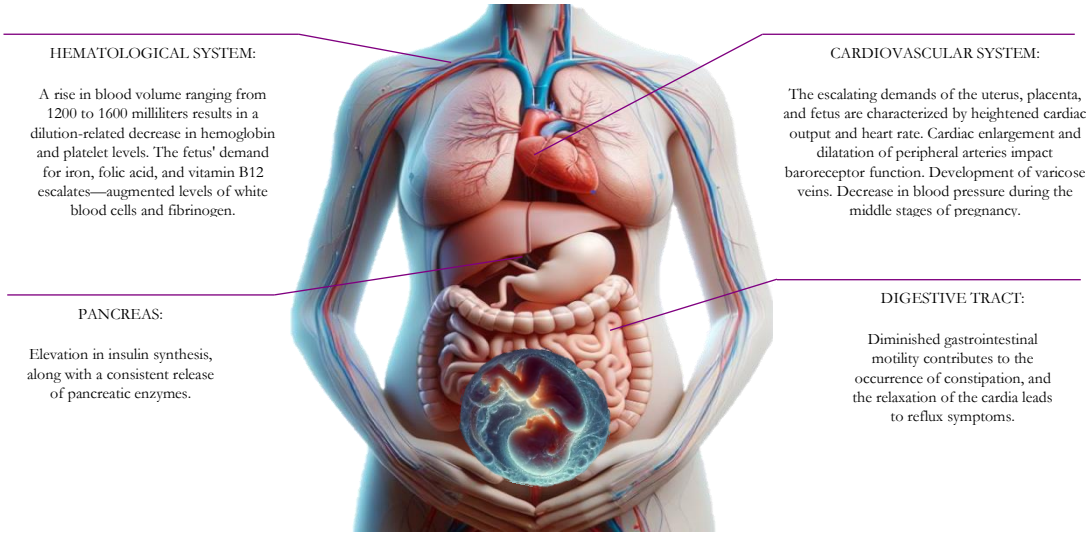

Figure 1. Some maternal adaptations physiological during a normal pregnancy. Adopted and modified from (Vinnars et al., 2023 [9]).

Pregnancy metabolism

The term "metabolism" refers to the chemical transformations occurring within living cells, encompassing anabolism (the synthesis of complex substances from simpler ones) and catabolism (the breakdown of complex substances into simpler molecules) [10].

During pregnancy, which is a critical period for human growth, there is a need for synchronization between the mother and the developing fetus. The mother's metabolism

undergoes significant adaptations to support the energy-demanding process of fetal growth and development [11,12]. From a metabolic perspective, pregnancy can be divided into two distinct phases. In the initial phase, characterized by the first two-thirds of pregnancy, developmental factors and hormones promote fat storage in the mother's body, ensuring the availability of nutrients for later fetal growth. This anabolic phase allows the mother to accumulate the necessary nutrients and fat reserves critical for sustaining fetal energy demands as pregnancy progresses [12–14].

As pregnancy advances into the later stages, the fetus grows substantially, leading to increased transport of fat molecules and heightened lipolytic activity. This results in elevated concentrations of glucose and fatty acids in the mother's bloodstream. The mother's metabolism shifts towards a catabolic state to meet the fetus's increased nutritional needs. Anabolic-to-catabolic transitions in lipid metabolism prioritize lipids as the primary energy source for the mother while maintaining sufficient glucose levels for fetal development, particularly evident in adipose tissue lipolysis [14–16].

These metabolic changes represent normal physiological responses crucial for supporting fetal growth and development during pregnancy [17]. A successful pregnancy relies on the mother's ability to provide adequate energy and nutrients, necessitating precise metabolic adjustments [18]. Effective metabolic regulation is essential throughout pregnancy to ensure optimal outcomes [19]. Dysregulation of metabolism can lead to complications such as high Blood Pressure (BP), gestational diabetes, and premature birth, underscoring the critical importance of metabolic homeostasis during pregnancy for maternal and fetal health [17,20]. **Figure 2** shows the overall overview of metabolic adaptations during pregnancy.

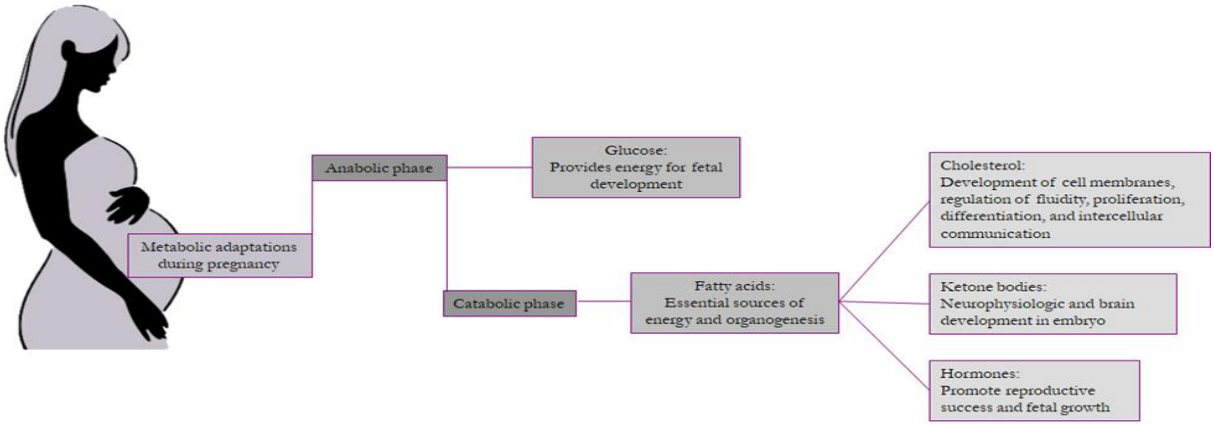

Figure 2. Maternal metabolic adaptations during a normal pregnancy. Adopted and modified from (Zhandong Zeng et al., 2017 [21]).

1.1. Changes in the body weight and Gestational Weight Gain

One of the important aspects of pregnancy that is influenced by changes in the physiology and metabolism of the mother and fetus is weight gain [2]. Pregnancy brings with it several metabolic changes that alter the mother's energy needs. These needs increase by an average of 85 kcal per day, 285 kcal per day, and 475 kcal per day throughout the first, second, and third trimesters, respectively [22]. The expansion of maternal tissues (such as increased blood volume and extracellular fluid, uterine and mammary gland enlargement, and increased adipose tissue) and fertilization products (such as the fetus, amniotic fluid, and placenta) are the two main causes of pregnancy-related weight gain [2].

Pregnancy causes women to naturally acquire weight. This weight gain follows a trend. The average weekly weight gain during the first trimester is often less than 0.18 kg, but as the pregnancy progresses into the middle stage, it climbs dramatically. So, in the second trimester, it increases by 0.54 kg per week, and in the third, it decreases to 0.49 kg per week [23] (**Figure 3**). These changes cause weight gain in the following trimesters to be correlated with the weight of the fetus, amniotic fluid, and maternal fat reserves, whereas in the first trimester, weight gain is mostly linked to fat storage [24]. Typically, this weight increase pattern follows a sigmoid curve, meaning that only around 5% of the total weight gain happens during the first trimester and the remaining 95% is acquired gradually over subsequent periods [2].

However, so far, the ideal pattern for gaining weight during pregnancy has not yet been established. The United States Institute of Medicine (IOM) set standards for weight increase in women with varying body mass index (BMI) in 1990 after concluding that one of the most significant determinants of fetal growth is prenatal weight gain [25]. According to these recommendations, pre-pregnancy weight-normal women should gain between 11.5 and 16 kg, overweight women between 7 and 11.5 kg, and obese women between 5 and 9 kg [26] (**Figure 3**). The fact that many pregnant women gain weight outside of these ranges raises worries regarding the long-term effects on the unborn child, and evidence suggests that this trend is increasing [26,27].

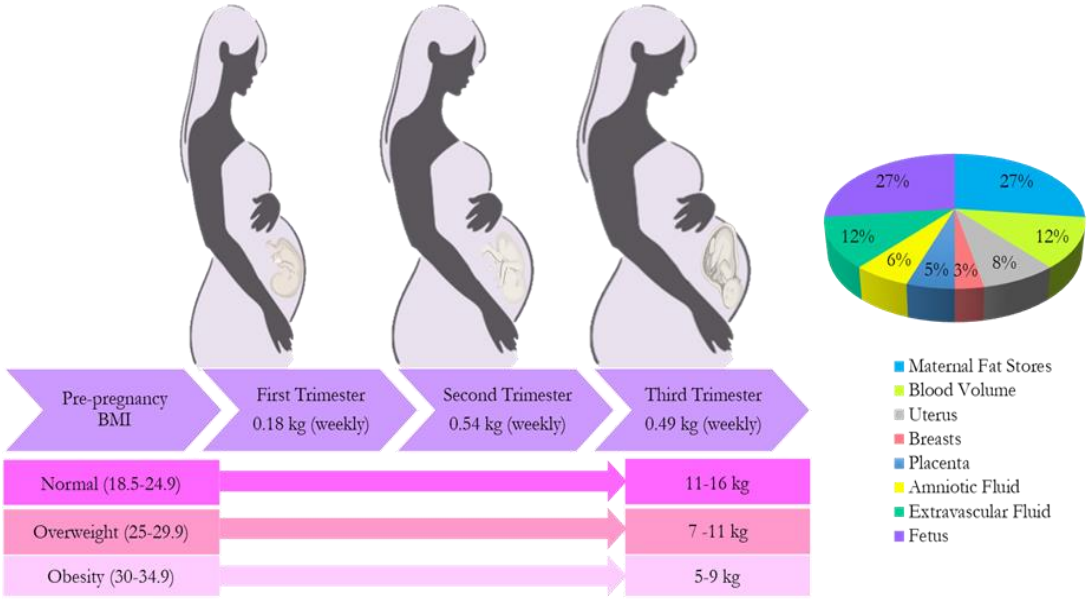

Figure 3. Maternal weight gain is based on pregnancy-related components during a normal pregnancy. Adopted and modified from (Champion et al., 2020 [28]; Thaller et al., 2022 [29]).

1.2. Changes in cardiovascular markers

1.2.1. Glucose parameters metabolism

During pregnancy, significant changes occur in glucose metabolism parameters, including glucose, insulin, and insulin resistance (IR) (**Figure 4**). Initially, pregnancy induces an increase in insulin sensitivity, facilitating greater glucose absorption and utilization to meet fetal demands. As pregnancy progresses, hormonal shifts such as elevated levels of human placental lactogen, progesterone, cortisol, and prolactin contribute to reduced insulin sensitivity in peripheral tissues [30]. This decrease in sensitivity is further exacerbated by alterations in inflammatory mediators and cytokines [31]. To counterbalance reduced insulin sensitivity, pancreatic beta cells enhance insulin secretion and increase beta cell mass [32,33]. As gestation advances into the second trimester, the secretion of diabetogenic hormones (human placental lactogen, growth hormone, progesterone, cortisol, and prolactin) intensifies, potentially elevating the risk of gestational diabetes [34]. Insulin levels gradually rise through the third trimester, peaking around 32 weeks, correlating with an increased body fat percentage [35]. These adaptations are pivotal for maintaining glucose homeostasis and supplying sufficient nutrients to support fetal growth and development. The gradual rise in IR during pregnancy is a normal physiological response to ensure adequate energy provision

for fetal growth, altering maternal glucose absorption and utilization accordingly. In later pregnancy, metabolic changes transition towards a catabolic state, characterized by elevated levels of free fatty acids, reduced maternal adipose tissue storage, increased IR, enhanced lipolysis, and heightened hepatic glucose synthesis. Notably, insulin-mediated peripheral glucose disposal decreases to prioritize glucose transfer to the fetus. Following delivery and placental expulsion, glucose homeostasis swiftly normalizes, suggesting the placenta's crucial role in gestational IR development and resolution. These intricate hormonal and metabolic adjustments ensure optimal maternal-fetal nutrient exchange and support fetal growth and development throughout pregnancy [36,37].

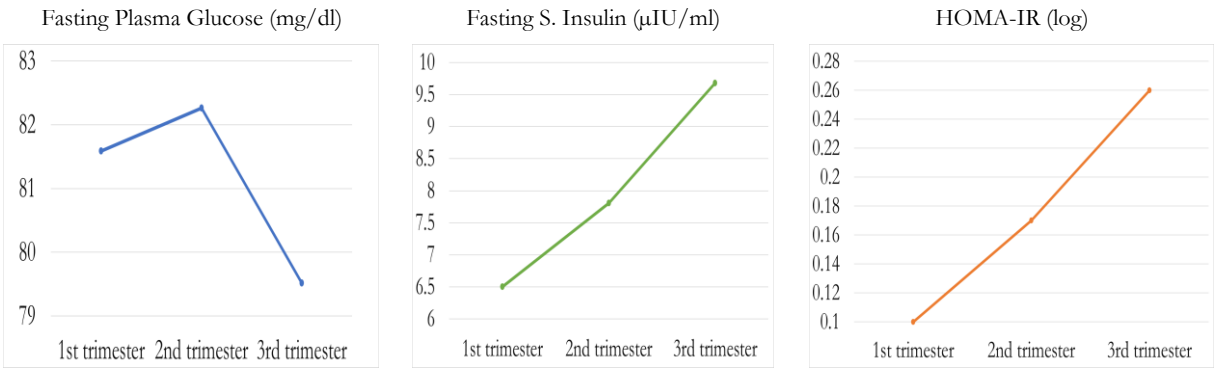

Figure 4. Trajectory of maternal fasting plasma glucose parameters in a normal pregnancy. Adopted and modified from (Sonagra, Amit D. et al., 2014 [38]).

1.2.2. Lipid profile metabolism

Although alterations in glucose metabolism are often considered the primary metabolic adaptations during pregnancy, significant alterations occur in lipid metabolism as well, particularly during this period. The "anabolic phase" of pregnancy, when the mother's metabolism alters to assist the fetus's growth and development. These alterations include elevated levels of progesterone, insulin, and estrogen, which promote fat accumulation and prevent lipolysis in maternal tissues. The levels of plasma lipids fall as a result of increased fatty acid production and increased lipoprotein lipase (LPL) activity, which aid in TG absorption inside cells [39]. In the following, from the tenth week of pregnancy until the second trimester, there is an increase in lipid activity in the blood [40]. During this time, TG cholesterol, and other lipoproteins begin to rise after initially falling [16,41–43]. These increases occur gradually

throughout the pregnancy and finally reverse to some extent after birth. TG and lipoproteins that transport fat are also elevated in the mother's blood as a result of de novo lipogenesis and elevated LPL activity in adipose tissue. These alterations happen along with the increase in fat accumulation in the mother's stores and the increase in the mother's hyperphagia, and their main effects go back to the first two-thirds of pregnancy [21,44] (**Figure 5**).

Anabolic processes, such as elevated progesterone and growth hormone levels, persist during the second trimester of pregnancy and heighten the mother's appetite, promoting the accumulation of body fat. This stage is associated with an increase in body weight and an increase in lipid activity levels in the blood [15,16]. While some lipoprotein types, such as high-density lipoprotein, rise initially and then progressively fall by the end of the term, they nevertheless average 15% higher than levels seen in non-pregnant women [34]. During this period, the lipolytic activity of fat tissue increases, which leads to the catabolic process, that is, the breakdown of fat substances. Increasing hormone-sensitive lipases while decreasing LPL enzyme activity increases fat breakdown and triglyceride levels in the circulation. Moreover, increased internal use of glycerol leads to the accumulation of TG in maternal tissues through glycerol-3-phosphate production [21]. At this point, the maternal system experiences net lipolysis and increased glycerol turnover, which are related to IR and reflect physiological changes in the mother to support fetal development [45]. A gradual increase in insulin, as well as an increase in progesterone and cortisol, increases the anabolic storage of lipids [46]. Although triglyceride levels are higher than they were previously, no atherogenic alterations are present. Changes in the concentrations of TG, fatty acids, cholesterol, lipoproteins, and phospholipids persist, and High-Density Lipoprotein-cholesterol (HDL-c) increases in response to estrogen and remains elevated throughout pregnancy. Decreased LPL activity in the adipose and liver, along with increased activity in the placenta, also affects very low-density lipoprotein (VLDL) clearance [16]. Hormonal levels and breastfeeding may impact the ongoing rise in TG, cholesterol, and lipoproteins [47–49]. At this point, the rise in fat tissue mass is halted, and the production of fatty acids in fat tissue is reduced. Furthermore, LPL activity is low and does not contribute to the conversion of circulating TAGs into maternal adipose tissue [50]. These alterations, together with an increase in adipose tissue lipolytic activity, result in reduced fat deposition in the mother's reserves [51,52]. Overall, during this period, anabolic effects decrease and catabolism increases.

During the third month of pregnancy, known as the catabolic phase, metabolic changes take place to meet the energy needs of the mother and fetus. At this time, the mother's high level of IR forces her to use lipids as her main energy source while saving glucose and amino acids for the developing fetus [16,53]. Reduced lipoprotein lipase activity causes an increase in plasma lipid activity, particularly TG, thereby increasing maternal lipid activity [54]. These modifications fulfill the energy requirements of both the mother and the fetus. Also, higher Low-Density Lipoprotein-cholesterol (LDL-c) is important for the synthesis of placental steroids [34].

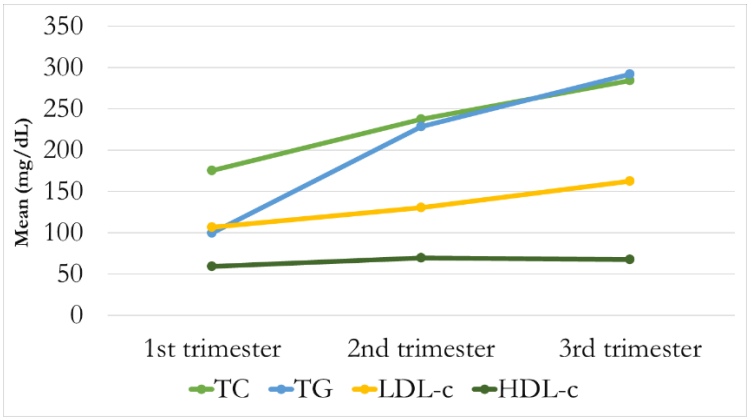

Figure 5. Trajectory of maternal plasma lipid profile in a normal pregnancy. Adopted and modified from (Abbassi-Ghanavati. et al., 2009 [55]).

1.2.3. Blood pressure levels

The maternal cardiovascular system undergoes progressive adaptations throughout pregnancy. Arterial BP, or more accurately, vascular pressure, represents the ability of the cardiovascular system to diversify the mother's organs and the fetal-placental unit, which is based on a product of two factors, namely cardiac function and systemic vascular resistance [56]. In simpler terms, BP equals the volume of blood that the vein receives. The Systolic Blood Pressure (SBP) is defined as the highest pressure in the arterial walls during cardiac contraction, while the Diastolic Blood Pressure (DBP) shows the lowest pressure on the walls of the arterial at rest. The average pressure throughout the heart cycle is the same as the average pressure in the arteries. Also, pulse pressure is the difference between SBP and DBP, which indicates heart performance and vascular resistance [57]. Hormonal changes

during pregnancy lead to significant changes in the intravenous physiology of the mother's heart, which include increased estrogen, progesterone, and relixin (a hormone that, like progesterone, mediates the release of nitric oxide) [58–61], which causes vascular expansion, and at the same time, strengthens the renine-angiotensin-aldosterone (RAAS) system for salt and water retention, resulting in an increase in plasma volume [62]**.** During the first trimester of pregnancy, a woman's heart rate increases, and changes in circulatory system resistance occur, leading to a drop in BP. However, as the pregnancy progresses, BP gradually rises and eventually returns to normal after childbirth [31,61] (**Figure 6**).

There is a continuum of risk associated with changes in BP throughout gestation [63,64]. These changes are mainly due to natural physiological adjustments during pregnancy, which indicate the body's adaptation to the different conditions of this period. Overall, in healthy pregnant women, arterial BP decreases gradually in the first three months of pregnancy. The decrease in BP reaches a nadir by midpregnancy, about 22–24 weeks, when the BP starts a gradual increase, returning to or exceeding pre-pregnancy levels by term [65]. Women who do not present this drop in BP in the middle of the gestational period may have an early indication of hypertensive disorders [66]. Moreover, evidence indicates that even a slightly elevated maternal BP level, that is, pre-hypertension (120–140/80–90 mmHg), confers a risk of gestational and postpartum complications [67–69], indicating this as an important measure for prenatal care [70]. In this regard, it has been suggested that DBP is often found to be a stable marker of BP during pregnancy and to determine health outcomes [71].

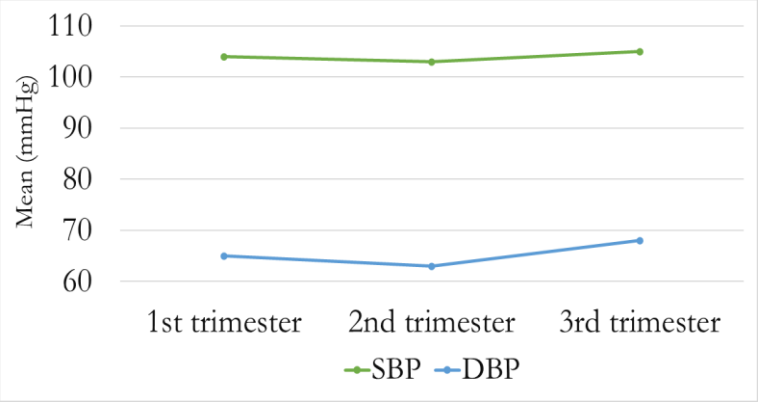

Figure 6. Longitudinal changes in maternal blood pressure in a normal pregnancy. Adopted and modified from (Mahendru, Amita A. et al., 2014 [72]).

2. Prenatal factors influencing the maternal cardiometabolic risk markers during pregnancy

"Cardiometabolic" is the term commonly used in epidemiology to refer to cardiovascular and metabolic risk factors collectively [73]. In the pregnant population, higher pre-pregnancy BMI (i.e., overweight/obesity), excessive GWG, pregnancy high TG, low HDL-c, hyperglycemia, IR, and raised BP are commonly recognized as cardiometabolic risk factors that aggregate to increase the risk of adverse obstetric outcomes [74,75]. Thus, cardiometabolic health is determined by assessing these parameters, whose changes in metabolism during a normal pregnancy have been discussed in previous sections of this dissertation.

In this context, it's important to emphasize that the maternal cardiometabolic state during pregnancy plays a significant role in modulating serious complications that affect the health of both the mother and child. In turn, maternal sociodemographic, lifestyle, and clinical characteristics may potentially contribute to the etiology of cardiometabolic disorders during gestation (**Figure 7**). This section discusses several maternal sociodemographic and lifestyle-related factors examined in this dissertation, which are linked to the components of cardiometabolic risk in pregnant women.

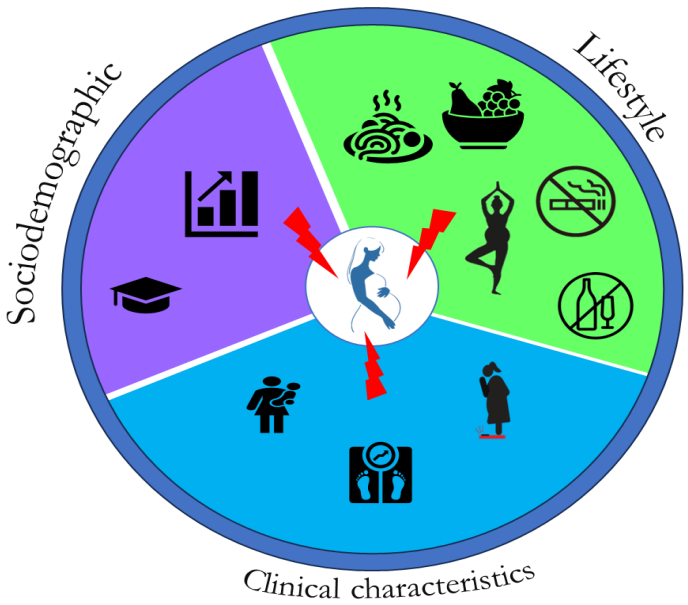

Figure 7. Summary of prenatal factors influencing cardiometabolic risk markers during pregnancy.

2.1. Sociodemographic factors

Social class

Health today is seen as a wider and more complex issue, and health-defining social factors are recognized as one of the most challenging and complex topics in health policy [76]. These factors include social, economic, and political factors, culture, social system functioning, and structural factors such as education, income, gender, ethnicity, and employment status [77]. Socioeconomic status (SES) refers to the economic and social factors that determine the position of an individual or group in society. SES is considered one of the key factors in determining health disparities that indicate preventable differences in the burden of illness or opportunities for desired health [78–80].

Most research on low SES impact and maternal cardiometabolic traits during pregnancy has used indicators such as average household income, education level, occupation, and marital status as representatives of SES [81–83]. Overall, studies show that in high-income countries, pregnancy outcomes (preterm birth, mode of delivery, perinatal and maternal mortality, and birth weight) are more unfavorable for women living in deprived communities [84–86].

However, there is some controversial data regarding how the SES affects early pregnancy overweight/obesity status and excessive GWG, which are among the strongest predictors of cardiometabolic risk (e.g., high BP, adiposity, glycemia, and dyslipidemia) during pregnancy, both in early and late stages. While some studies confirm meaningful relationships between these factors [87,88], others have not seen this link in their findings [89]. These differences may be due to the influence of SES factors on behavioral, social, and biological factors [76], as in addition to SES conditions, biological, metabolic, and psychological factors have been identified as determining factors for GWG in pregnancy [90]. Additional studies, however, have found a relationship between low SES and an increased risk of Gestational Diabetes Mellitus (GDM) [83,91–95]. Although some data suggests that it loses statistical significance after accounting for possible confounders [96]. Also, SES can affect the lipid profile of the mother, and it should be noted that few studies have been done in this regard. While most studies have focused on ethnic differences as an indicator of SES [97–101], the results of one study that considered other factors, including net income, showed that high SES was generally associated with higher concentrations of HDL-c in maternal serum

[102]. In this context, because of the inconsistent results of earlier research, the association between SES variables and changes in BP during pregnancy is still unclear. Some research has demonstrated that SES characteristics, such as low income and receiving government medical aid, increase the chance of developing preeclampsia [103–106], whereas other studies have found no evidence linking SES factors to preeclampsia or other blood pressure issues during pregnancy [107–109]. Thus, it may be possible to state that a higher SES leads to better outcomes during pregnancy.

Educational level

Mother education level, as a multidimensional variable, has an impact on mother and children's health and well-being via social and biological mechanisms [110]. However, equitable access to educational opportunities is not available in all communities; hence, the influence of education on cardiometabolic health in pregnant women varies by community [111–113]. Furthermore, research has indicated that educational levels are associated with other maternal lifestyle factors such as maternal nutrition, smoking, and body weight status, all of which have an impact on maternal and children's health outcomes [114].

The research has shown that when the mother's level of education is considered as one of the SES factors, different results are achieved. Some studies have shown that being overweight during pregnancy is significantly linked to lower educational levels [89,111], while others have suggested that there is no meaningful relationship [112], and it has even been observed that people with higher educational levels may gain more weight [113]. At the same time, some researchers have shown that a low education level is considered a risk factor for the occurrence of GDM [83,91,115], but not all [116]. It has also been found that the likelihood of developing preeclampsia and pregnancy hypertension is higher in women with a lower education level [96,117,118]. Although it is noteworthy that this relationship decreased after control of the pre-pregnancy BMI [119].

Age

Over the past few decades, there has been a global trend toward conception at an advanced age, particularly in wealthy nations, which has increased the average age of mothers [120]. This pattern is also seen in nations throughout Europe. For instance, the average life expectancy at birth in Spain went from 76 years in 1978 to 85.7 years in 2017, and as a result,

the average age at which a woman becomes pregnant likewise climbed from 26 to 32 years [121–123]. The emphasis on jobs and education is one of the main reasons why people are delaying starting a family. Advancements in preventative and reproductive technology, including egg donation, as well as cultural, societal, and economic shifts, have also influenced this phenomenon [124–127]. In general, advanced maternal age (AMA) is defined as women above the age of 35, while other research utilizes an older age range [120,124,126].

Many unfavorable pregnancy outcomes are linked to AMA [122]. Fetal growth at this time depends on the appropriate transfer of nutrients, particularly glucose, from the mother to the fetus across the placenta. Even after adjusting for other confounding factors, women with AMA often have higher fasting glucose levels [128]. It is also possible to argue that age-related IR and beta-cell malfunction are the causes of GDM in older pregnant women. Because the proliferation of mature beta cells can also increase during pregnancy, this increases at a faster rate before the age of 30. Moreover, maternal insulin secretion normally falls at a 0.7% annual rate. As a result, this disturbance in glucose metabolism causes the needs of the fetus and mother to not be fully met during pregnancy [129–132] . Maternal age is one of the most significant independent risk factors for GDM, or gestational diabetes (DM), according to another research as well [127,133,134]. In this context, some research indicates that the risk of GDM escalates in a linear fashion with the mother's age [135], however, other research indicates that the incidence of GDM rises with age initially, peaking between 35 and 39 years of age, and subsequently declines in women between 40 and 50 years of age, also it has been shown that women between the ages of 30 and 34 have the highest frequency of GDM [136,137]. In actuality, insulin sensitivity declines, and IR progressively rises with age, hastening the development of glucose intolerance. This is often linked to an increase in the body's lipid profile, which raises cholesterol and TG [138–140]. The likelihood of BP issues also rises exponentially with the mother's age and is associated with undesirable outcomes including preeclampsia, gestational hypertension, and SBP [127,128,141].

2.2. Lifestyle

Diet

Pregnant women's nutritional demands are difficult to measure because of the ongoing changes in their metabolism and circulation of nutrients, as well as how these changes affect concentration in tissues and fluids and alter nutrient efficiency [2]. Pregnancy

significantly impacts the health of the mother and her offspring, making it an important period. Improper diets are a behavioral risk factor for chronic illnesses because they are rich in calories but low in nutrients [144–147]. In fact, maternal diet quality is a potentially modifiable behavior involved in the etiology of cardiometabolic disorders during gestation [142–146]. Reinforcing this evidence, epidemiologic studies have reported that dietary approaches to prevent hypertension, such as a healthy diet comprising a high intake of fruit, vegetables, whole grains, and low-fat dairy products, produced beneficial effects on glucose, lipid profile, and BP during pregnancy [143,145]. In this regard, dietary patterns provide a thorough analysis of the connection between dietary quality and pregnancy's aftereffects. For this reason, the Mediterranean diet is recommended as a healthy model, especially during pregnancy, because it reduces the cardiometabolic risk of pregnant mothers and prevents the occurrence of problems such as GWG and GD [142,144]. Of course, it should be noted that the effects of maternal nutrition on the fetus are not only dependent on the mother's diet but also on the nutrients stored and the increase in the circulation of proteins and fats in the tissues of the mother, which indicates the importance of nutrition throughout life [39]. According to this, a nutritious diet may greatly impact a child's future health, and it is important to consider this.

Alcohol

Alcohol use is another important behavioral risk factor that is known to affect cardiometabolic health [75,147]. Wo men's alcohol metabolism differs from men's, resulting in greater and longer blood alcohol concentrations [148]. Additionally, changes in physiology and metabolism during pregnancy can affect how medications and other substances are metabolized, changing their effects. Furthermore, alcohol consumption and nutritional intake during pregnancy could impact fetal development negatively. Alcohol consumption during pregnancy can disrupt fetal-mother nutrition, and malnutrition can amplify the effects of alcohol. Constant alcohol consumption can also have a negative impact on nutrition, either directly or indirectly. The toxic effects of the exposure of the uterus to alcohol due to the continuous consumption of alcohol during pregnancy can cause physical, behavioral, and cognitive problems, commonly known as fetal alcohol spectrum disorder (FASD) or alcohol-related birth defects (ARBD) [149].

Alcohol is a teratogen, one of the most widespread addictions, and, regrettably, a substance that women who are of reproductive age consume the most [150,151]. Pregnancy-

related alcohol use is still a serious public health concern. The estimated percentage of pregnant women who drink alcohol differs across nations. For instance, around 10% of women worldwide, 16% of women in Europe, and 22.7% of women in Spain reported drinking at least a little while pregnant [152,153]. Women who consume alcohol frequently or heavily before becoming pregnant may continue to do so throughout pregnancy. Pre-pregnancy alcohol consumption predicts patterns of maternal alcohol intake during pregnancy [154–157].

Within the same framework, it is recognized that maternal alcohol use alters lipid metabolism during pregnancy [158–160]; While data regarding hypertensive disorders of pregnancy are sparse and range from null to a protective effect[147,161,162]. Although, it has been suggested that the apparent inverse relationship observed in some studies is probably not causal but rather influenced by lifestyle factors of pregnant women. Concerning infants, maternal alcohol intake can interfere with healthy brain and organ development since it passes through the placenta [163]. Due to its fetotoxic effects, advising abstention from alcohol during pregnancy should continue, aiming to minimize both immediate and long-term harm.

Smoking

Another well-established risk factor is smoking during pregnancy. The use of tobacco during pregnancy, as a factor that can be easily prevented, is the biggest factor related to the morbidity and mortality of newborns. It also represents the biggest public health disaster of the 20th century [164]. The prevalence of smoking during pregnancy is estimated to be 1.7% worldwide. However, the percentage is far higher in Europe, where 8.1 percent of pregnant women use tobacco. Meanwhile, in Spain, this prevalence is significantly higher and reaches 26.4% [165].

There are thousands of identified harmful compounds in tobacco smoke. Among them are nicotine and carbon monoxide, both of which are proven human carcinogens [166]. As a drug, nicotine can cause dependency and recurrent usage. It is important to quit smoking during pregnancy since it can have a major positive impact on public health [164]. Several studies have also linked prenatal maternal smoking to multiple adverse health outcomes for both mother [167] and child [168].

Maternal smoking can raise the risk of gestational hypertension [169], yet some research contradicts this assertion and shows a decreased risk [170]. In addition, studies have demonstrated an independent correlation between passive smoking and a higher risk of GDM [171,172]. Although, there are contradictory findings on the link between tobacco use and GDM [173]. Moreover, the harmful consequences of smoking start when a fetus is exposed to tobacco in the womb. These effects might include altered cardiorespiratory responses, musculoskeletal defects, wheezing and asthma, and cardiovascular/heart defects [174–176]. Additionally, low birth weight (LBW) might result from smoking [177]. However, the role of maternal smoking on glucose and lipid metabolism disturbances during pregnancy has been less studied [178–180]. No study has explored this link in Mediterranean pregnant populations where other women's socio-demographic traits and Mediterranean lifestyle might protect against cardiovascular risks. Thus, future evidence from prospective studies is needed.

Physical activity

Physical inactivity (PA) poses a significant threat to cardiometabolic health [181]. Therefore, medical recommendations emphasize its importance in reducing health risks, covering both intentional activities, such as exercise, and unintentional movements like everyday tasks [182].

The health effects of physical exercise on pregnant women have become a hot topic in pregnancy health care. Pregnancy is an appropriate and crucial time when interventions or health recommendations are more likely to be followed since it is the period when individuals are in frequent touch with health experts and may have sufficient desire to modify their lifestyle [183]. 2020 saw the release of the most recent American College of Obstetricians and Gynecologists (ACOG) guidelines for activity and exercise during pregnancy, which advised moderate-intensity aerobic, resistance, and stretching exercises for 150 minutes a week throughout pregnancy or to get at least 30 minutes of moderate physical exercise a day [184]. It is thought that a pregnant woman who engages in moderate physical exercise can safely carry her unborn child into the future [185].

Aside from the various advantages of PA, these activities during pregnancy help minimize the risk of GWG [186]. Regular exercise during pregnancy can reduce the risk of GDM while also lowering the likelihood of type 2 diabetes [187,188]. In addition, there is evidence that exercise intervention during pregnancy is beneficial to lower or normalize BP [189] and

may decrease the risk of gestational hypertensive disorders like preeclampsia; however, research in this area has yielded conflicting results, particularly in uncomplicated pregnancies [190]. Furthermore, despite evidence that exercise improves lipid profiles in non-pregnant populations, in pregnant women, this evidence is scarce. Recent research supports the benefit of supervised PA on TG levels during pregnancy [191]; however, outcomes with other lipids appear to be less consistent [192] . While the major causes remain unknown, these controversial results could be attributed to differences in the trimester of pregnancy (i.e., timing of the outcome measurement) or other confounding factors related to a healthy lifestyle acquired during pregnancy. With the aim of providing certain evidence for cardiometabolic health care for pregnant women, this dissertation seeks to expand the epidemiological understanding of physical exercise and cardiometabolic traits throughout pregnancy.

3. Clinical characteristics

Body Mass Index and Gestational Weight Gain

Maternal overweight and obesity rates are rising, as is the rate of excessive GWG [193]. Maintaining a healthy pre-pregnancy BMI and achieving appropriate weight gain during pregnancy are critical, as they directly impact pregnancy outcomes and the health of both the mother and the baby [194]. With an emphasis on monitoring the mother's gain appropriately, recommended increases vary depending on their early BMI. It is advised that women with a BMI of less than 18.5 acquire between 13 and 18 kg of weight, whereas women with a BMI between 18.5 and 24.9 should gain between 11 and 16 kg. For women with a BMI between 25 and 29.9, a weight gain of 7 to 11 kg is advised, and for those with a BMI over 30, a weight gain of 5 to 9 kg is advised [26]. However, adherence to these GWG recommendations is low. Consequently, several adverse prenatal outcomes have been linked to inadequate GWG, whether it's above or below recommended levels, according to studies [195].

Pregnancy complications, including preeclampsia, gestational hypertension, GDM, and delivery of a preterm or growth restricted baby, are common for both women with overweight/obesity and women who gain excess weight during their pregnancy [193]. Additionally, maternal obesity before and during pregnancy is a major factor in the development of IR during pregnancy, which has a negative impact on the pregnancy's lipid metabolism [196]. Despite the importance of higher maternal pre-pregnancy BMI and excessive GWG for the subsequent development of cardiovascular and metabolic alterations during

pregnancy [193], to our knowledge, this dissertation assesses this relationship for the first time using a composite cardiometabolic risk score. In this context, a cluster of cardiometabolic factors has been reported to be more strongly associated with adverse pregnancy outcomes than just one factor [197]. Using this factor-cluster approach would help to better identify high-risk women during pregnancy. It is also important to prospectively reassess the cardiometabolic risk of pregnant women in order to determine whether this risk is stable or whether it progresses over the course of pregnancy according to their weight status.

Parity

Among the different reproductive factors investigated, parity has been a matter of discussion for many years due to its potential relationship with the subsequent risk of future metabolic alterations and cardiovascular disease [198–200]. It should be noted that, although the term "parity" is now widespread in clinical practice and epidemiological evidence, there is still no standard definition of parity. Parity has been used to refer to the number of conceptions, pregnancies, births, offspring, babies, and children[201–203]. Although there is reasonable consensus among obstetricians and midwives that parity refers to the number of previous pregnancies reaching 24 completed weeks or above, irrespective of outcome [201,204,205].

As previously mentioned, pregnancy is a time-limited condition characterized by a gradual increase in and transient peripheral IR [36]. Although earlier studies [206–209] suggest that maternal IR returns to pre-pregnancy levels by 1 year postpartum, the recent literature casts some doubt on this premise [210,211]. It has been hypothesized that recurrent maternal IR episodes due to repeated pregnancies (i.e., parity) result in a progressive worsening of the glucose tolerance with each subsequent pregnancy, manifesting in GD, or that they may even permanently disturb glucose homeostasis in women in later life [210–213]. Nevertheless, the underlying mechanisms for parity-related IR during pregnancy are largely unknown, complex, and most likely reflect a range of factors, such as placental hormones, lifestyle modifications, and genetic and epigenetic contributions [214].

Until now, in alignment with the dissertation objective, most studies have focused on the role of parity in the development of GDM or recurrent GDM during later pregnancies [213,215]. However, the results are not entirely convincing. As suggested by some studies, the

high rate of GD among multiparous women may not be causal but could be confounded or mediated by other factors, such as advanced maternal age or increased body adiposity [216,217]. It is interesting to note that GDM is typically diagnosed in the latter half of pregnancy (at 24-28 weeks) [218], which might be too late to completely reverse the intrauterine hyperglycemia-induced adverse effects on offspring that can occur in the early stages of pregnancy [219]. Alternatively, maternal IR in the first trimester, measured by the homeostasis model assessment of the IR index Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), could act as potential early markers for later metabolic and cardiovascular dysfunction. In fact, IR has been suggested as a reliable predictor of future GDM [220,221]. In this context, to the best of our knowledge, only 3 studies have investigated the relationship between parity and IR, mainly focusing on middle and late pregnancy rather than very early pregnancy, and their findings are inconsistent [222–224]. On the other hand, it is well known that overweight/obesity before and during pregnancy predisposes the woman to a higher metabolic dysregulation, in pregnancy [225] including early IR. From a prevention perspective, an arguably important research question would be to determine whether repeated parity confers an independent effect on IR in very early pregnancy. And a further point requiring clarification is whether parity contributes, in combination with high maternal BMI, to a worse IR. Thus, to shed light on these questions and reveal the underlying mechanism, further studies are warranted.

4. Maternal cardiometabolic alterations during pregnancy and fetal growth

The Barker hypothesis, also known as the fetal programming hypothesis, argues that offspring exposed to 'inadequate nutrition' during intrauterine development are more likely to suffer from comorbidity and cardiovascular diseases as adults [226] . This hypothesis has been expanded beyond undernutrition to other early-life environmental exposures, such as maternal smoking, low socioeconomic resources, and infections during pregnancy. It is now accepted that structural, functional, and metabolic changes that occur in the fetus as an adaptive response to an adverse or suboptimal intrauterine environment persist into postnatal life, which leads to a greater risk of disease in adulthood [226,227] (**Figure 8**). In this context, fetal size and fetal growth trajectories are important indicators of fetal health [228]. In fact, fetal growth restriction (FGR), with low birthweight as a major indicator, is the best-characterized prenatal risk factor for metabolic (including obesity, diabetes mellitus, and

metabolic syndrome) and cardiovascular disease in adult life [229–231], with metabolic programming being the primary hypothesis to explain this association [232–234] . Yet excess birthweight is not only at risk of fetal brachial plexus injury, cerebral hemorrhage, and shoulder dystocia during labor [235] but also has an increased risk of metabolic problems later in life [236,237].

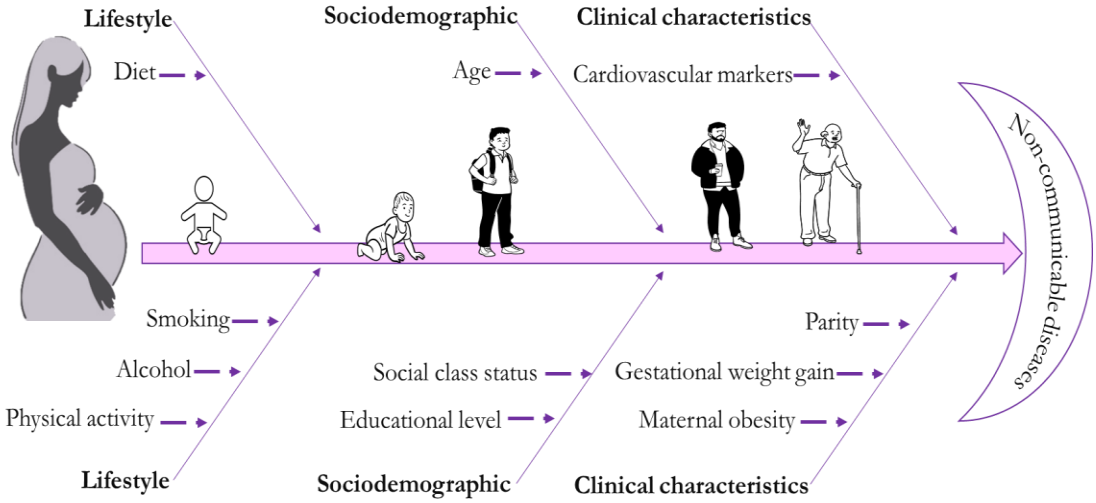

Figure 8. Fishbone diagram that summarizes the impact of maternal perinatal factors (the focus of this study) on child health. This diagram is based on the Developmental Origins of Health and Disease (DOHaD) theory, which proposes that non-communicable diseases can be influenced by the fetal developmental period.

Abnormal fetal growth is commonly diagnosed using criteria such as low birthweight (< 2500 g) and macrosomia (birth weight ≥ 4000 or ≥ 4500 g), Small-for-Gestational-Age (SGA), and Large-for-Gestational-Age (LGA). Low birth weight and macrosomia are indices of size with substantial utility for their ease of measurement and significant association with adverse perinatal outcomes. The limitation of the low birthweight index is the lack of consideration for gestational age, leading to a heterogeneous mix of preterm and SGA fetuses. For this reason, in clinical practice and research, international and/or national newborn growth charts, with varying methodologies, are used to identify SGA (an indication of fetal growth restriction) and LGA (an indication of rapid fetal development) infants, usually defined as birth weight below 10th and above 90th percentiles, respectively. Importantly, SGA refers to both infants who are constitutionally small and fall within the

lower tail of the distribution and those with intrauterine growth restrictions due to various adverse factors [238].

A point of debate is the choice between customized and population-based references. It's important to highlight that population charts illustrate birthweight distributions of infants born in a particular population adjusted for gestational age, whether or not accounting for fetal sex. While customized birth weight percentiles provide a more personalized assessment of growth potential by additionally accounting for maternal characteristics known to influence birthweight, such as ethnicity, height, weight, and parity [239]. In this regard, most studies have advocated the continued use of local or customized charts [240,241]. Nonetheless, the use of local charts is only relevant to the population and time from which they were derived, making it impossible to compare populations and studies. Recently, two international fetal growth standards were developed for global use: The World Health Organization (WHO) [242] and the International Fetal and Newborn Growth Consortium for the Twenty-First Century (INTERGROWTH-21st) standards [243]. The INTERGROWTH-21st study established a multinational standard for newborn weight, demonstrating that in populations not constrained by societal, dietary, or medical factors, infant growth worldwide is remarkably comparable. Thus, its newborn standards and references offer a reliable multinational tool for the assessment of newborn size and physical status and are currently the most widely used for categorizing newborns into sub-groups.

Importantly, there is a substantial disparity in the prevalence of SGA babies (4.6–15.3%) across Europe [244] and LGA babies (5–20%) [245] as well as a huge deviation in the prevalence of macrosomia (birthweight ≥4000 g) [246] in developed countries. Higher rates of SGA births are more apparent in developing countries. Socio-environmental factors, population differences, and the broad variations in assessment standards across studies are the main causes of the disparities in SGA and LGA rates [246,247]. Based on studies conducted in Spain, the prevalence of SGA infants ranged from 9.4% to 14.0% [248–250], and that of LGA infants 15% [251]. Thus, from a clinical perspective, the priority would be to reduce abnormal fetal growth to avoid short- and long-term health consequences [252–254].

The etiology of abnormal fetal growth, often assessed by newborn size, is a complex combination of genetic factors, fetal hormones, uterine constraints, and maternal risk factors that vary in their influence throughout pregnancy. In this regard, prenatal exposure to

common maternal metabolic disturbances, such as hyperglycemia, dyslipidemia, and hypertension [255] during intrauterine development, could result in fetal growth abnormalities. Thus, understanding the impact of an abnormal maternal metabolic profile on inappropriate fetal growth can help determine potential prevention strategies.

In terms of glucose homeostasis in pregnancy, the vast majority of prospective studies have clearly shown that higher glucose levels, even in the absence of GDM, in early [256] and mid-pregnancy [257] are consistently related to fetal overgrowth and an increased risk of LGA/macrosomia. However, the data are still limited and inconsistent [207,258–260] regarding the effect of maternal IR, as measured by the HOMA-IR during early and late pregnancy (two different vulnerable periods for the developing fetus), on newborn size, especially in women without abnormal glucose tolerance. This might be attributed, at least in part, to the fact that IR is not a routine prenatal examination. Therefore, this aspect still requires further evaluation.

Unlike hyperglycemia, fewer studies have examined the role of an abnormal maternal lipid profile in a normal pregnancy on fetal growth. Although some studies have found evidence of an association, the findings about the type of lipid biomarker and study designs (i.e., timing of the exposure measurement and the neonatal anthropometry evaluated) are inconsistent. For instance, two recent studies based on a large population of Chinese pregnant women reported that high maternal triglyceride levels in early pregnancy (6–8 gestational weeks) were associated with LGA newborns [261,262]. Similarly, a cross-sectional cohort study on Dutch women also found that high TG may be related to larger embryonic size in early pregnancy, particularly in overweight women, while no associations for Total cholesterol (TC), LDL-c, or HDL-c concentrations were found [263]. A pattern of seemingly lacking associations regarding these maternal lipid levels throughout pregnancy and fetal growth measurements at birth (i.e., newborn weight, or LGA) was also observed in other earlier research with Chinese and Turkish populations [44,264]. However, a U.S. study found that elevated TG and TC were associated with a larger newborn size in terms of birthweight (but not with LGA), while HDL-c measured on average at three time points during pregnancy was associated with reduced size in terms of birthweight and head circumference (HC) [265]. In contrast, a cohort study from rural Gambia found that decreased HDL-c in early and mid-pregnancy, but not at the end of pregnancy, was associated with an increased risk

of low birthweight [266]. Thus, future prospective studies are needed to determine whether unfavorable lipid biomarkers throughout pregnancy have an impact on newborn size.

Many studies on BP in Chinese, Dutch, Swedish, English, and American pregnant women show that increases in maternal BP in mid-to-late pregnancy, although not reaching the clinical criteria for hypertension, seem to be associated with reduced fetal growth and a risk of giving birth to SGA neonates [63,267,268]. Paradoxically, other studies assessing preconception hypertension [269,270] or gestational hypertension/preeclampsia after 20 weeks of gestation [271] did not detect any association. Healthy behaviors adopted by pregnant women after being diagnosed with hypertension (i.e., a balanced diet, exercise, non-smoking, or appropriate weight gain) most likely contribute to adequate growth and may explain certain discrepancies [272]. Therefore, these factors are potential confounders; however, not all studies that link the maternal metabolic profile to neonatal size address them.

Moreover, despite inconsistencies and gaps in evidence on this topic, most studies assessed metabolic biomarkers measured at a single gestational time point, mainly in the second or third trimester. Given that the metabolic profile changes throughout pregnancy, further research is required to explore multiple time points. No study has evaluated the association of maternal cardiometabolic profile throughout pregnancy with on newborn size in non-complicated pregnancies among healthy pregnant Mediterranean women.

5. Justification

Maternal cardiometabolic health during pregnancy is a critical determinant of both maternal and fetal outcomes, necessitating a comprehensive investigation. Understanding the influence of prenatal factors on maternal cardiometabolic health is essential, as it provides insights into potential interventions to mitigate adverse pregnancy outcomes. By examining prenatal factors such as dietary habits, PA, and pre-pregnancy weight, we can gain foundational knowledge to guide public health policies and prenatal care practices aimed at enhancing maternal health and reducing the risk of gestational complications.

Furthermore, the relationship between the number of pregnancies (parity) and the development of IR in early pregnancy represents a significant area of study. IR is a major predictor of GDM, which is associated with adverse maternal and fetal outcomes. Understanding the impact of parity on IR underscores the necessity for tailored screening and intervention strategies for women with multiple pregnancies, thus enhancing prenatal care protocols and reducing the incidence of GDM.

Lastly, examining the direct impact of maternal cardiometabolic health on fetal growth parameters, including birth weight and length, reveals the long-term implications for the child's health. Identifying specific cardiometabolic factors that affect fetal growth informs strategies for monitoring and managing at-risk pregnancies. This emphasizes the need for comprehensive maternal health assessments to ensure favorable fetal development and reduce the incidence of IUGR and other growth-related complications.

In summary, this body of research underscores the multifaceted nature of maternal cardiometabolic health and its profound implications for both maternal and fetal outcomes. By addressing the associations between prenatal factors, parity, maternal cardiometabolic status, and fetal growth, this research provides a robust framework for developing targeted interventions aimed at optimizing health during pregnancy and beyond.

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Hypothesis And Objectives

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HYPOTHESIS AND OBJECTIVES

Hypothesis: Certain prenatal factors, including sociodemographic, lifestyle, and clinical parameters, actively contribute to the exacerbation of maternal cardiometabolic risk biomarkers during pregnancy. Additionally, we posit that elevated levels of lipids, glucose metabolism parameters, and blood pressure among expectant mothers during pregnancy negatively influence newborn growth within a Mediterranean population of pregnant women.

- **Objective 1:** To investigate the association between prenatal sociodemographic, lifestyle, and clinical characteristics and CCR and its components in the first and third- trimesters of pregnancy.

- **Objective 2:** To assess the associations between parity and combinate parity and BMI-based weight status with IR in the first trimester of pregnancy.

- **Objective 3:** To evaluate the associations between maternal cardiometabolic profile during the first and T3 of pregnancy and newborn size and the risk of SGA and LGA infants.

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Material And Methods

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MATERIAL AND METHODS

1. Study design and participants

A longitudinal prospective cohort study was conducted with 265 healthy pregnant women. Serum cardiometabolic marker data were collected after overnight fasting at approximately 12 weeks (first trimester) and 36 weeks (third trimester) of gestation. Additionally, neonatal anthropometric data were measured at delivery (**Figure 9**). This study is part of the ECLIPSES study [273]. The Ensayo CLInico Para Suplementar con hierro a EmbarazadaS (ECLIPSES) study www.clinicaltrialsregister.eu (ID: EUCTR-2012-005480-28) and www.clinicaltrials.gov (ID: NCT03196882)) is a randomized controlled clinical trial from 2013 to 2017. Ethics approval was obtained from the Research Ethics Boards of the Jordi Gol Institute for Primary Care Research and the Pere Virgili Institute for Health Research. The purpose of the study and the entire research methodology are available elsewhere [273].

The research project recruited a group of pregnant women who were in optimal health and devoid of anemia, all prior to entering their 12th week of pregnancy. Subsequently, all individuals interested in participating completed written informed consent forms. Recruitment took place during the women's initial prenatal appointment at ten primary care centers associated with the Catalan Sexual and Reproductive Health Service of the Catalan Institute of Health. In order to be eligible, participants had to be at least 18 years old, within the first 12 weeks of pregnancy, without anemia (with a hemoglobin concentration above 110 g/L), proficient in either Spanish or Catalan, and willing to provide informed consent. Exclusion criteria encompassed multiple pregnancies, iron intake exceeding 10 mg in the three months prior to the 12th week of gestation, hypersensitivity to egg protein (due to the iron prescription containing ovalbumin), previous serious illnesses (such as immunosuppression, heart disease, or endocrine disorders), chronic conditions impacting nutritional status (including cancer, malabsorption, or diabetes type 1 or 2), alcoholism, liver diseases (such as chronic hepatitis or cirrhosis), morbid obesity, maternal infections, and adverse obstetric histories (such as previous occurrences of preeclampsia, uterine malformations, uterine surgeries, suspected fetal malformations, or recurrent perinatal deaths). In the end, the ECLIPSES research selected 791 healthy expectant mothers who had not yet reached the 12th week of pregnancy.

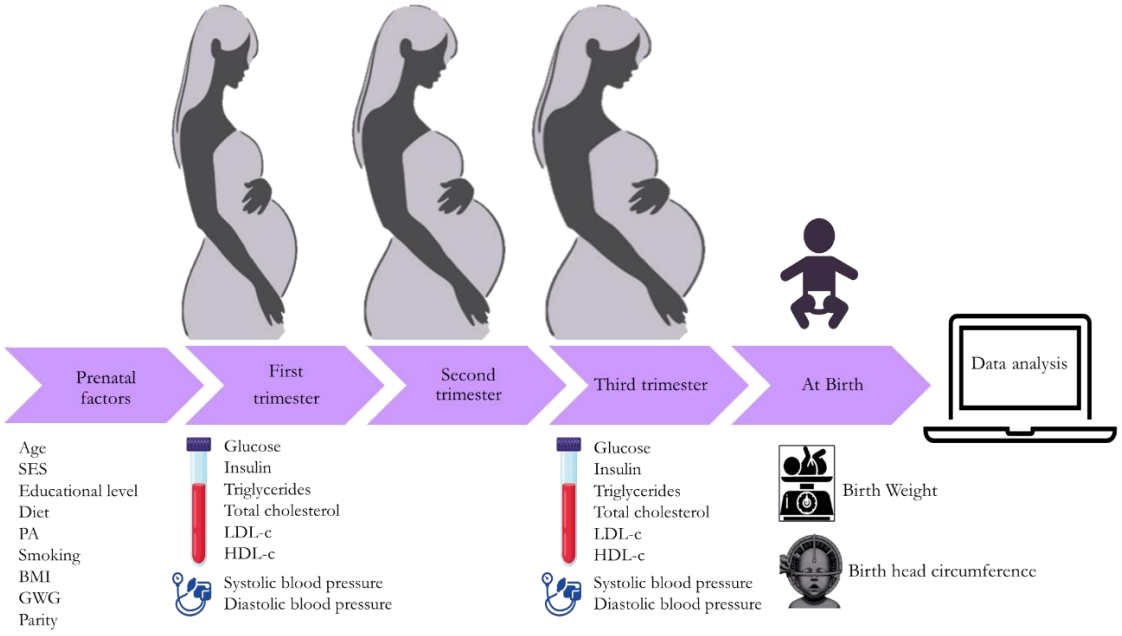

Figure 9. Design of study.

2. Assessment of maternal prenatal variables

2.1. Maternal sociodemographic variables

At enrollment, we gathered sociodemographic data, including age, SES, and educational attainment, through standardized questionnaire-based interviews. We integrated occupational status data and classified it using the Catalan categorization of occupations (CCO-2011) [274] in order to compute SES. Furthermore, data on education was divided into three levels: elementary school or less, secondary education, and university education or more.

2.2. Maternal lifestyle variables

2.2.1. Diet

The primary dietary assessment tool in ECLIPSES was a food frequency questionnaire (FFQ) capable of evaluating food category consumption, energy intake, and macronutrient intake with reproducibility and validity [275]. Nutritionists used the data set obtained from this 45-item self-administered questionnaire to calculate dietary pattern scores, which allowed them to conduct a thorough analysis of the group's adherence to the Mediterranean diet.

The consumption of six dietary groups (fruits, legumes, vegetables, grains, olive oil, and fresh fish) had a positive score, which, when added together, had a maximum score of 9. Conversely, the consumption of dairy products, alcohol, and all meat had a negative score. This information was important to include when calculating the overall relative Mediterranean Diet (rMED) score. As a result, the overall rMED score varied from 0 points, which represents the lowest level of adherence to the Mediterranean diet, to 18 points, which represents the highest level of adherence.

2.2.2. Physical activity

Physical activity (PA) was assessed using the short version of the International Physical Activity Questionnaire (International Physical Activity Questionnaire-Short version (IPAQ-S)), which is a valid report based on the self-administered method. The IPAQ, which captures four levels of PA intensity, including: 1) vigorous-intensity activity such as aerobics; 2) moderate-intensity activity such as leisure cycling; 3) walking; and 4) sitting, has been proposed as a cost-effective method to It is widely used to assess PA. Then, following the IPAQ scoring protocol, IPAQ responses were converted to total metabolic equivalent task minutes per week (METs-min/wk) [276].

2.2.3. Smoking

The Fagerström questionnaire (Fagerström_Q) was used to ascertain the smoking status of subjects. The Fagerstrom Test is a standardized tool used to assess nicotine dependency linked to smoking [277].

2.3. Maternal clinical variables

2.3.1. Body mass index (BMI)

Measurements of the mother's height (cm) and weight (kg) were taken during the initial clinic appointment. Consequently, weight (kg)/height (m^2) was used to calculate BMI.

2.3.2. Gestational weight gain (GWG)

Total GWG was calculated as the difference between the weights recorded at the first and last prenatal visits, taking the beginning BMI into account.

2.3.3. Blood pressure

An automated digital monitor (Omron HEM-705CP) was utilized to measure SBP and DBP.

2.3.4. Parity assessment

According to women who answered a questionnaire given by the interviewer, parity was defined as the number of singleton pregnancies lasting at least 20 weeks (independent of whether the child was born alive or not) and also answered about planned pregnancy.

2.4. Cardiometabolic risk markers during pregnancy

Fasted venous blood samples were drawn and processed according to standard procedures from each participant at two time points before gestational week 12 (first trimester (T1)) and after gestational week 36 (third trimester (T3)). After centrifugation and coding, serum samples were immediately transferred to freezers at 80°C until analysis.

Glucose concentration and lipid parameters (TC, HDL-c, and serum TG in mmol/L) were evaluated simultaneously using conventional automated enzymatic procedures. Also, the ADVIA Centaur analyzer using a commercial kit (ADVIA Centaur IRI, Siemens Healthcare Diagnostics Inc., Tarrytown, USA) measured fasting insulin levels via chemiluminescence immunoassay.

After the findings were known, LDL-c concentrations were calculated using the Friedewald equation. TC - HDL-C - (TG/5). For the IR indication, the HOMA-IR index was employed, which is computed using the equation below. HOMA-IR = [fasting glucose (mmol/L) x fasting insulin (μIU/ml)]/22.5.

2.4.1. Clustered cardiometabolic risk

By adding together all of the standardized z-scores (z=value-mean/SD of the whole population) for the seven cardiometabolic indicators that were evaluated—BMI, SBP, glucose, HOMA-IR index (log), TG (log), LDL-c, and HDL-c—a cluster cardiometabolic risk (CCR) score was produced. We determined HDL-c by multiplying the results by -1 since it has an inverse relationship with metabolic risk. The strong association between SBP and DBP led us to consider SBP alone for the CCR score. A higher cardiometabolic risk corresponds with a higher CCR score. Prior pregnancy research that employed a comparable

risk score and criteria served as the foundation for the selection of this CCR score and its constituent parts [278].

All biochemical analyses were performed at the ICS Camp de Tarragona-Terres de l'Ebre accredited laboratory, Joan XXIII University Hospital in Tarragona.

3. Infant anthropometric measurements

The newborn's anthropometrics, such as HC (cm) and birth weight (gram), were measured upon delivery by a gynecologist or midwife using accepted techniques. We defined infant as small-for-gestational-age (SGA) if any of these two anthropometric features dropped below the 10th percentile and as Large-for-Gestational-Age (LGA) if they were above the 90th percentile based on the gestational age- and sex-specific reference growth curves using the international INTERGROWTH-21st newborn standards [243].

4. Statistical analysis statistical

For all papers, descriptive statistics such as frequency, mean, and standard deviation (SD) were employed to investigate the basic characteristics of exposure and/or outcome variables. If the variable had a normal distribution, descriptive statistics were generated by calculating the mean and SD; if not, they were computed by determining the median and interquartile range (IQR). Descriptive statistics were used in the investigation to explain differences between the individuals' clinical and sociodemographic characteristics. As appropriate, for continuous variables, student's t-tests were employed; chi-square tests were used for categorical variables; and one-way ANOVA with Bonferroni's test was utilized for post-hoc comparisons. Accordingly, descriptive statistics yielded numerical values (%) for categorical variables and mean ±SD for quantitative variables, and relationships were deemed statistically significant at a p-value <0.05 throughout the whole analytic process. All statistical analyses were conducted using SPSS statistical software, version 29.0. Each paper's statistical analysis section provides a thorough description of the statistical analysis that was done.

In briefly:

For the first paper the "*Prenatal factors associated with maternal cardiometabolic risk markers during pregnancy: the ECLIPSES study*" was examined using a multivariable linear regression model. The adjusted model in this paper was used to identify the determinants of the independent contributions of selected sociodemographic and lifestyle characteristics of the

pregnant women on the CCR score and each cardiometabolic risk factor in the T1 and T3 of pregnancy. The models were run separately for each cardiometabolic risk marker, and estimates were presented as β coefficients (β) and 95% confidence intervals (CIs).

For the second paper the "*Association of parity with IR early in pregnant women: ECLIPSES study*" the linear regression approach was employed to get a better understanding of the association of parity as the main exposure variable with IR. An additional separate linear regression analysis was also performed to evaluate the joint association of parity and ep-BMI-based weight status in two groups as predictors for each outcome.

For the third paper the "*Longitudinal associations of maternal cardiometabolic factors during pregnancy with measures of fetal growth at birth: ECLIPSES study*" after adjusting for potential confounders, a linear regression model was employed to determine the association between the exposure and outcome variables. Multiple logistic regression models were also used to estimate odds ratios (ORs) and 95% CIs for LGA and SGA at birth linked to each maternal cardiometabolic marker (in separate models), assessed as both continuous and categorical exposure variables (based on two groups: normal-low (<75th percentile as a reference) and high (≥75th percentile)) levels.

Confounders and mediators were taken into account in some or all of the analytical models, including: sociodemographic factors (social class (low/medium (ref.), high); educational level (low/medium (ref.), high); age categories (<25 (ref.), 25-29, ≥30 years)); life style factors (Mediterranean diet score tertile (T1: ≤8 (ref.), T2: 9-11, T3: ≥12 points); PA tertile (T1: ≤1070 (ref.), T2:1071-3335, T3: ≥3336 METs-min/week); smoking status (never/former smoker (ref.), current smoker)); clinical characteristics (BMI categories: normal weight (ref.), overweight/obesity); GWG (insufficient (ref.), adequate, excessive) only for T3 analysis; parity (nulliparous, multiparous); planned pregnancy (no (ref.), yes); sex infant; and first-trimester Red-blood-cell folate folate levels (nmol/L).

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Results

This section presents insight from the result of this dissertation, which comprise three original manuscripts. These manuscripts are summarized in Table 1.

Table 1. Reference, impact factor, category and journal rank of the publications presented in the current doctoral dissertation.

Title	Journal	Category	Journal Metric	Status
Publication 1				
Prenatal factors associated with maternal cardiometabolic risk markers during pregnancy: the ECLIPSES study. DOI: 10.3390/nu15051135.	*Nutrients*	NUTRITION & DIETETICS	IF: 4.8 Q: 1 (2023)	Published
Publication 2				
Association of parity with insulin resistance early in pregnant women: ECLIPSES study. DOI: 10.1210/clinem/dgad594.	*J. Clin Endocrinol Metab.*	ENDOCRINOLOGY & METABOLISM	IF: 5.0 Q: 1 (2023)	Published
Publication 3				
Associations of maternal cardiometabolic factors during pregnancy with measures of fetal growth at birth: a longitudinal cohort study.	*J. Endocrinological Investigation*	ENDOCRINOLOGY & METABOLISM	IF: 3.9 Q: 2 (2023)	Under review (Ref: JENI-D-24-01003)

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Publication 1. Prenatal factors associated with maternal cardiometabolic risk markers during pregnancy: the ECLIPSES study.

Ehsan Motevalizadeh, Andrés Díaz-López, Francisco Martín-Luján, Josep Basora and Victoria Arija.

Overview of the novelty and significance of this work

Literature Review

- ✓ The extant body of literature recognizes the profound impact of sociodemographic, lifestyle, and clinical variables on cardiometabolic risk throughout the course of pregnancy.
- ✓ Prior research indicates a positive correlation between OWO and heightened cardiometabolic risk among pregnant women.
- ✓ PA is recognized as a protective factor against cardiovascular risk during pregnancy.

Novelty Contribution

- ✓ This study enriches understanding by uncovering specific associations between sociodemographic, lifestyle, and clinical factors and cardiometabolic risk markers during pregnancy within a Catalonia, Spain, cohort. Here, we assessed this relationship for the first time using a composite cardiometabolic risk score.
- ✓ It delineates the impact of educational level, PA, GWG, and SES on cardiometabolic risk during pregnancy within this population.
- ✓ The findings underscore the necessity of considering a comprehensive array of factors, encompassing sociodemographic and lifestyle dimensions, in evaluating cardiometabolic risk among pregnant women.

Conclusion

- ✓ OWO during pregnancy emerges as a significant contributor to heightened cardiometabolic risk, while factors such as insufficient GWG and higher SES are associated with reduced risk.Initiating pregnancy with normal weight, higher socioeconomic and educational levels, being a non-smoker, non-consumer of alcohol, and engagement in PA were identified protective factors against cardiovascular risk during pregnancy among Catalan women.

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Results

nutrients

MDPI

Article

Prenatal Factors Associated with Maternal Cardiometabolic Risk Markers during Pregnancy: The ECLIPSES Study

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Abstract: To examine the associations of sociodemographic, lifestyle, and clinical factors with cardiometabolic risk and each of its components during pregnancy in a pregnant population from Catalonia (Spain). A prospective cohort study of 265 healthy pregnant women (39 ± 5 years) in the first and third-trimesters. Sociodemographic, obstetric, anthropometric, lifestyle and dietary variables were collected, and blood samples were taken. The following cardiometabolic risk markers were evaluated: BMI, blood pressure, glucose, insulin, HOMA-IR, triglycerides, LDL, and HDL-cholesterol. From these, a cluster cardiometabolic risk (CCR)-z score was created by summating all z-scores (except insulin and DBP) computed for each risk factor. Data were analyzed using bivariate analysis and multivariable linear regression. In the multivariable models, the first-trimester CCRs was positively associated with overweight/obesity status (β: 3.54, 95%CI: 2.73, 4.36) but inversely related to the level of education (β: −1.04, 95%CI: −1.94, 0.14) and physical activity (PA) (β: −1.21, 95%CI: −2.24, −0.17). The association between overweight/obesity and CCR (β:1.91, 95%CI: 1.01, 2.82) persisted into the third-trimester, whereas insufficient GWG (β: −1.14, 95%CI: −1.98, −0.30) and higher social class (β: −2.28, 95%CI: −3.42, −1.13) were significantly associated with a lower CCRs. Starting pregnancy with normal weight, higher socioeconomic and educational levels, being a non-smoker, non-consumer of alcohol, and PA were protective factors against cardiovascular risk during pregnancy.

Keywords: cardiometabolic risk; pregnancy; HOMA-IR; gestational weight gain; ECLIPSES

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1. Introduction

Significant metabolic and physiological changes sustain a typical pregnancy and promote fetal growth and development [1]. However, inadequate adaptation to these changes (e.g., interrelated cardiometabolic alterations such as maternal obesity, elevated fasting glucose, insulin resistance and/or hyperinsulinemia, dyslipidemia, and elevated blood pressure (BP)) sometimes leads to serious complications that affect the health of both mother and child. It is therefore critically important to study cardiometabolic risks in pregnant women since several maternal sociodemographic and lifestyle-related risk factors can negatively influence the cardiometabolic status of pregnant women [2–4].

Regarding lifestyle, maternal diet quality is a potentially modifiable behavior involved in the etiology of cardiometabolic disorders during gestation [5–9]. Reinforcing this evidence, epidemiologic studies have reported that dietary approaches to prevent

hypertension, such as a healthy diet comprising a high intake of fruit, vegetables, whole grains, and low-fat dairy products produced beneficial effects on glucose, lipid profile, and BP during pregnancy [6,8]. For example, a Mediterranean-style diet (MedDiet) has been associated with lower prenatal maternal BP [7] and cardiometabolic risk among pregnant women [5].

Evidence also suggests that a lack of physical activity (PA) from the first-trimester increases the risk of pregnancy complications (e.g., gestational hypertension, gestational diabetes mellitus (GDM), pre-eclampsia, and excessive gestational weight gain (GWG) [10]. Another well-established risk factor is smoking during pregnancy. Several studies have also linked prenatal maternal smoking to multiple adverse health outcomes for both mother [11] and child [12]. However, the role of maternal smoking on glucose and lipid metabolism disturbances during pregnancy has been less studied [13–15]. Similarly, the available evidence of maternal alcohol consumption is particularly sparse [16,17]; among its main complications are cesarean delivery, stillbirth, high birth weight, and infant mortality.

Unhealthy lifestyles adopted by women of reproductive age also predispose them to overweight/obesity in pregnancy, associated with cardiometabolic risk factors such as insulin resistance [18] and worse lipid profile [19,20]. It has been suggested that inappropriate GWG, especially in later pregnancy, may also increase the risk of adverse obstetric outcomes [21,22].

Previous studies on maternal lifestyle behaviors and cardiometabolic risk during pregnancy have focused on specific cardiometabolic risk markers and only a few studies [5,23] have considered whether combinations of biological risk factors formed a clustered cardiometabolic risk (CCR) score. In this context, a cluster of cardiometabolic factors has been reported to be more strongly associated with adverse pregnancy outcomes than just one factor [24]. Using this factor-cluster approach would help to better identify high-risk women during pregnancy. It is also important to prospectively reassess the cardiometabolic risk of pregnant women in order to determine whether this risk is stable or whether it progresses over the course of pregnancy.

It can generally be stated that cardiometabolic risk markers during pregnancy are influenced by multiple factors specific to each population. However, few studies have been conducted specifically among pregnant populations in the Mediterranean area, where the socio-demographic and Mediterranean lifestyle traits of women can be regarded as protective factors against cardiovascular risks. The key to planning effective strategies to prevent and treat future obstetric complications is to understand which maternal factors have favorable effects on cardiometabolic risk during pregnancy and define critical periods in which this relationship is most affected.

To further knowledge in this area, we aimed to investigate the association between prenatal sociodemographic, lifestyle, and clinical characteristics and clustering cardiometabolic risk and its components in the first and third-trimester of pregnancy in a population of pregnant women from a Mediterranean region in northern Spain.

2. Materials and Methods

2.1. Study Design

A population-based prospective cohort study of healthy pregnant women who participated in the ECLIPSES study was conducted from the first to the third-trimester of pregnancy. A description of ECLIPSES has been published elsewhere [25]. Eligible participants were healthy adult women over 18 years with ≤12 weeks of gestation. Details of the inclusion/exclusion criteria can be found elsewhere [25].

Of the 793 pregnant women initially enrolled in the study, for the present analysis, all women who had data regarding serum cardiometabolic markers in the first (12 weeks) and/or third (36 weeks) trimester of pregnancy were included. The total study sample therefore comprised 265 pregnant women (Figure 1). All participants signed an informed

consent form. The study was approved by the Ethical Committee of the Jordi Gol Institute for Primary Care Research and the Pere Virgili Institute for Health Research (approval ID: 118/2017. Date: 28 September 2017) and complied with the tenets of the Helsinki declaration.

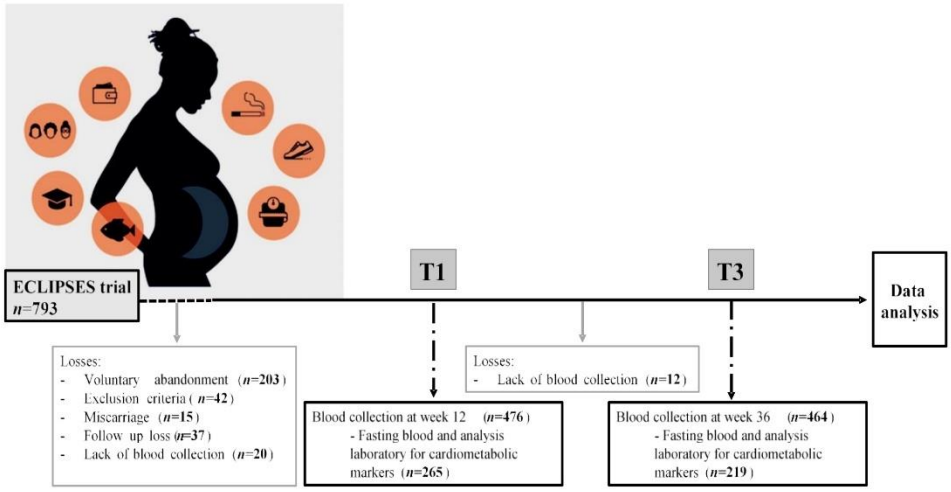

Figure 1. Flow chart of the study population.

2.2. Data Collection

Midwives and nutritionists collected the participants' medical and obstetric history, gestational age, socioeconomic information, and education level. In the first and third-trimesters of pregnancy, lifestyle habits (PA, smoking, diet, and alcohol consumption), BP, and anthropometric measurements were also collected. The socioeconomic level was classified as low, mid, or high according to the Catalan classification of occupations (CCO-2011) [26]. Education level was classified as low (primary), medium (high school), and high (university studies or above). PA was measured using the short version of the International PA Questionnaire (IPAQ-S) [27]. Derived from total metabolic equivalents (METs-min/week) and based on the frequency and duration of walking and moderate and vigorous-intensity activity, this variable was divided into tertiles for analysis. The Fagerström questionnaire [28] was used to assess smoking, with women divided into three groups: current, former, and never smokers.

Eating habits were assessed through a self-administered food frequency questionnaire (FFQ) based on 45 food groups previously validated in our population [29]. Herein, we focused on women's overall diet quality assessed using the relative rMedDiet score based on the intake of nine food groups [30]. This index, which was previously used in our published paper [30], is a modified version of the original MedDiet Score [31]. The resulting score ranged from 0 to 18 points, with larger values indicating greater diet quality. Since there are no pre-established cut-off points for the pregnant population, we divided the score into tertiles. Alcohol consumption was assessed as 'yes' or 'no'.

Anthropometric measures were weight (kg) and height (cm). BMI was calculated from these measures (weight(kg)/height(m)^2). Women were classified following WHO criteria [32] into normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), or obesity (BMI ≥ 30 kg/m^2) in the first-trimester. Total GWG, calculated from the difference between the weights measured in the first and third-trimester visits and taking into account initial BMI, was categorized as insufficient, adequate, or excessive in accordance with 2009 IOM recommendations [33].

Results

2.3. Cardiometabolic Risk Markers

Blood samples were collected at weeks 12 and 36 of pregnancy after an overnight fast and stored at −80 °C inside the Biobank until analysis. The fasting serum cardiometabolic biomarkers assessed included glucose, insulin, and lipids, which were analyzed at the accredited Laboratori Clínic ICS Camp de Tarragona-Terres de l'Ebre, Joan XXIII University Hospital in Tarragona (Spain). All samples were thawed and analyzed at the same time to minimize inter-batch variation. Simultaneously, glucose, total cholesterol, HDL cholesterol (HDL-c), and triglyceride (TG) concentrations were measured using standard enzymatic automated methods. Intra- and interassay coefficients of variation (CVs) were below 2.2% for all. LDL cholesterol (LDL-c) was calculated using the Friedewald formula (LDL-c = total cholesterol-HDL-c-triglycerides/5). Serum insulin levels were assayed by a chemiluminescent immunoassay method on an ADVIA Centaur analyzer using a commercial kit (ADVIA Centaur IRI, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). Lower and upper detection limits were 0.5 and 300 mUI/L, respectively. The intra- and interassay CV ranges were 3.3–4.6% and 2.6–5.9%, respectively.

Insulin resistance was estimated by homeostasis model assessment (HOMA-IR) using the following equation: HOMA-IR = fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5.

SBP and DBP were measured in both trimesters using an automatic digital monitor (Omron HEM-705CP).

A clustered cardiometabolic risk (CCR) score was created by summing all standardized z-scores (z = value-mean/SD of the whole population) of the seven cardiometabolic markers assessed (BMI, SBP, glucose, HOMA-IR index (log), TG (log), LDL-c, and HDL-c). HDL-c was calculated after values were multiplied by −1 since it is inversely related to metabolic risk. Only SBP was considered in the CCR score since SBP and DBP were highly correlated. A higher CCR score entails greater cardiometabolic risk. The rationale for selecting this CCR score and its components were based on a previous pregnancy study that used a similar risk score and factors [5].

The continuous CCR score was estimated for 264 women and 215 women whose seven health parameters were measured in the first and third trimester of pregnancy, respectively. In this study, the CCR score and each cardiometabolic factor were the primary and secondary outcomes, respectively.

2.4. Statistical Analysis

All statistical analyses were performed using the 15.0 version of STATA software (Stata Corp LP, College Station, TX, USA). Descriptive statistics were used to characterize the population. Data are expressed as mean ± SD for quantitative variables and number (%) for categorical variables.

The normality of the data was tested using both statistical (Shapiro–Wilk test) and graphical methods (histograms and scatter plots). Variables non-normally distributed were logarithmically transformed for analyses (insulin, HOMA-IR, and TG). The between-group differences in each cardiometabolic risk variable in both trimesters were analyzed by one-way ANOVA with Bonferroni's test for post hoc comparison and Student's T-test, as appropriate. Paired-samples *t*-tests were performed to evaluate intra-group differences for the cardiometabolic risk variables between the first and the third trimesters.

Multivariable linear regression analyses were performed to evaluate the independent contributions of selected sociodemographic and lifestyle characteristics of the pregnant women on the CCR score and each cardiometabolic risk factor (BMI, SBP, DBP, glucose, insulin, HOMA-IR, TG, HDL-c, LDL-c) in the first and third trimesters of pregnancy. A multivariable linear regression analysis was also performed to evaluate the independent contribution of the first-trimester CCR score to the third-trimester CCR score. We used our prior knowledge to select the following prenatal characteristics: age (<25, 25–29, ≥30 years), social class (lower/medium, high), education level (primary/secondary, university

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studies), smoking status (non-smoker, current/former smoker), alcohol consumption (no, yes) PA (METs-min/week, tertiles), rMedDiet score (tertiles), and GWG (insufficient, adequate, excessive). Estimates were presented as β coefficient (β) and 95% confidence intervals (CIs). Multicollinearity was assessed by inspecting the tolerance (1/VIF) values and variance inflation factors (VIFs) for this multivariable model. All tolerance values were above 0.7 and all VIFs were below 2.0, which suggests there were no concerns over multicollinearity. Statistical significance was set at $p < 0.05$.

3. Results

The sociodemographic and lifestyle characteristics of pregnant women are shown in Table 1. The mean age of the women was 29.6 (SD, 4.7), with 57% of them over 30 years old. Their mean initial BMI was 24.1 (3.5) kg/m2, with roughly 36% of them classified as overweight/obese with a BMI ≥25.0 kg/m2. Their mean GWG was 10.4 (3.6) kg. According to IOM recommendations, 37% of the women met the criteria for GWG, while 45% fell below them and 18% exceeded them. A third of the women (32%) had received a university education, 19% of them were from a high social class, and 31% were former smokers or smoked during pregnancy. Mean PA was 475.8 (701.9) METs-min/week and the mean rMedDiet score was 9.4 (2.4).

Table 1. Sociodemographic and lifestyle characteristics of pregnant women in the first trimester of pregnancy (n = 265).

General Characteristics	Summary Statistics
Age (years), mean ± SD	29.6 ± 4.7
Age categories (years), n (%)	
<25	40 (15)
25–29	73 (28)
≥30	152 (57)
Weight (kg), mean ± SD	63.3 ± 9.6
BMI (kg/m²), mean ± SD	24.1 ± 3.5
BMI categories, n (%)	
18.5–24.9 (normal weight)	169 (64)
25.0–29.9 (overweight)	82 (31)
≥30 (obesity)	14 (5)
GWG (kg), mean ± SD	10.4 ± 3.6
IOM GWG recommendations, n (%)†	
Insufficient	119 (45)
Adequate	99 (37)
Excessive	47 (18)
Educational level, n (%)	
Low (primary or below)	83 (31)
Medium (secondary)	97 (37)
High (university or above)	84 (32)
Social class, n (%)	
Low	35 (13)
Medium	180 (68)
High	49 (19)
Smoking status, n (%)	
Never smoker	185 (70)
Former smoker	42 (16)
Current smoker	37 (14)
Alcohol consumption	
No	222 (87)

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Yes	33 (13)
Physical Activity (METs-min/week)	
T1 (<1070)	87 (33)
T2 (1070–3336)	117 (44)
T3 (≥3336)	60 (23)
rMedDiet score (point)	
T1 (<9)	92 (36)
T2 (9–12)	107 (42)
T3 (≥12)	56 (22)

Values are expressed in means ± SD (standard deviation) or number (%, percentage). Abbreviations: BMI, body mass index; GWG, gestational weight gain; IOM, Institute of Medicine; METs, metabolic equivalents; T, tertile; rMedDiet, Mediterranean diet; [1]Recommendations for GWG according to IOM guidelines are: initial BMI < 18.5 kg/m², total weight gain 12.5–18 kg; BMI 18.5–24.9 kg/m², total weight gain 11.5–16 kg; BMI 25.0–29.9 kg/m², total weight gain 7–11.5 kg; and BMI ≥ 30 kg/m², total weight gain 5–9 kg.

All cardiometabolic markers and lipid parameters increased between the first and third trimesters, while fasting glucose decreased (all $p < 0.05$).

Comparisons between the characteristics of pregnant women in relation to their CCR score and its components between the first and third-trimesters are shown in Supplementary Tables S1 and S2, respectively. Results from multivariate-adjusted regression analyses in the first trimester are shown in Table 2. These cross-sectional analyses showed that, irrespective of other factors: age above 30 years was significantly associated with greater HDL-c levels; university education was associated with lower BMI and SBP; and a higher level of PA was associated with lower LDL-c levels (all $p < 0.05$). Multiple regression analysis, on the other hand, showed that obese/overweight status in early pregnancy was, as expected, independently and positively associated with BMI, SBP, DBP, insulin, HOMA-IR, and LDL-c levels (all $p < 0.05$).

Prospective multivariate-adjusted analyses (Table 3) showed that the associations between overweight/obesity status and higher BMI and lower HDL-c levels persisted in the third-trimester even after potential confounders were controlled (all $p < 0.05$). Similarly, BMI and SBP levels were higher in women with excessive GWG, while HDL-c levels increased. Moreover, multivariate analysis showed that smoking and drinking alcohol in pregnancy were independent factors associated with fasting TG and LDL-c, and both SBP and DBP, respectively, as time progressed. However, BMI, SBP and DBP levels and fasting glucose concentrations showed a significant inverse association with insufficient GWG. Additionally, women with a university education showed smaller increases in BMI during their pregnancy, while high social class was inversely associated with lower fasting glucose, insulin, and HOMA-IR levels at the end of pregnancy (all $p < 0.05$).

Table 2. Multivariate-adjusted linear regression models of the associations between sociodemographic and lifestyle characteristics[1] of pregnant women and cardiometabolic risk markers in the first trimester of pregnancy.

	Cardiometabolic Risk Markers in the First Trimester																	
	BMI (kg/m²)		SBP (mm Hg)		DBP (mm Hg)		Glucose (mg/dL)		Insulin (mU/L)†		HOMA-IR‡		Triglycerides (mg/dL)†		HDL-c (mg/dL)		LDL-c (mg/dL)	
Characteristics	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Age categories (years)																		
<25 vs. 25–29	−0.09	0.843	1.62	0.491	1.73	0.269	2.97	0.188	−0.20	0.085	−0.16	0.208	−0.13	0.095	4.88	0.068	−1.90	0.714
<25 vs. ≥30	0.04	0.920	2.02	0.371	1.93	0.199	3.34	0.123	−0.08	0.442	−0.04	0.731	−0.05	0.508	6.93	**0.007** **	2.24	0.652
BMI categories																		
Normal weight vs. overweight/obesity	5.83	**<0.001** **	5.42	**0.001** **	3.64	**<0.001** **	1.95	0.188	0.30	**<0.001** **	0.33	**<0.001** **	0.09	0.067	−2.56	0.144	6.80	**0.045** *
Educational level																		
Low/medium vs. high	−0.68	**0.030** *	−4.12	**0.017** *	−1.61	0.158	−1.46	0.373	0.01	0.923	−0.01	0.937	−0.08	0.162	2.92	0.132	0.31	0.934
Social class																		
Low vs. medium/high	−0.05	0.889	1.96	0.383	0.06	0.969	0.23	0.916	−0.18	0.107	−0.16	0.186	−0.00	0.998	0.17	0.947	1.18	0.811
Smoking status																		
Never smoker vs. current/former smoker	−0.20	0.489	−2.62	0.103	−0.99	0.353	2.33	0.130	−0.05	0.492	−0.01	0.893	−0.09	0.081	−1.54	0.395	−3.63	0.303
Alcohol consumption																		
No vs. yes	0.02	0.970	3.21	0.144	1.70	0.243	−0.44	0.834	−0.08	0.473	−0.07	0.529	−0.04	0.547	0.48	0.845	0.97	0.840
PA (METs-min/week)																		
T1 vs. T2	0.05	0.875	−0.32	0.851	−1.50	0.181	0.46	0.775	0.017	0.839	0.01	0.871	−0.06	0.307	0.11	0.954	−2.98	0.420
T1 vs. T3	−0.57	0.113	−0.94	0.632	−1.45	0.265	0.85	0.648	−0.08	0.421	−0.07	0.497	−0.12	0.068	2.38	0.282	−9.83	**0.023** *
rMedDiet score (point)																		
T1 vs. T2	−0.31	0.308	−1.33	0.422	−0.32	0.770	0.74	0.643	−0.01	0.968	0.00	0.993	0.09	0.087	−0.63	0.738	3.02	0.407
T1 vs. T3	−0.45	0.216	−0.20	0.919	−0.30	0.823	1.32	0.487	−0.09	0.357	−0.07	0.517	0.11	0.077	0.48	0.829	−3.78	0.387

Multivariate linear regression models were used to calculate the β coefficient (β). The models were run separately for each cardiometabolic risk marker. The models were mutually adjusted for all characteristics displayed in this table. Abbreviations: BMI, body mass index; PA, Physical Activity; METs, metabolic equivalents; T, tertile; rMedDiet, Mediterranean diet; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-cholesterol. [1] In the first trimester of pregnancy. †Natural log-transformed values. * The significance of the numbers in bold is *p*-value < 0.05. ** The significance of the numbers in bold is *p*-value < 0.001.

Table 3. Multivariate-adjusted linear regression models of the associations between sociodemographic and lifestyle characteristics[1] of pregnant women and cardiometabolic risk markers in the third trimester of pregnancy.

	Cardiometabolic Risk Markers in the Third Trimester																	
	BMI (kg/m²)		SBP (mm Hg)		DBP (mm Hg)		Glucose (mg/dL)		Insulin (mU/L)‡		HOMA-IR†		Triglycerides (mg/dL)‡		HDL-c (mg/dL)		LDL-c (mg/dL)	
Characteristics	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Age categories (years)																		
<25 vs. 25–29	0.50	0.225	−0.92	0.705	−0.41	0.822	2.48	0.276	−0.15	0.264	−0.11	0.444	−0.02	0.844	3.49	0.278	6.05	0.456
<25 vs. ≥30	0.50	0.200	0.25	0.913	−0.69	0.696	3.03	0.164	−0.19	0.140	−0.15	0.283	−0.04	0.712	3.07	0.317	8.81	0.256
BMI categories																		
Normal weight vs. over weight/obesity	4.14	**<0.001** **	−0.79	0.669	2.33	0.097	−1.99	0.252	0.16	0.120	0.11	0.305	0.11	0.180	−5.10	**0.039** *	−1.21	0.845
IOM GWG recommendations																		
Adequate vs. insufficient	−1.32	**<0.001** **	−4.07	**0.018** *	−3.45	**0.008** *	−3.38	**0.036** *	−0.05	0.584	−0.10	0.340	0.09	0.229	0.90	0.690	−0.27	0.962
Adequate vs. excessive	2.15	**<0.001** **	5.76	**0.017** *	1.01	0.580	−0.58	0.795	0.10	0.448	0.11	0.441	0.04	0.730	8.02	**0.012** *	4.46	0.576
Educational level																		
Low/medium vs. high	−0.58	0.053	0.16	0.929	−0.74	0.577	−1.28	0.436	−0.09	0.323	−0.11	0.297	−0.08	0.330	2.23	0.336	1.12	0.060
Social class																		
Low vs. medium/ high	−0.38	0.342	−1.78	0.447	−0.64	0.719	−5.87	**0.008** *	−0.40	**0.002** *	−0.49	**<0.001** **	−0.15	0.153	2.32	0.454	−7.57	0.335
Smoking status																		
Never smoker vs. current/former smoker	0.29	0.311	−0.43	0.799	1.27	0.321	−0.77	0.625	0.09	0.304	0.08	0.395	0.18	**0.016** *	3.07	0.168	1.19	**0.034** *
Alcohol consumption																		
No vs. yes	−0.20	0.586	4.74	**0.032** *	3.57	**0.034** *	1.41	0.493	−0.02	0.859	0.01	0.959	−0.00	1.000	−1.94	0.503	1.57	**0.032** *
PA (METs-min/week)																		
T1 vs. T2	0.19	0.523	1.99	0.257	−1.15	0.388	1.33	0.414	0.00	0.960	0.03	0.789	−0.09	0.230	1.54	0.504	−2.35	0.685
T1 vs. T3	−0.52	0.130	0.62	0.760	−1.72	0.263	−1.75	0.356	0.13	0.237	0.09	0.465	−0.01	0.877	0.67	0.801	−4.47	0.508
rMedDiet score (point)																		
T1 vs. T2	0.21	0.491	−1.27	0.470	0.66	0.624	−1.99	0.226	−0.02	0.819	−0.06	0.536	0.05	0.562	3.66	0.117	−7.02	0.233
T1 vs. T3	−0.19	0.587	1.42	0.494	0.14	0.931	−0.84	0.665	−0.11	0.339	−0.12	0.333	0.06	0.527	2.12	0.438	−2.89	0.675

Multivariate linear regression models were used to calculate the β coefficient (β). The models were mutually adjusted for all characteristics displayed in this table. Abbreviations: BMI, body mass index; GWG, gestational weight gain; IOM, Institute of Medicine; PA, Physical Activity; METs, metabolic equivalents; T, tertile; rMedDiet, Mediterranean diet; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-cholesterol. [1]In the first trimester of pregnancy (except for GWG). ‡Geometric means of log-transformed values. * The significance of the numbers in bold is *p*-value < 0.05. ** The significance of the numbers in bold is *p*-value < 0.001.

Figure 2, which shows subgroup analyses by different variables of interest, reveals statistically significant associations between CCR scores and overweight/obesity status (positive), university education (negative), and higher levels of PA (negative) at the beginning of pregnancy (all $p < 0.05$). Note that the associations between overweight/obesity status and CCR score persisted into the third-trimester. Moreover, a significant association was found between women with insufficient GWG and those with high social class and lower CCR scores (all $p < 0.05$). In the third-trimester, no significant association with other factors was found.

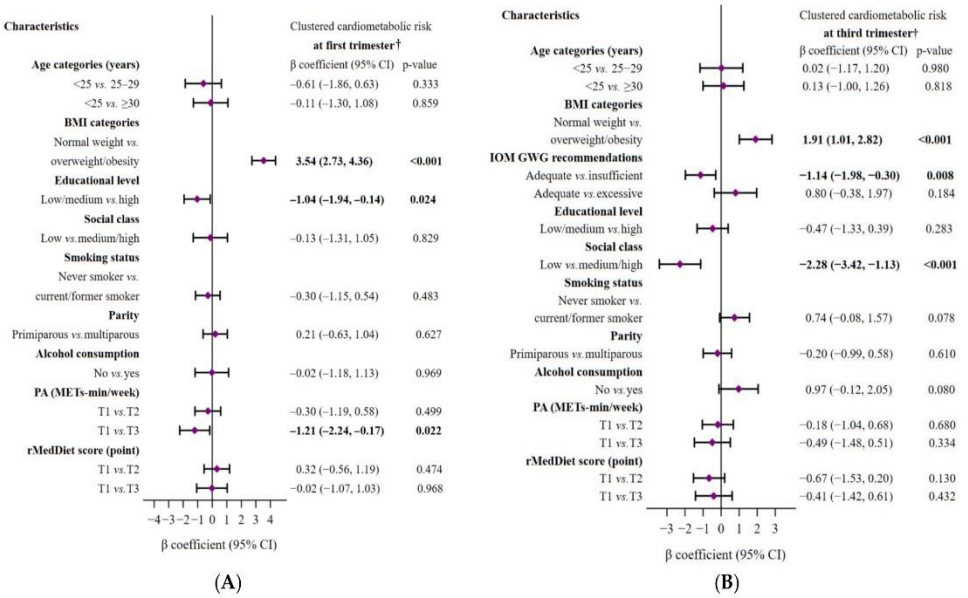

Figure 2. Multivariate-adjusted linear regression models of the associations between sociodemographic and lifestyle characteristics of pregnant women and clustered cardiometabolic risk in the first (**A**) and third (**B**) trimesters of pregnancy. The models were mutually adjusted for all characteristics displayed in each figure. The diamonds represent the β coefficient (β), and the whisker plots represent 95% CIs. The significance of the numbers in bold is *p*-value < 0.05. Abbreviations: BMI, body mass index; GWG, gestational weight gain; IOM, Institute of Medicine; PA, Physical Activity; METs, metabolic equivalents; T, tertile; rMedDiet, Mediterranean diet. †A higher clustered cardiometabolic status signifies higher cardiometabolic risk.

After adjusting for confounding factors, we found that the first-trimester CCR score was significantly and independently related to the third trimester CCR score (β: 0.31, 95%CI: 0.19, 0.43; $p < 0.001$).

4. Discussion

This study describes the association between maternal factors (socio-demographic and lifestyle characteristics) and clustering cardiometabolic risk and its components throughout pregnancy in a Spanish population of healthy pregnant women. Our main findings are that potentially modifiable prenatal factors, such as having a normal weight in early pregnancy, lower GWG, and more PA, as well as higher education and social class levels, were significantly and independently associated with lower CCR. Smoking and drinking alcohol during pregnancy also showed a non-significant trend towards higher CCR at the end of pregnancy. The results of each cardiometabolic biomarker also maintained the same relationship. Interestingly, the women's CCR score in the first trimester

was an independent predictor of their CCR score in the third trimester, which suggests cardiometabolic risk progressed as pregnancy advanced.

We can hypothesize from our findings that BMI at pregnancy baseline is more relevant than GWG when predicting cardiometabolic risk during pregnancy. Indeed, we found that early pregnancy overweight/obesity was the strongest predictor of the CCR score in both early and late pregnancy. Despite the importance of maternal obesity for the subsequent development of cardiovascular and metabolic alterations, to our knowledge, this is the first time that this relationship has been described in pregnant women using a composite risk score. Moreover, overweight/obese women had a less favorable cardiometabolic profile, with higher SPB, DPB, insulin resistance, and LDL-c in the first-trimester than their normal-weight counterparts. As our results and those of other studies conducted in the first-trimester of pregnancy show, being overweight/obese increases the risk of hypertension in pregnant women [34,35].

We found that SBP and DBP in women with insufficient GWG decreased in the third-trimester. These findings are consistent with a recent meta-analysis of observational studies, which showed that excessive GWG is associated with a higher risk of hypertensive disorders during pregnancy [36] and should therefore be avoided.

Our data support previous evidence that showed that overweight/obese pregnant women had significantly higher insulin and HOMA-IR, especially in the first-trimester [37]. However, the effect of GWG on glucose metabolism is less studied and the few data published are somewhat contradictory [38–40]. In the present study, women who did not gain enough weight during pregnancy had lower blood glucose levels in the third trimester than those with adequate weight gain. It has been argued that, just like outside pregnancy, an increase in maternal adiposity during pregnancy causes a higher systemic inflammatory response and greater oxidative stress, which in turn promote hyperglycemia and, eventually, insulin resistance [41,42].

Serum lipid concentrations are known to increase as pregnancy progresses [19,43,44]. However, this pregnancy-associated hyperlipidemia appears to be exacerbated in overweight/obese women, probably as a result of insulin resistance [39,45–47]. In line with previous studies [45,46], our data suggest that overweight/obese pregnant women are more likely to present a more pro-atherogenic lipid profile. Our data also showed a positive association between excessive GWG and a significant increase in HDL-c in the third-trimester. In accordance with this observation, a recent study suggested that high levels of HDL-c in the third-trimester, especially in women with excessive GWG, may be considered a high-risk indicator of small size for gestational age [48].

From our findings and the above evidence, it is imperative that overweight/obese women of reproductive age should be encouraged to undertake preconception-intensive behavioral lifestyle interventions for weight loss and improve their metabolic status before and during very early pregnancy [49]. As Catalano suggests [50], unfavorable maternal status in terms of weight or cardiometabolic profile in early pregnancy is a harbinger of future abnormalities in late pregnancy and beyond. Those findings are also supported by our study, which found a significant association between first and third-trimester CCR scores.

With regard to lifestyle factors such as diet, there is clear evidence that certain individual nutrients and food groups are associated with cardiovascular risk also in the pregnant population [5–8]. However, our study did not show a relationship between the quality of the maternal diet (using the Mediterranean diet score) and cardiometabolic risk during pregnancy. Nevertheless, our results support the importance of adhering to this healthy dietary pattern since it protects against maternal obesity, excessive GWG, and other adverse short-term and long-term maternal and child outcomes [51]. A more specific study focused on individual dietary components (nutrients or food groups) could establish a relationship.

Similar to other Spanish studies [52], 13% of the pregnant women in our study consumed alcohol. Our findings support previous results [16] that showed that in the third-

trimester, SBP, DBP, and LDL-c were higher in women who consumed alcohol than in those who did not.

Exposure to tobacco smoke during pregnancy also influences lipid-profile parameters. We also found that pregnant smokers had significantly higher third trimester levels of TG and LDL-c, even after adjusting for BMI and GWG, as well as a tendency towards a worse cardiometabolic risk profile. The two epidemiological studies conducted in this field so far have also revealed a more unfavorable lipid profile in pregnant smokers than in pregnant non-smokers [14,15]. Increased lipoprotein lipase (LPL) activity may be responsible for elevated LDL-c levels through the LPL-mediated degradation of TG-rich chylomicrons and VLDL, which, probably induced by nicotine, is markedly higher in smokers [53]. Another effect of nicotine on lipid metabolism is impaired LDL-c clearance [54]. Moreover, nicotine also increases circulating free fatty acid through enhanced lipolysis resulting from sympathoadrenal stimulation [55]. Thus, smoking and the presence of lipid disorders are inadvisable during pregnancy since they may also contribute to deleterious cardiovascular and atherogenic effects.

With regard to maternal PA, our results agree with those of earlier studies which suggest that habitual PA reduces TG and total cholesterol during early pregnancy [56,57], and LDL-c in the last two trimesters [56,57]. This highlights the importance of promoting PA to control lipid disorders, especially in the first-trimester when the fetal organs are formed, and the placenta begins to develop [58].

In the present study, socio-environmental factors, especially higher levels of education (in relation to lower BMI and SBP) and social class (in relation to lower fasting glucose, insulin, and HOMA-IR) were also strongly associated with better cardiometabolic markers and lower CCRs in the first and third-trimesters of pregnancy, respectively. Generally, these findings are supported by those of previous studies [3,59,60]. However, the nature of such associations during pregnancy remains unclear. They probably reflect a combination of social/psychological factors and healthier behaviors (in those with higher education) that result directly or indirectly in cardiometabolic benefits. We found, for example, that pregnant women with higher social and educational levels were older and had lower early pregnancy BMI. In the present study, these factors appear to be associated with a better metabolic phenotype during gestation.

The main strength of our study is the analysis of cardiometabolic health during pregnancy using a clustering of cardiometabolic risk factors, which provides greater overall risk than any individual factor on its own. This approach has rarely been used in previous studies. Moreover, we decided to use a CCR score that combined clinical and biochemical parameters, including adiposity, BP, insulin resistance, and lipids, since these can be measured easily in routine clinical practice and, even more importantly, are all major risk factors for cardiovascular disease. Additionally, the continuous CCR score is statistically more sensitive and less prone to error than categorical forms. Another advantage of our study is its prospective design and relatively large sample size, reinforcing the usefulness of our results. However, certain study limitations should also be considered. Namely, we use the maternal final weight at around 36 weeks to calculate GWG, which may cause misclassification of the GWG category, especially among overweight/obese women, thus reducing the estimated effect. Additionally, the CMR score is specific to this study sample, and we assumed that each component has equal weight in predicting metabolic risk.

5. Conclusions

Our findings provide evidence of the effects of sociodemographic, lifestyle, and clinical characteristics during pregnancy on cardiometabolic health in a Spanish Mediterranean population of healthy pregnant women. The most protective modifiable prenatal factors of cardiometabolic risk during pregnancy were being of normal weight, having higher levels of education and social class, engaging in greater PA, being a non-smoker, and not drinking alcohol. These findings will help policymakers to improve metabolic status in women before and/or during very early pregnancy in order to prevent obstetric

Results

complications. Further prospective studies are needed to determine whether clustering cardiometabolic risk variables helps to determine the risk of adverse mother and fetus/child outcomes more than individual risk factors.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu15051135/s1, Table S1: Comparisons of selected sociodemographic and lifestyle characteristics† of pregnant women for single risk factors and cardiometabolic risk scores in the first trimester of pregnancy. Table S2: Comparisons of selected sociodemographic and lifestyle characteristics† of pregnant women for single risk factors and cardiometabolic risk scores in the third trimester of pregnancy.

Author Contributions: V.A. designed and conducted the research. V.A. performed data curation. A.D.-I.. and E.M. analyzed the data and wrote the article. E.M., A.D.-I.., F.M.-I.., J.B., and V.A. revised the manuscript for important intellectual content and read and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no one who meets the criteria has been omitted. V.A. is the guarantor of this work, as such, she has had full access to all study data and takes responsibility for their integrity and for the accuracy of the data analysis. E.M., A.D.-I.., F.M.-I.., J.B., and V.A. have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was registered both in ClinicalTrials.gov (identification number NCT03196882) and the EU Clinical Trials Register (EUCTR-2012-005480-28). The study was approved by the Ethical Committee of the Jordi Gol Institute for Primary Care Research and the Pere Virgili Institute for Health Research Research (approval ID: 118/2017. Date: 28 September 2017) and complied with the tenets of the Helsinki declaration.

Informed Consent Statement: All participants signed an informed consent form.

Data Availability Statement: The datasets generated and/or analyzed during the current study are not publicly available due to subject confidentiality but are available from the corresponding author on reasonable request.

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MATERNAL CARDIOMETABOLIC HEALTH AND FETAL DEVELOPMENT: INSIGHTS FROM PRENATAL TO POSTNATAL LIFE
Ehsan Motevalizadeh

Publication 2. Association of parity with insulin resistance early in pregnant women: ECLIPSES study.

Ehsan Motevalizadeh, Andrés Díaz-López, Francisco Martín, Josep Basora, Victoria Arija.

Overview of the novelty and significance of this work

Literature Review

- ✓ The relationship between high early-pregnancy IR and parity has not been well understood by previous studies.
- ✓ The role of OWO in exacerbating the potential effect of parity on early-pregnancy IR remains unclear.

Novelty Contribution

- ✓ This study contributes novel insights by demonstrating a positive association between parity and early-pregnancy insulin levels as well as the HOMA-IR index, indicating a potential negative impact of parity on IR during early pregnancy.
- ✓ It elucidates that maternal OWO may intensify this association, implying a synergistic effect of parity and OWO on early pregnancy IR.

Conclusion

- ✓ The findings of this investigation illustrate the potential adverse effect of parity on early-pregnancy IR, with maternal OWO exacerbating this association.

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Clinical Research Article

Association of Parity With Insulin Resistance Early in Pregnant Women: ECLIPSES Study

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Abstract

Context: Little is known about whether parity is associated with elevated early-pregnancy insulin resistance (IR), or whether overweight/obesity contributes to increasing the possible effect.

Objective: We determined the associations between parity and glucose metabolism parameters in the first trimester of pregnancy in a Mediterranean pregnant population, and whether these associations are affected by overweight/obesity.

Methods: A cross-sectional study was conducted of 264 healthy pregnant women from the ECLIPSES study who were recruited at 12 weeks of gestation. At baseline, details on socioeconomic status, obstetric history (including parity, ie, number of births), lifestyle factors, anthropometry, and blood samples were collected. Fasting serum glucose, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) index were assessed in the first trimester. Elevated IR was defined as the upper HOMA-IR tertile (≥1.58). Multivariable linear regression and Cox regression model with constant time were performed.

Results: Parity ranged from 0 to 4. After multivariable adjustment, the insulin levels (β [% change]: 20.92; 95% CI, 4.08-37.71) and HOMA-IR index (β [% change]: 19.72; 95% CI, 2.43-40.49) were positively associated with parity. Additionally, multiparous women, as compared to nulliparous, were more likely to have higher HOMA-IR levels (primiparous [1 birth], β [% change[: 16.88; 95% CI, −1.00 to 37.99; multiparous [≥2 births), β [% change]: 32.18; 95% CI, 3.56-68.71), and an increased relative risk (RR) of an elevated IR (primiparous [1 birth], RR: 1.55; 95% CI, 1.03-2.36; multiparous (≥2 births), RR: 1.72; 95% CI, 1.05-2.83). The combination of multiparity and overweight/obesity conferred a 3.04-fold increase in the RR of elevated IR, which increased proportionally to the number of parities.

Conclusion: This study demonstrates that parity may have a negative effect on early-pregnancy IR and that maternal overweight/obesity appears to further aggravate this relationship.

Key Words: parity, multiparous, insulin resistance, pregnancy, ECLIPSES

Abbreviations: ECLIPSES, Ensayo CLInico Para Suplementar con hierro a EmbarazadaS; ep-BMI, early-pregnancy body mass index; GD, gestational diabetes mellitus; HOMA-IR, homeostasis model assessment of insulin resistance; MET, metabolic equivalent; NW, normal weight; OWO, overweight/obesity; PA, physical activity; rMedDiet, Relative Mediterranean Diet; RR, relative risk; SES, socioeconomic status; T, tertile; VIF, variance inflation factor.

Pregnancy is a time-limited condition, in which women undergo significant physiological and metabolic changes. These changes lead to maternal fat accumulation and a gradual increase in peripheral insulin resistance (IR) (1) throughout pregnancy to accommodate the growing fetus (2). However, it is important to note that excessive maternal hyperglycemia- and hyperinsulinemia-induced IR in early pregnancy is a hallmark of a metabolic disorder. This condition has recently emerged as the prominent cause of pregnancy complications and adverse perinatal outcomes, including gestational diabetes mellitus (GD) (3); preeclampsia (4); macrosomia, being large for gestational age; and cesarean delivery (5).

Moreover, although earlier studies (1, 2, 6, 7) suggest that maternal IR returns to prepregnancy levels by 1 year postpartum, the recent literature casts some doubt on this premise (8, 9). It has been hypothesized that recurrent maternal IR episodes due to repeated pregnancies lead to a progressive worsening of the glucose tolerance in each pregnancy, manifesting in GD or it may even permanently disturb glucose homeostasis in women in later life (8-11). Nevertheless, the underlying mechanisms for parity-related IR during pregnancy are largely unknown, complex, and most likely reflect a range of factors, such as placental hormones, lifestyle modifications, and genetic and epigenetic contributions (12).

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In this regard, the effect of the multiparity on the GD or recurrent GD during later pregnancies has been a topic of research for the last few years (11, 13). Nonetheless, the results are not completely convincing, that is, the high rate of GD among multiparous women could be due to the confounding effect of higher maternal age or body adiposity (14, 15). In addition, the diagnosis of GD is not made until the latter half of pregnancy (at 24-28 weeks) (16), which might be too late to completely reverse the intrauterine hyperglycemia-induced adverse effects on offspring that can occur in the early stages of pregnancy (17). Alternatively, maternal IR in the first trimester, assessed by the homeostasis model assessment of the IR index (HOMA-IR), has been proposed as a reliable marker to predict subsequent GD (3, 18). In this context, there are few studies examining whether repeated parity could be associated with an increased risk of IR in very early pregnancy. This is possibly because IR is not routinely assessed during prenatal examinations.

To the best of our knowledge, only 3 studies have researched this relationship; however, their findings are inconsistent (19-21). Two studies have found a positive association between IR in middle pregnancy (20-30 weeks' gestation) and parity (20, 21), which was not confirmed by the study by Seghieri et al (19). In this last study, the authors (19) found that parity is not directly linked to insulin sensitivity/secretion during the last trimester in pregnant women at high risk of GD; however, high pregestational body mass index (BMI) was strongly related to a considerable impairment in insulin sensitivity during this period. In accordance with these findings, at least in part, we recently found that maternal BMI in early pregnancy is more relevant than gestational weight gain for predicting cardiometabolic risk during pregnancy (22).

Nevertheless, it remains undetermined whether parity confers an independent effect on early-pregnancy IR, and particularly in a healthy Mediterranean pregnant population, in which the sociodemographic and Mediterranean lifestyle traits of women can be regarded as protective factors against IR. It is also necessary to determine whether parity contributes, in combination with high maternal BMI, to a worse IR. Thus, the aim of the present study is to assess how parity is related to glucose metabolism parameters measured early in pregnancy in a pregnant population from a Mediterranean region of northern Spain, and assess whether these associations vary according to overweight/obesity status.

Materials and Methods

Study Design and Participants

We conducted a retrospective study analyzing data from 264 healthy pregnant women with singleton pregnancies and without previous history of diabetes. These women had data available on parity history, fasting serum glucose, and insulin concentrations in the first trimester (at ~12 weeks' gestation). Women participated in the ECLIPSES (Ensayo CLInico Para Suplementar con hierro a EmbarazadaS) study, in which a total of 791 pregnant women were recruited during their first antenatal visit in 12 sexual and reproductive health care services (ASSIR) of the Catalan Institute of Health (Catalonia, Spain) between 2013 and 2017. Briefly, the ECLIPSES aimed to determine the highest level of effectiveness of iron supplementation based on hemoglobin levels in early pregnancy to optimize maternal and child health. Details of the study's protocol, as well as inclusion/exclusion criteria, have been described elsewhere (23). The ECLIPSES study was registered at www.clinicaltrialsregister.eu (ID: EUCTR-2012-005480-28) and at www.clinicaltrials.gov (ID: NCT03196882). Ethical approval for the study was obtained from the Jordi Gol Institute for Primary Care Research and the Pere Virgili Institute for Health Research. The research complies with the tenets of the Helsinki Declaration. Participants provided written informed consent.

Data Collection

Midwives and nutritionists collected data on demographic characteristics (age, socioeconomic information, and education level), health behaviors (physical activity [PA], smoking, and diet), medical and obstetric history (planned pregnancy [yes, no]), as well as anthropometric measurements in the first trimester of pregnancy (at week 12). Familiar socioeconomic status (SES) was calculated by combining information on occupational status, classified according to the Catalan classification of occupations (CCO-2011), and educational level. It was then classified as low, middle, or high. The women's educational level was classified into 3 groups: low (primary school or less), medium (secondary studies), and high (university studies or more).

PA was measured using the short version of the International Physical Activity Questionnaire (IPAQ-S) (24). This was derived from total metabolic equivalents (METs-min/week) values based on frequency and duration of walking and moderate and vigorous-intensity activity and divided into tertiles (T1: <1070, T2: 1070-3336, T3: ≥ 3336 METs-min/week).

Smoking was assessed with the Fagerström questionnaire (25) and women were classified into 3 groups: current, former, and never smokers. Eating habits were assessed by dietitians using a 45-item self-administered food frequency questionnaire validated in our population (26). Herein, we focused on women's overall diet quality assessed by using a relative Mediterranean Diet (rMedDiet) score, which has been used in the previous ECLIPSES studies (27). For this study, based on the participant distributions, the continuous rMedDiet score (ranging from 0 to 18 points) was categorized into tertiles (T1: <9, T2: 9-12, T3:≥12 points). Alcohol consumption was assessed as yes or no.

Maternal weight (kg) and height (cm) were also measured. Early-pregnancy BMI (ep-BMI) (ie, at week 12) was calculated from these measurements (weight [kg]/height [m^2]), and women were classified into 2 groups: normal weight (NW, ep-BMI <25.0) and overweight/obesity (OWO, ep-BMI ≥25.0) for this analysis.

Parity Assessment

Parity was defined as the number of singleton pregnancies of at least 20 weeks (regardless of whether the child was liveborn) as reported by women on the interviewer-administered questionnaire. For this analysis, pregnant women were classified as nulliparous (no prior viable pregnancies) or multiparous (given birth to 1-4). To more accurately examine the effect of parity, in secondary analyses women were categorized as having no children (nulliparous), 1 child, and 2 or more children.

Outcome Ascertainment

Blood samples were collected from pregnant women in the first trimester of pregnancy (12 weeks). Serum was separated from blood cells by centrifugation and stored in Biobank at −80 °C until analysis of the fasting glucose and insulin. We included in the analysis only women who underwent blood tests after an overnight fast. Fasting glucose concentrations were measured using standard automated enzymatic methods. The coefficient of variation was 1.74%. Fasting insulin level was measured by chemiluminescence immunoassay on an ADVIA Centaur analyzer using a commercial kit (ADVIA Centaur IRI, Siemens Healthcare Diagnostics Inc). The lower and upper limits were 0.5 and 300 mUI/L, respectively, and coefficient of variation was 4.88%. All measurements were conducted at the Institut Català de la Salut Camp de Tarragona-Terres de l'Ebre–accredited laboratory, Joan XXIII University Hospital in Tarragona.

IR was assessed according to the HOMA-IR index, calculated according to the following equation: HOMA-IR = [fasting glucose (mmol/L) × fasting insulin (μIU/mL)]/22.5. The HOMA-IR index was analyzed as a continuous variable, with a larger HOMA-IR value indicating more severe IR. In addition, to classify the group at higher risk, HOMA-IR was categorized in tertiles (cutoff points were 1.04 and 1.58), and, while considering statistical power, IR was defined as being in the upper tertile. This HOMA-IR threshold of 1.58 is within the range of the cutoff values of HOMA-IR (1.51-2.31) in the first trimester for predicting GD (18).

Statistical Analysis

Data were analyzed using STATA (15.0, Stata Corp LP). Descriptive data are expressed as mean ± SD for quantitative variables and number (%) for categorical variables. Between-group comparisons were performed with *t* test, chi-square, or analysis of variance test, as appropriate. Since insulin and HOMA-IR were right-skewed, as expected, both were log-transformed to improve normality prior to analysis.

Unadjusted and multivariable-adjusted linear regression models were fitted to estimate the associations of parity, as the main exposure variable, separately with each outcome (fasting glucose, insulin, and HOMA-IR levels). Parity was analyzed using 2 different approaches: as a binary categorical explanatory variable (nulliparous: reference and multiparous), and as an ordinal categorical explanatory variable with 3 categories (0 [nulliparous[: reference, 1 child, and >2 previous children). An additional separate linear regression analysis was also performed to evaluate the joint association of parity and ep-BMI–based weight status in 2 groups (NW and OWO) as predictor, with each outcome. For this analysis, women were grouped into 4 categories: nulliparous + NW (reference), multiparous + NW, nulliparous + OWO, and multiparous + OWO. Based on previously known or association/risk factors for either the exposure, the outcome, or both (12, 22, 28), we considered the following a priori selected covariates as possible confounders: age (<25: reference, 25-29, ≥ 30 years), ep-BMI categories (NW: reference, OWO; except in the parity + ep-BMI analysis, where it was integrated into the composite explanatory variable itself), educational level (low [primary school or less]/medium [secondary studies]: reference, high [university studies or more]), smoking status (never smoker: reference, current/former smoker), alcohol consumption (no: reference, yes), planned pregnancy (no: reference, yes), PA (as T: T1 ≤ 1070: reference, T2 1071-3335, T3 ≥ 3336 METs-min/week), and rMedDiet score (as T: T1 ≤ 8: reference, T2 9-11, T3 ≥ 12 points). Because dietary covariates (MedDiet score and alcohol intake, both 3.2%, n = 9) had missing values, we employed multiple imputation with the chained-equations method to impute missing data (29) based on the correlation of missing variables with other participant characteristics such as maternal age and BMI. For each analysis, we created 20 imputed data sets and pooled the results using the "mi" command in Stata. Estimates were presented as β coefficients (β) with 95% CIs. In the case of log-transformed outcomes (insulin and HOMA-IR), estimates were reported as percentage changes calculated using the equation: (e^β–1) × 100%). The multicollinearity test was carried out by looking at the tolerance (1/VIF) values and variance inflation factors (VIFs). All tolerance values were greater than 0.10 and all VIFs were less than 2.0, so there was no multicollinearity.

In addition, a separate multivariable-adjusted Cox regression model with constant follow-up time set at t = 1 for all individuals (given the cross-sectional design) and robust variance rather than logistic regression was applied to estimate the relative risks (RR) and 95% CI (30) for elevated HOMA-IR index (≥1.58 points) according to parity (nulliparous as reference) and parity + ep-BMI categories (nulliparous + NW as reference) (in separate models); these included the same covariates as the linear models. A test for linear trend was calculated by treating ordinal categorical exposure variable as continuous variable.

Finally, supplementary subgroup multivariable analyses, examining the association of parity with each outcome, were performed stratified by ep-BMI–based weight status (NW and OWO). The interaction between weight status and parity in these associations was assessed by calculating the likelihood ratio test between the fully adjusted model and the same model, including the interaction product term, in the complete data set (n = 255), as it cannot be performed with multiply imputed data. The level of statistical significance was set to 2-sided *P* values less than .05.

Results

The characteristics of the study participants are shown in Table 1. The average age of our sample was 29.6 ± 4.7 years, and a large percentage of the women were older than 30 (57%). The mean ep-BMI was 24.1 ± 3.5, which falls within the normal classification (18.5-24.9), but the prevalence of overweight/obesity was 36.0% at early pregnancy. The analyzed cohort of women did not exhibit significant differences in sociodemographic and lifestyle characteristics when compared to nonparticipants, except for age and ep-BMI, which was lower (both $P < .05$) (data not shown). The parity of our population ranged from 0 to 4; 57.6% of women were multiparous women. The multiparous women were significantly older, less educated, and more likely to be from a higher SES, than nulliparae (see Table 1).

The average fasting glucose, insulin, and HOMA-IR levels were 70.2 ± 10.7 mg/dL, 7.77 ± 1.76 mU/L, and 1.32 ± 1.85 points, respectively, for the total study population (Table 2). We observed that multiparous women had higher insulin and HOMA-IR levels than nulliparous women. Similarly, the HOMA-IR index was significantly higher in overweight/obese women compared to NW peers. This gradually

Results

Table 1. Sociodemographic and lifestyle characteristics of pregnant women

General characteristics	Overall (n = 264)	Parity		P^a
		Nulliparous women (n = 112)	Multiparous women (n = 152)	
Age, mean ± SD, y	29.6 ± 4.7	28.6 ± 4.5	30.6 ± 4.7	**<.001**[c]
Age categories, n (%), y				
<25	40 (15)	25 (22)	15 (10)	
25-29	73 (28)	34 (30)	39 (26)	**.005**[b]
≥30	152 (57)	53 (47)	98 (64)	
Weight, mean ± SD, kg	63.3 ± 9.6	62.9 ± 9.9	63.5 ± 9.5	.57
Ep-BMI, mean ± SD	24.1 ± 3.5	23.9 ± 3.7	24.3 ± 3.4	.48
Ep-BMI categories, n (%)				
Normal weight (BMI < 25)	169 (64)	76 (68)	93 (61)	
Overweight/obesity (BMI ≥ 25)	95 (36)	36 (32)	59 (39)	.264
Educational level, n (%)				
Low (≤ primary)	83 (31)	28 (25)	55 (36)	
Medium (secondary)	97 (37)	36 (32)	61 (40)	**.004**[b]
High (≥ university)	84 (32)	48 (43)	36 (24)	
Familiar SES, n (%)				
Low	35 (13)	7 (6)	28 (18)	
Medium	180 (68)	77 (69)	103 (68)	**.003**[b]
High	49 (19)	28 (25)	21 (14)	
Smoking status, n (%)				
Never smoker	185 (70)	74 (66)	111 (73)	
Former smoker	42 (16)	23 (20)	19 (13)	.21
Current smoker	37 (14)	15 (13)	22 (14)	
Alcohol consumption				
No	222 (84)	95 (85)	127 (84)	.30
Yes	33 (13)	11 (10)	22 (14)	
Missing	9 (3)	6 (5)	3 (2)	
Physical activity (METs-min/wk)				
T1 (≤1070)	87 (33)	36 (32)	51 (34)	
T2 (1071-3335)	117 (44)	51 (45)	66 (43)	.94
T3 (≥3336)	60 (23)	25 (22)	35 (23)	
rMedDiet score (point)				
T1 (≤8)	92 (35)	37 (33)	55 (36)	
T2 (9-11)	107 (41)	41 (37)	66 (44)	.34
T3 (≥12)	56 (21)	28 (25)	28 (18)	
Missing	9 (3)	6 (5)	3 (2)	
Planned pregnancy				
No	62 (23)	22 (20)	40 (26)	.21
Yes	202 (77)	90 (80)	112 (74)	

Values are expressed in means ± SD or number (%, percentage).
Abbreviations: Ep-BMI, early-pregnancy body mass index; MET, metabolic equivalent; rMedDiet, Mediterranean diet; SES, socioeconomic status; T, tertile.
[a]*P* value for the differences across primiparous vs multiparous women as derived from *t* test or chi-square test, as appropriate.
[b]The significance of the numbers in bold is *P* less than .05 compared with reference category.
[c]The significance of the numbers in bold is *P* less than .001 compared with reference category.

increased according to parity and ep-BMI categories, and the mean HOMA-IR was significantly higher in the multiparous + OWO group compared with the nulliparous + NW group (see Table 2). The fasting glucose concentrations were similar in all groups.

We further tested for possible associations between parity and each glucose metabolism parameter separately with a univariate- and multivariable-adjusted linear regression model (Table 3). In the univariate model, multiparity was significantly associated with higher fasting insulin levels (β coefficient for % change: 22.14; 95% CI, 6.72-40.49; *P* = .006) and a higher HOMA-IR index (β [% change]: 23.37; 95% CI, 6.18-43.33; *P* = .011). These variables increased significantly from 1 to 2 or more parities (*P*-for-trend >.007). In the fully adjusted main effects model, these associations did not change appreciably from the unadjusted associations. Multiparity was

Results

Table 2. Comparison of glucose metabolism parameters by parity, maternal early-pregnancy body mass index (ep-BMI)–based weight status, and combined parity + ep-BMI–based weight status categories in the first trimester of pregnancy

Variables	No.	Glucose, mg/dL Mean ± SD	Insulin, mU/L[a] Mean ± SD	HOMA-IR[a] Mean ± SD
Overall	264	70.2 ± 10.7	7.77 ± 1.76	1.32 ± 1.85
Parity				
Nulliparous	112	69.8 ± 9.4	6.89 ± 1.75	1.18 ± 1.82
Multiparous	152	70.4 ± 11.5	**8.41 ± 1.78**[c]	**1.44 ± 1.87**[c]
Ep-BMI categories				
Normal weight (BMI < 25)	169	69.5 ± 10.4	6.89 ± 1.70	1.17 ± 1.84
Overweight/obesity (BMI ≥ 25)	95	71.5 ± 11.4	**9.49 ± 1.70**[c]	**1.65 ± 1.79**[c]
Parity + ep-BMI categories				
Nulliparous + NW	76	68.5 ± 9.3	6.35 ± 1.71	1.07 ± 1.78
Multiparous + NW	93	70.4 ± 11.3	7.39 ± 1.78	1.26 ± 1.88
Nulliparous + OWO	36	72.8 ± 9.4	8.16 ± 1.77	1.46 ± 1.84
Multiparous + OWO	59	70.7 ± 12.2	**10.48 ± 1.65**[c]	**1.80 ± 1.75**[c]

Values are expressed in means ± SD.
Abbreviations: ep-BMI, early-pregnancy body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; NW, normal weight (BMI < 25); OWO, overweight/obesity (BMI ≥ 25).
[a]Geometric means of log-transformed.
Statistical significance of numbers in bold is [b]*P* less than .05 and [c]*P* less than .001 compared with the first category as derived from *t* test or analysis of variance, as appropriate.

consistently related to the insulin levels (β [% change]: 20.92; 95% CI, 4.08-37.71; $P = .016$) and the HOMA-IR index (β [% change]: 19.72; 95% CI, 2.43-40.49; $P = .03$) independently of confounding factors such as maternal ep-BMI modeled either categorically or in its continuous form (data not shown). We observed similar positive trends between parity and insulin and the HOMA-IR index in OWO and non-OWO women (Supplementary Table S1 (31)), although the association of parity or 2 or more with the HOMA-IR index, compared to being in the nulliparous group, seemed to be stronger in OWO women. However, cross-product terms between weight status and parity for their associations with each outcome (glucose, insulin, and HOMA-IR) were not statistically significant ($P > .14$ for all interactions, as shown in Supplementary Table S1 (31)). When the parity number was increased in combination with being OWO, that is, when analyzed together, the positive relationships with insulin and HOMA-IR gradually and significantly increased (see Table 3). Specifically, in the full model, the group of multiparous + OWO women was associated with a greater increase in mean insulin levels of 64.87% (95% CI, 34.99-101.38; $P < .001$) and in the mean HOMA-IR index of 68.20% (95% CI, 35.12-110.01; $P < .001$) compared with those in the nulliparous + NW group (see Table 3). The multivariable-adjusted geometric means of the HOMA-IR according to combined parity + maternal ep-BMI categories are shown in Fig. 1.

According to the HOMA-IR cutoff point of 1.58 or greater, the prevalence of elevated IR was 41.0% and 49.0% for multiparous women and OWO women, respectively. Among the multiparous and OWO women, the prevalence increased to 57.6% (Fig. 2). After adjustment for confounders, multiparity was associated with a 1.59-fold (95% CI, 1.07-2.36; $P = .021$) increase in the relative risk of elevated IR and, with a trend (P-for-trend = .018) toward increased parity-associated risk of elevated IR as parity increased (parity = 1, RR: 1.55; 95% CI, 1.03-2.36; $P = .036$ and parity ≥ 2, RR: 1.72; 95% CI, 1.05-2.83; $P = .031$). Interestingly, multiparous women with OWO were nearly 2 times as likely to have elevated IR than the total multiparous population (RR: 3.04; 95% CI, 1.70-5.47; $P < .001$). The biggest difference in the RR was between the parity of 2 or more children + OWO group and the nulliparous + NW group (RR: 3.85; 95% CI, 1.98-7.76; $P < .001$). Results are shown in detail in Fig. 2.

Discussion

This study researched the relationship between parity and glucose metabolism parameters in the first trimester of pregnancy among healthy pregnant women from a Mediterranean region. We found a statistically significant positive association between multiparity and IR as assessed by HOMA-IR index, even after considering several traditional confounding factors. Women with one or more parity also had a 1.59-fold increased RR of having elevated IR compared with nulliparous women, which increased proportionally to the number of parities. This positive relationship between parity and greater RR of IR was more robust in combination with being OWO.

The results of our study highlight the clinical relevance of early assessment for IR in pregnant women who have had multiple pregnancies, particularly in pregnant women with OWO. According to our selected HOMA-IR threshold of 1.58, the prevalence rate of early-pregnancy IR among multiparous pregnant women was 41.0%, about 50% among the OWO group, and 57.6% among women who met both conditions. Although there is no standardized cutoff value of HOMA-IR for identifying IR in pregnancy (32), it is worth noting that Cohen et al (33) validated the use of HOMA-IR as a surrogate for the hyperinsulinemic-euglycemic clamp technique "gold standard" as a measure of IR in early pregnancy, even in obese women. In our study, the decision to define the upper tertile of HOMA-IR as the threshold for IR could be viewed as somewhat arbitrary; however, it is not inconsistent with published data on other measures of IR that identify IR individuals as being in the top tertile (34, 35).

Table 3. Linear regression models of the associations of parity (modeled separately as nulliparous vs multiparous and as parity categories [0: nulliparous, 1, and ≥2 children]) and combined parity + early-pregnancy body mass index categories with glucose metabolism parameters

	No.	Glucose, mg/dL		Insulin, mU/L (% change)[a]		HOMA-IR index (% change)[a]	
		Model 1 (n = 264) β (95% CI)	Model 2 (n = 264) β (95% CI)	Model 1 (n = 264) β (95% CI)	Model 2 (n = 264) β (95% CI)	Model 1 (n = 264) β (95% CI)	Model 2 (n = 264) β (95% CI)
Parity							
Nulliparous	112	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Multiparous	152	0.60 (−2.03 to 3.24)	0.15 (−2.68 to 3.00)	**22.14 (6.72 to 40.49)**[c]	**20.92 (4.08 to 37.71)**[c]	**23.37 (6.18 to 43.33)**[c]	**19.72 (2.43 to 40.49)**[c]
Nulliparous	112	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1 previous child	115	0.35 (−2.46 to 3.16)	−0.24 (−3.21 to 2.72)	**19.72 (3.67 to 39.10)**[c]	**18.06 (1.41 to 37.44)**[c]	**19.94 (2.12 to 40.78)**[c]	16.88 (−1.00 to 37.99)
≥2 previous children	37	1.38 (−2.63 to 5.40)	1.71 (−2.67 to 6.11)	**30.47 (5.65 to 61.28)**[c]	**29.18 (3.28 to 61.61)**[c]	**32.45 (5.34 to 66.70)**[c]	**32.18 (3.56 to 68.71)**[c]
P for trend[b]		.52	.58	**.007**	**.010**	**.011**	**.014**
Parity + ep-BMI categories							
Nulliparous + NW	76	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Multiparous + NW	93	1.87 (−1.39 to 5.12)	1.53 (−1.94 to 5.01)	15.03 (−2.47 to 35.93)	15.49 (−2.96 to 37.71)	17.47 (−1.98 to 40.49)	17.35 (−3.25 to 42.62)
Nulliparous + OWO	36	**4.31 (0.04 to 8.57)**[c]	3.95 (−.39, 8.28)	**28.27 (3.15 to 59.36)**[c]	**27.51 (2.12 to 59.20)**[c]	**36.48 (7.79 to 72.98)**[c]	**34.99 (6.18 to 72.29)**[c]
Multiparous + OWO	59	2.18 (−1.48 to 5.83)	1.64 (−2.29 to 5.58)	**66.70 (38.40 to 99.37)**[d]	**64.87 (34.99 to 101.38)**[d]	**69.89 (39.10 to 109.59)**[d]	**68.20 (35.12 to 110.01)**[d]
P for trend[b]		.152	.265	**<.001**	**<.001**	**<.001**	**<.001**
Parity + ep-BMI categories							
Nulliparous + NW	76	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1 previous child + NW	71	2.09 (−1.39 to 5.57)	1.57 (−2.07 to 5.20)	13.88 (−4.88 to 34.99)	15.03 (−4.88 to 39.10)	16.18 (−4.30 to 40.49)	16.18 (−4.88 to 42.76)
≥2 previous children + NW	22	1.13 (−3.96 to 6.24)	1.56 (−4.02 to 7.15)	20.92 (−6.76 to 56.83)	18.53 (−10.42 to 58.41)	22.14 (−8.61 to 61.61)	22.14 (−10.42 to 66.53)
Nulliparous + OWO	36	**4.30 (0.04 to 8.57)**[c]	3.97 (−0.36 to 8.31)	**28.40 (3.05 to 60.00)**[c]	**28.40 (2.22 to 60.01)**[c]	**36.34 (7.25 to 73.33)**[c]	**35.53 (6.18 to 71.60)**[c]
1 previous child + OWO	44	1.15 (−2.83 to 5.15)	.37 (−3.91 to 4.64)	**63.23 (32.31 to 99.37)**[d]	**58.41 (27.12 to 99.37)**[d]	**63.23 (31.00 to 105.44)**[d]	**59.36 (24.61 to 101.38)**[d]
≥2 previous children OWO	15	5.16 (−0.79 to 11.13)	5.44 (−0.86 to 11.45)	**78.60 (31.00 to 141.09)**[d]	**85.89 (33.64 to 156.00)**[d]	**91.55 (37.71 to 166.45)**[d]	**99.37 (40.48 to 185.38)**[d]
P for trend[b]		.129	.192	**<.001**	**<.001**	**<.001**	**<.001**

Linear regression models were used to calculate the β coefficient (β) and 95% CI. Model 1: unadjusted model. Model 2: model adjusted for age categories (<25 [ref.], 25-29, ≥ 30 years), BMI categories (NW [ref.], OWO; not for adjusted in the parity + ep-BMI categories analysis, where it was integrated into the composite explanatory variable itself), educational level (low/medium [ref.], high), smoking status (never smoker [ref.], current/former smoker), alcohol consumption (no [ref.], yes), planned pregnancy (no [ref.], yes), physical activity tertile (T1: ≤ 1070 [ref.], T2:1071-3335, T3: ≥ 3336 METs-min/wk), and Mediterranean diet score tertile (T1: ≤ 8 [ref.], T2: 9-11, T3: ≥ 12 points).
Abbreviations: ep-BMI, early-pregnancy body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; MET, metabolic equivalent; NW, normal weight (BMI < 25); OWO, overweight/obesity (BMI ≥ 25); Ref., reference.
[a]Natural log-transformed; parameter estimates (β coefficient) have been back transformed to reflect the percentage change in each outcome (insulin and HOMA-IR) associated with a 1-unit increase in each exposure variable.
[b]*P* value for trend was calculated by treating ordinal categorical exposure variable as continuous variable
Statistical significance of numbers in bold is [c]*P* less than .05 and [d]*P* less than .001 compared with the reference category.

Results

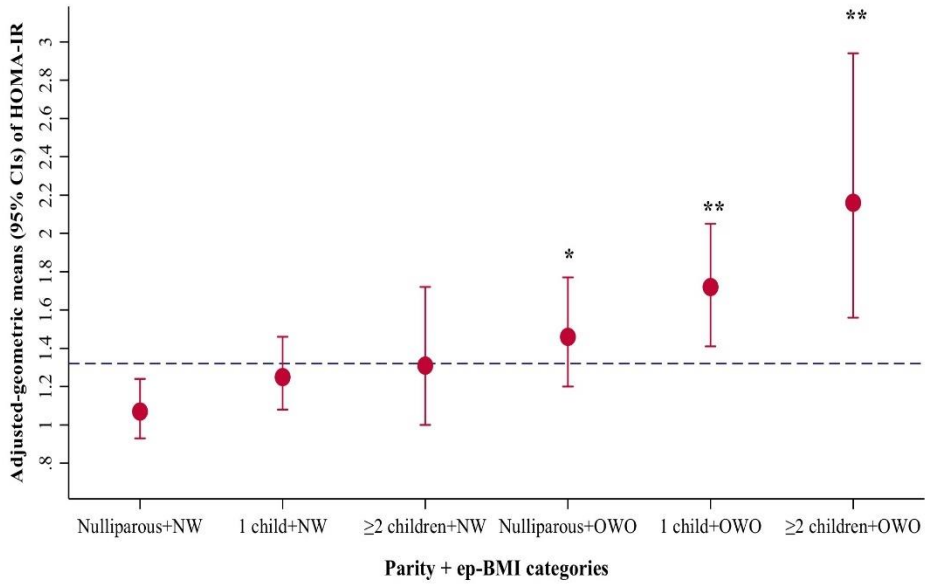

Figure 1. Multivariable-adjusted geometric means and 95% CIs of HOMA-IR index in the first trimester of pregnancy according to parity and maternal early-pregnancy BMI categories (n = 264). Adjusted means were calculated by analysis of covariance (ANCOVA). Models were mutually adjusted for age categories (<25 [ref.], 25-29, ≥ 30 years), educational level (low/medium [ref.], high), smoking status (never smoker [ref.], current/former smoker), alcohol consumption (no [ref.], yes), planned pregnancy (no [ref.], yes), physical activity tertile (T1: ≤ 1070 [ref.], T2: 1071-3335, T3: ≥ 3336 METs-min/week), and Mediterranean diet score tertile (T1: ≤ 8 [ref.], T2: 9-11, T3: ≥ 12 points). *P less than .05 and **P less than .001 compared with the reference category (nulliparous + NW). Points represent adjusted geometric means and whisker plots represent 95% CIs. Horizontal line (dash line) represent the overall geometric mean. BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; MET, metabolic equivalent; NW, normal weight (BMI < 25); OWO, overweight/obesity (BMI ≥ 25).

Furthermore, maternal IR in early pregnancy, at HOMA-IR cutoff levels within the range from 1.51 to 2.31, has been reported as a reliable marker of subsequent GD (18, 36). Our HOMA-IR threshold of 1.58 is well within this range. In this context, previous researchers have also indicated that women with high HOMA-IR in early to mid-pregnancy have an increased risk of subsequent preeclampsia, excessive weight gain during pregnancy, and of giving birth to macrosomic and large-for-gestational-age neonates (4, 5, 37). Thus, exposure in early pregnancy to elevated maternal IR, especially in multiparous women, should not be ignored.

Regarding glucose homeostasis disorders in pregnancy related to repeat pregnancies, extensive research has been carried out to investigate the relationship between multiparity and GD or recurrent GD during later pregnancies (11, 13). However, few studies have focused on maternal IR in early pregnancy in healthy pregnant women without previous history of diabetes.

Supporting our results in the first trimester of pregnancy (~12 weeks), an earlier study conducted by Abdelsalam and Elamin (20) involving 300 pregnant Sudanese women aged 17 to 35 years in Khartoum State (Sudan) reported that both maternal fasting insulin levels and HOMA-IR in middle pregnancy (~20-30 weeks' gestation) increased significantly with higher parity compared to nulliparity. The highest levels were observed in grand multiparity (>5 times). Similarly, Jinlan et al (21), analyzing the data of 208 Chinese pregnant women aged 25 to 35 years in the Huzhou region, Zhejiang Province (Southeast China), stated that women with a second pregnancy were more likely to have higher glucose intolerance and HOMA-IR–based IR during the second to third trimester compared to primiparas (first-time pregnancy). In another study conducted by Seghieri et al (19) in a selected group of 1880 third-trimester pregnant women at higher risk for GD (ie, all women had glucose intolerance, OWO, and advanced age, >29 years), in the Pistoia area (Tuscany, Italy), it was found that ISI_{OGTT}-based insulin sensitivity during the third trimester decreased significantly only in pregnant women with parity greater than 3 compared to nulliparous. However, contrary to our findings, the earlier parity-to-insulin sensitivity relationship disappeared after adjustment for age, pregestational BMI, and weight gain, which are relevant confounders that are strongly related to worsening insulin sensitivity. These data could lead us to speculate on whether there is a true effect on this relationship or whether this could arise solely from confounding. Importantly, adjustment of our analyses for these factors simultaneously with other behavioral factors (including educational level, smoking, PA, and eating habits) did not change the associations observed. Therefore, we can state that our results are robust under different modeling approaches. The apparent disagreement with the aforementioned findings could be due to differences in study design, population characteristics, and the methodologies used for evaluating IR, as well as the fact that in our study, the assessment period was in the first trimester.

Interestingly, supporting our results at least in part, the study by Seghieri et al (19) found that in comparison with the initial pregnancy, insulin sensitivity significantly decreased in the subsequent pregnancy. Similarly, Skajaa et al (6), studying pregnant women with type 1 diabetes, reported that daily insulin

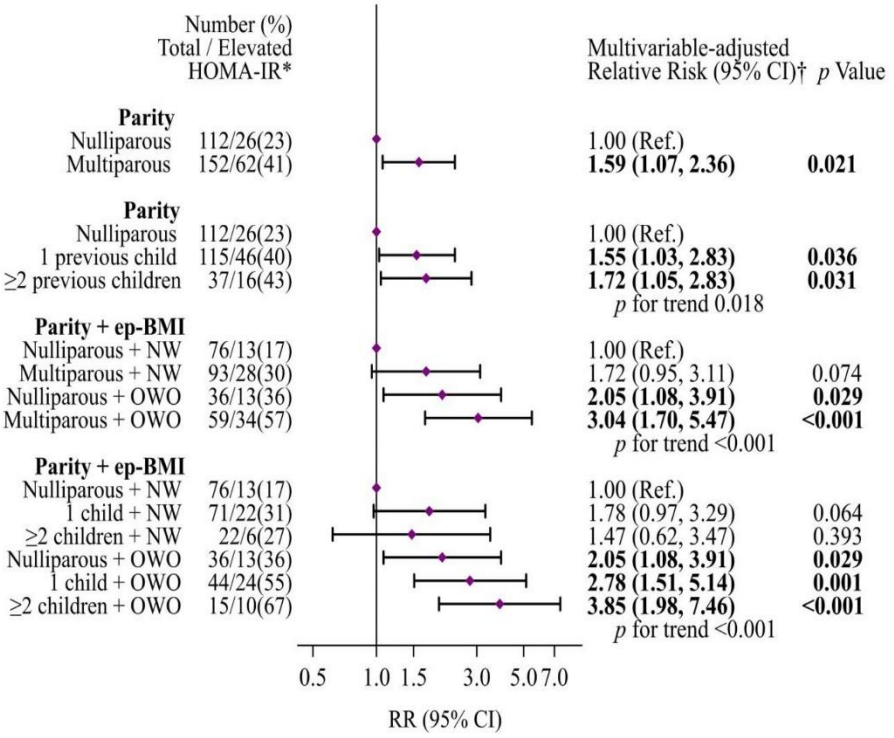

Figure 2. Multivariable-adjusted RR (95% CI) for elevated HOMA-IR according to parity and combined parity + ep-BMI categories. Multivariable-adjusted Cox regression models with constant follow-up time set at t = 1 for all individuals and robust variance were used to calculate the RR and 95% CI. †Models were mutually adjusted for age categories (<25 [ref.], 25-29, ≥ 30 years), BMI categories (NW [ref.], OWO; not for adjusted in the parity + ep-BMI categories analysis, where it was integrated into the composite explanatory variable itself), educational level (low/medium [ref.], high), smoking status (never smoker [ref.], current/former smoker), alcohol consumption (no [ref.], yes), planned pregnancy (no [ref.], yes), physical activity tertile (T1: ≤ 1070 [ref.], T2: 1071-3335, T3: ≥ 3336 METs-min/week), and Mediterranean diet score tertile (T1: ≤ 8 [ref.], T2: 9-11, T3: ≥ 12 points). Statistical significance of numbers in bold was set at *P* less than .05. Diamonds represent RR and whisker plots represent 95% CIs. BMI, body mass index; ep-BMI, early-pregnancy BMI; HOMA-IR, homeostasis model assessment of insulin resistance; NW, normal weight (BMI < 25); OWO, overweight/obesity (BMI ≥ 25); Ref., reference; RR, relative risk. *Top tertile of HOMA-IR (≥ 1.58). *P* for trend was calculated by treating ordinal categorical exposure variable as continuous variable.

requirements from week to week increased significantly throughout pregnancy with increasing parity after adjusting for BMI, age, and prepregnancy glycated hemoglobin A_{1c}. This last study also revealed that the individual total insulin requirement in the woman's first pregnancy increased with each pregnancy during pregnancy but did not in nonpregnant status. This reaffirms, in part, our results and further strengthens the hypothesis that parity per se negatively affects insulin sensitivity during pregnancy, thereby increasing insulin requirement.

In addition, our findings are also consistent with the evidence from published studies indicating a relationship between multiparity and GD (11, 13), and most researchers report increased risk of diabetes in the later life of women with high parity (8, 9). However, it has been suggested that a woman would need to have at least 4 pregnancies for the risk of diabetes to be affected (8, 9). Unfortunately, our data do not permit us to test the effect of having more than 3 (n = 3) or 4 (n = 1) children on first-trimester IR because of the small number of women with these pregnancies; however, it is worth examining in future research.

It is well known that being OWO before and during pregnancy predisposes the woman to a higher metabolic dysregulation in pregnancy (38) including early IR, as observed in our study. According to our results, OWO women were more IR at the start of their pregnancy compared with NW women regardless of parity. This finding is in accordance with previous reports (22, 38). An original aspect of this study that deserves attention is the association of the combination of parity and OWO with IR in early pregnancy, which has not been previously researched. According to our study findings, nulliparous pregnant women with an ep-BMI of 25.0 or greater had an almost 3 times higher risk of IR compared to NW nulliparous women. It is interesting to note that OWO multiparous pregnant women had a 6 times higher risk of IR. Moreover, in this vulnerable group, the risk of IR showed an increasing trend with increasing parity. The above data suggest that the combination of parity and maternal OWO may result in additive adverse effects that contribute to a worse IR early in pregnancy.

The relationship between parity and maternal IR early in pregnancy is complex and still not fully understood. This probably reflects a combination of sociodemographic/environmental factors and placental hormone changes due to repeated pregnancies that result indirectly or directly in a

progressive worsening of IR. We found, for example, that multiparous pregnant women were older and were less likely to have a university education and more likely to belong to a higher social class than nulliparae. In the present study, the last 2 factors were significantly related to higher ep-BMI, which in turn were independently and positively associated with early IR.

Multiparity is also an independent predictor for obesity (39). About three-quarters of women are unable to reach their prepregnancy weight 1 year after delivery (40), this leads to interpregnancy accumulation of adipose tissue, thereby contributing to IR in successive pregnancies and beyond (41). Nevertheless, our data do not allow us to draw conclusions about this issue. It has also been argued that, just like outside pregnancy, obesity in pregnancy promotes a high production of proinflammatory factors and oxidative stress due to the accumulation of adipose tissue macrophages, which induces IR (39, 42). Thus, obese multiparous pregnant women could have even greater metabolic consequences, including IR, as confirmed in our study. This is probably explained by either the greater adiposity, repeated episodes of inflammatory response, or a combination of these. Furthermore, regardless of obesity, an increase in the production of placental hormones, such as progesterone, estrogen, and placental lactogens, in pregnancy to accommodate the growing fetus (43) leads to a relative IR. This effect can accumulate, especially for multiparous women (39).

Taken together, our study offers new knowledge about the role of multiparity in maternal IR in subsequent pregnancies, which provides an opportunity for an early targeted intervention. However, it is necessary to consider several limitations when interpreting our findings. First, our population consisted of healthy pregnant women living in the Mediterranean region with specific sociodemographic and healthy Mediterranean lifestyle traits, which prevents the generalization of the findings to other populations. In addition, due to limited resources, it was not feasible to use the "gold-standard" hyperinsulinemic-euglycemic clamp test in early pregnancy to quantify IR (33). However, the HOMA-IR is a noninvasive, cost-effective, and simple surrogate measure of this parameter widely used in large epidemiologic studies and has also been validated in studies with pregnant women (44). Moreover, the fact that we did not have information on stillbirths due to early miscarriages and intrauterine fetal demise could have induced a classification bias. Last, previous findings support the importance of other potential factors mediating the recurrence of GD, such as the interpregnancy interval and percentage of body fat or fat distribution pattern through successive pregnancies (45); not having these data is, therefore, another potential weakness.

In summary, our study suggests that multiparity may have a negative effect on maternal IR, which is already detectable during the early stages of pregnancy, and that OWO appears to further aggravate this relationship. Therefore, it is strongly recommended that all pregnant women who have given birth previously, especially those with overweight or obesity, undergo early IR screening during subsequent pregnancies. Undoubtedly, identifying elevated IR at a very early stage in these high-risk pregnant women would make it possible to implement earlier interventions involving lifestyle modifications and/or pharmacological treatment to avoid future complications that could affect both the mother and baby.

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Author Contributions

V.A. designed and conducted the research and performed data curation. A.D. and E.M. analyzed the data and wrote the article. All authors revised the manuscript for important intellectual content and read and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no one who meets the criteria has been omitted. V.A. is the guarantor of this work and as such has had full access to all study data and takes responsibility for their integrity and for the accuracy of the data analysis.

Disclosures

The authors declare that they have no conflict of interest.

Data Availability

The data sets generated and/or analyzed during the present study are not publicly available because of subject confidentiality; however, they are available from the corresponding author on reasonable request.

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Publication 3. Associations of maternal cardiometabolic factors during pregnancy with measures of fetal growth at birth: a longitudinal cohort study.

Ehsan Motevalizadeh, Andrés Díaz-López, Cristina Jardí, Cristina Rey-Reñones, Francisco Martín, and Victoria Arija

Overview of the novelty and significance of this work

Literature Review

- ✓ Existing research acknowledges some links between maternal cardiometabolic markers measured at a single gestational time-point and fetal development, often assessed by newborn size.
- ✓ The specific association between maternal cardiometabolic markers throughout pregnancy and newborn size is not well understood.

Novelty Contribution

- ✓ By investigating the effect of maternal cardiometabolic variables during early and late pregnancy (two different vulnerable periods for the developing fetus) on newborn growth in a cohort of healthy pregnant persons from the Spanish Mediterranean area, this study augments current knowledge.
- ✓ It emphasizes how crucial it is to continuously monitor the mother's cardiometabolic markers during the whole gestation period in order to mitigate any potential negative consequences on the size of the newborn.

Conclusion

- ✓ The findings underscore the pivotal role of maternal cardiometabolic indicators, particularly lipid levels and BP, in determining neonatal size.
- ✓ Sustained monitoring of these markers during pregnancy emerges as paramount, offering avenues for preemptive interventions to mitigate adverse neonatal outcomes.

UNIVERSITAT ROVIRA I VIRGILI
MATERNAL CARDIOMETABOLIC HEALTH AND FETAL DEVELOPMENT: INSIGHTS FROM PRENATAL TO POSTNATAL LIFE
Ehsan Motevalizadeh

Journal of Endocrinological Investigation

Associations of maternal cardiometabolic factors during pregnancy with measures of fetal growth at birth

--Manuscript Draft--

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Funding Information:	Instituto de Salud Carlos III (PI12/02777) — Dr. Victoria Arija Instituto de Salud Carlos III (PI17/01754) — Dr. Victoria Arija
Abstract:	Purpose: Although some maternal cardiometabolic markers during pregnancy have been related to fetal growth, these findings remain unclear. We examined whether maternal cardiometabolic markers, measured at two time points during pregnancy, influence neonatal size in a Mediterranean population of healthy pregnant women. Methods: A longitudinal study including 264 mother-neonate pairs. Maternal metabolic markers (glucose, triglycerides, total cholesterol, HDL-c, and LDL-c, and blood pressure (BP)) were assessed in the first (T1) and third (T3) trimesters. Birthweight and head circumference (HC) were assessed in the newborns. Small (SGA, <10th percentile) and large (LGA, >90th percentile) for-gestational-age were outcomes. Multivariable-adjusted linear and logistic regressions were performed. Results: Overall, based on weight and HC at birth, there were 10.5% and 6.4% SGA infants, while 8.1% and 16.7% were LGA, respectively. After adjustments for confounders, maternal T1 triglyceride levels were positively associated with birthweight (βcontinuous: 2.01, p=0.006; βQ1 (ref.) vs. Q4: 175.98; p=0.023), and LDL-c levels at T1 were associated with an increased risk of LGA (OR:1.02, p=0.046). BP levels, especially in the T3, had a negative association with birthweight (β: -10.86; p=0.010) and HC (β: -0.04; p=0.008). Similarly, BP≥75th percentile and a 1 mmHg increment in BP at T3 were also associated with SGA for weight (OR:3.54, p=0.022), and HC (OR:1.21, p=0.016) at birth, respectively. Conclusions: Maternal cardiometabolic markers, particularly lipids and blood pressure, were linked to unfavorable neonatal size among healthy pregnant women residing in the Spanish Mediterranean region, highlighting the importance of monitoring maternal metabolic health throughout pregnancy to maximize neonatal well-being.
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Author Comments:	Journal of Endocrinological Investigation Dear Board of Editors Reus, June 18th, 2023 Please find attached our manuscript entitled "Associations of maternal cardiometabolic factors during pregnancy with measures of fetal growth at birth". We would like to have it considered for publication as Full Length Article in "Journal of Endocrinological Investigation". Although some maternal cardiometabolic markers (glucose, triglycerides, total cholesterol, HDL-c, LDL-c and blood pressure (BP)) during pregnancy have been related to fetal growth, these findings remain unclear. In addition, most studies assessed metabolic biomarkers measured at a single gestational time-point, mainly third trimester. Given that the metabolic profile changes throughout pregnancy, further prospective research is required to explore multiple time points. Moreover, no study has evaluated this association among pregnant Mediterranean women without medical complications, whose socio-demographic and lifestyle traits might mitigate cardiovascular risk, optimizing fetal growth. With a view to adding knowledge in this field, our study explored whether maternal cardiometabolic risk indicators, assessed at two time points during pregnancy (early and late), affects neonatal anthropometric measures and is associated with adverse birth outcomes, such as SGA and LGA in a Mediterranean cohort of healthy pregnant women (n=264 mother–child dyads). We found that, after multivariable adjustment, first-trimester triglyceride levels were positively associated with birthweight (βcontinuous: 2.01, p=0.006; βQ1 (ref.) vs. Q4: 175.98; p=0.023) and LDL-c levels at first-trimester were associated with an increased risk of LGA in terms of birthweight (OR: 1.02, p=0.046). At the same time, diastolic BP levels were also associated with increased risk for SGA in terms of head circumference (HC) (OR:1.13; 95% CI: 1.02, 1.24, p= 0.015). Third-trimester diastolic BP levels were found to be inversely associated with birthweight (β: -10.86; p=0.010) and HC (β: -0.04; p=0.008). Similarly, diastolic BP ≥75th percentile and a 1 mmHg increment in diastolic blood pressure at third trimester were also associated with SGA for weight (OR: 3.54, p=0.022), and HC (OR: 1.21, p=0.016) at birth, respectively. The results of this investigation show that maternal cardiometabolic markers, particularly lipids and blood pressure, were linked to unfavorable neonatal size among healthy pregnant women residing in the Spanish Mediterranean region. Thus, it would be beneficial to provide health education before pregnancy and to screen women early for lipid and blood pressure disorders as well as actively monitor these maternal cardiometabolic risk factors throughout pregnancy to maximize neonatal well-being and their future health. These findings will help policy makers to improve metabolic status in women before and/or during very early pregnancy in order to prevent obstetric complications and to reduce future related morbidities of both mother and offspring. We believe that this manuscript is important and appropriate for publication in Journal of Endocrinological Investigation because it is in line with the critical objective of fostering responsible and balanced debate on crucial issues of cardiometabolic dysregulations early research in pregnancy that affect medicine, health, health care, and health policy. Hereby I certify that, 1. The corresponding author and all co-authors have read and approved the final version of the manuscript that is hereby submitted and are prepared to take responsibility for its content. 2. Neither this manuscript nor one with substantially similar content have been previously published or submitted for publication elsewhere. 3. None of the authors had any potential conflict of interest. Wishing that this manuscript is of your interest, we would appreciate for your consideration. Yours sincerely, Victoria Arija, Prof Corresponding authors: Victoria Arija, Prof Universitat Rovira i Virgili.

Associations of maternal cardiometabolic factors during pregnancy with measures of fetal growth at birth

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Abstract

Purpose: Although some maternal cardiometabolic markers during pregnancy have been related to fetal growth, these findings remain unclear. We examined whether maternal cardiometabolic markers, measured at two time points during pregnancy, influence neonatal size in a Mediterranean population of healthy pregnant women.

Methods: A longitudinal study including 264 mother-neonate pairs. Maternal metabolic markers (glucose, triglycerides, total cholesterol, HDL-c, and LDL-c, and blood pressure (BP)) were assessed in the first (T1) and third (T3) trimesters. Birthweight and head circumference (HC) were assessed in the newborns. Small (SGA, <10th percentile) and large (LGA, >90th percentile) for-gestational-age were outcomes. Multivariable-adjusted linear and logistic regressions were performed.

Results: Overall, based on weight and HC at birth, there were 10.5% and 6.4% SGA infants, while 8.1% and 16.7% were LGA, respectively. After adjustments for confounders, maternal T1 triglyceride levels were positively associated with birthweight ($\beta_{continuous}$: 2.01, p=0.006; $\beta_{Q1\ (ref.)\ vs.\ Q4}$: 175.98; p=0.023), and LDL-c levels at T1 were associated with an increased risk of LGA (OR:1.02, p=0.046). BP levels, especially in the T3, had a negative association with birthweight (β: -10.86; p=0.010) and HC (β: -0.04; p=0.008). Similarly, BP≥75th percentile and a 1 mmHg increment in BP at T3 were also associated with SGA for weight (OR:3.54, p=0.022), and HC (OR:1.21, p=0.016) at birth, respectively.

Conclusions: Maternal cardiometabolic markers, particularly lipids and blood pressure, were linked to unfavorable neonatal size among healthy pregnant women residing in the Spanish Mediterranean region, highlighting the importance of monitoring maternal metabolic health throughout pregnancy to maximize neonatal well-being.

Keywords: Maternal cardiometabolic markers, small-for-gestational-age, large-for-gestational-age, infant size, pregnancy

Declarations

Conflict of interest: The authors declare that they have no conflict of interest.

Introduction

Pregnancy causes major changes in the mother's physiological, endocrine, and metabolic systems [1] in order to nurture and accommodate the developing fetus [1]. Changes in glucose and lipid metabolism, which are the primary sources of energy for organogenesis, are among these crucial adaptations [1]. However, prenatal exposure to common metabolic disturbances, such as hyperglycemia, dyslipidemia, and hypertension [2], could result in impaired intrauterine fetal growth. In this regard, unfavorable birth weight is a significant indicator of intrauterine adversities and, in turn, predicts adverse health effects later in life [3]. Being born small-for-gestational-age (SGA) confers a substantial risk of neurodevelopmental difficulties and morbidity (i.e., obesity, insulin resistance (IR), type 2 diabetes, and cardiovascular disease) in adulthood [4, 5]. On the contrary, large-for-gestational-age (LGA) neonates are not only at risk of fetal brachial plexus injury, cerebral hemorrhage, and shoulder dystocia during labor [6] but also have an increased risk of metabolic problems later in life [7]. Understanding the impact of an abnormal maternal metabolic profile on inappropriate fetal growth, often assessed by newborn size, can help determine potential prevention strategies.

In terms of glucose homeostasis in pregnancy, the vast majority of prospective studies have clearly shown that higher glucose levels, even in the absence of gestational diabetes (GD), in early [8] and mid-pregnancy [9] are consistently related to fetal overgrowth and an increased risk of LGA/macrosomia. However, the data are still limited and inconsistent [10–12] regarding the effect of maternal IR, as measured by the homeostatic model assessment of IR (HOMA-IR) during early and late pregnancy (two different vulnerable periods for the developing fetus), on newborn size, especially in women without abnormal glucose tolerance. This might be attributed, at least in part, to the fact that IR is not a routine prenatal examination. Therefore, this aspect still requires further evaluation.

Unlike hyperglycemia, fewer studies have examined the role of an abnormal maternal lipid profile in a normal pregnancy on fetal growth. Although some studies have found evidence of an association, the findings about the type of lipid biomarker and study designs (i.e., timing of the exposure measurement and the neonatal anthropometry evaluated) are inconsistent. For instance, two recent prospective studies based on a large population of Chinese pregnant women reported

that high maternal triglyceride levels in early pregnancy (6–8 gestational weeks) were associated with LGA newborns [13, 14]. Similarly, a cross-sectional cohort study on Dutch women also found that high triglycerides may be related to larger embryonic size in early pregnancy, particularly in overweight women, while no associations for total cholesterol (TC), LDL-c or HDL-c concentrations were found [15]. A pattern of seemingly lacking associations regarding to these maternal lipid levels throughout pregnancy and fetal growth measurements at birth (i.e., newborn weight or LGA) was also observed in other earlier research with Chinese and Turkish populations [16, 17]. However, a U.S. study found that elevated triglycerides and TC were associated with a larger newborn size in terms of birthweight (but not with LGA), while HDL-c measured on average at three time-points during pregnancy was associated with reduced size in terms of birthweight and head circumference (HC) [18]. In contrast, a cohort study from rural Gambia found that decreased HDL-c in early and mid-pregnancy, but not at the end of pregnancy, was associated with an increased risk of low birthweight (LBW, <2500 g) [19]. Thus, future prospective studies are needed to determine whether unfavorable lipid biomarkers throughout pregnancy have an impact on newborn size.

Many studies on blood pressure (BP) in Chinese, Dutch, Swedish, English, and American pregnant women show that increases in maternal BP in mid-to-late pregnancy, although not reaching the clinical criteria for hypertension, seem to be associated with reduced fetal growth and a risk of giving birth to SGA neonates [20–22]. Paradoxically, other studies assessing preconception hypertension [23] or gestational hypertension/preeclampsia after 20 weeks of gestation [24] did not detect any association. Healthy behaviors adopted by pregnant women after being diagnosed with hypertension (i.e., balanced diet, exercise, non-smoking, or appropriate weight gain) most likely contribute to adequate growth and may explain certain discrepancies [25]. Therefore, these factors are potential confounders; however, not all studies that link the maternal metabolic profile to neonatal size address them. In addition, most studies assessed metabolic biomarkers measured at a single gestational time-point, mainly in the second or third trimester. Given that the metabolic profile changes throughout pregnancy, further research is required to explore multiple time points. No study has evaluated this association among pregnant Mediterranean women, whose socio-demographic and lifestyle traits might mitigate

cardiovascular risk, optimizing fetal growth. Accordingly, this study explores whether the maternal cardiometabolic profile, assessed at two time points during pregnancy (early and late), affects neonatal anthropometric measures and is associated with adverse birth outcomes, such as SGA and LGA, while adjusting for potential maternal confounders, in a Mediterranean cohort of healthy pregnant women.

Materials and methods

Study design and participants

For the current prospective analysis, 264 mother-child pairs with available information on maternal cardiometabolic biomarkers during pregnancy (obtained after overnight fasting prior to blood tests) and neonatal anthropometric measurements at delivery were included. These data come from a larger study called ECLIPSES (Ensayo CLInico Para Suplementar con hierro a EmbarazadaS), which included healthy pregnant women older than 18 who enrolled before 12 weeks of gestation and continued until the birth of the child [26]. The ECLIPSES study was registered at www.clinicaltrialsregister.eu (ID: EUCTR-2012-005480-28) and www.clinicaltrials.gov (ID: NCT03196882). Everyone who participated signed an informed consent form.

Newborn anthropometric measurements

The infant's sex (male or female) and neonatal anthropometric measurements, including body weight (grams) and HC (cm), were measured just after birth by a trained study gynecologist or midwife following standardized procedures. Gestational age at delivery was established by obstetricians based on the first day of the last menstrual period reported at recruitment and corrected by ultrasound measurements recorded at about 12 gestational week.

Outcome variables used in the current study were birth weight and birth HC, along with SGA and LGA at birth. Newborns who were below the 10th percentile for both birth anthropometric measurements assessed separately were classified as SGA, while those who were above the 90th percentile were classified as LGA, based on the gestational age- and sex-specific reference growth curves using the international INTERGROWTH-21st newborn standards [27].

Measurement of maternal cardiometabolic markers

At weeks 12 and 36 of pregnancy, maternal blood samples were collected by trained research nurses. All blood samples were centrifuged, and aliquots of serum were immediately processed, coded, and stored at -80 °C inside the Biobank until analysis. For the current analysis, only women who underwent blood tests after an overnight fast were included. After thawing, cardiometabolic serum biomarkers were assessed at the accredited Laboratori Clínic of Joan XXIII University Hospital in Tarragona. The analyses included glucose and lipids. To reduce inter-batch variance, all samples were thawed and examined at the same time. Serum glucose, TC, HDL-c, and triglyceride concentrations were all tested at the same time using standard enzymatic automated procedures. Intra and inter-assay coefficients of variation (CVs) were below 2.2% for all samples. The Friedewald formula was used to determine LDL-c (LDL-c = TC- HDL-c - triglycerides/5). Serum insulin levels were measured with a chemiluminescent immunoassay using the ADVIA Centaur analyzer and a commercial kit (ADVIA Centaur IRI, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). The detection thresholds were set at 0.5 and 300 mUI/L, respectively. The CV values for intra- and inter-assay were 3.3-4.6% and 2.6-5.9%, respectively. The HOMA-IR index was used to assess insulin resistance, which was calculated using the following equation: HOMA-IR = [fasting glucose (mmol/L) x fasting insulin (μIU/ml)]/22.5. In both trimesters, systolic-BP and diastolic-BP were measured using an automated digital monitor (Omron HEM-705CP).

Assessment of covariates

Midwives and nutritionists collected data on demographic characteristics (age, socioeconomic information, and education level), health behavior (physical activity (PA), smoking, and diet), and obstetric history (including parity (nulliparous vs. multiparous) and planned pregnancy (yes, no)) in the first trimester of pregnancy (at week 12) through personal interviews and by using specific questionnaires. Family sociodemographic status (SES) was calculated by combining information on occupational status, classified according to the Catalan classification of occupations (CCO-2011) [27]. It was then classified as low, middle, or high. The educational level of the women was divided into three categories: low (primary school or less), medium (secondary studies), and high (university studies or more).

One of the behavioral factors was the quality Mediterranean Diet (MedDiet) score. Eating habits were assessed by using a 45-item self-administered food frequency questionnaire (FFQ), previously validated in our population [28]. The FFQ data allowed us to compute the percentage of people who adhere to the Mediterranean diet, which is considered a high-quality dietary pattern [29]. For this aim, the MedDiet score (ranging from 0 to 18 points) was divided into tertiles (T1 (<9), T2 (9-12), and T3 (≥12)). Physical activity was assessed using a shortened version of the International PA Questionnaire (IPAQ-S) [30], and participants were classified into three groups depending on their weekly metabolic equivalents (METs-min/week) (T1 (<1070), T2 (1070-3336), and T3 (≥3336)). The Fagerström questionnaire [31] was used to assess smoking, and women were classified as current smokers or non-smokers (former and never smokers). Furthermore, alcohol consumption was assessed as 'yes' or 'no'. The obstetric history included two fertility criteria (nulliparous and multiparous) and whether the pregnancy was planned (no, yes). Maternal weight (kg) and height (cm) were measured at enrolment and in each trimester thereafter. Body mass index (BMI) was computed as weight/height squared (kg/m^2) according to the World Health Organization, and women were classified into three groups: normal weight (BMI <24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), and obesity (BMI ≥30.0 kg/m^2). Total gestational weight gain (GWG) was calculated and conditioned by BMI, which was categorized into insufficient, adequate, and excessive according to the 2009 Institute of Medicine (IOM) standards [32].

Statistical analysis

The data were analyzed using the statistical software SPSS, version 29.0. Descriptive statistics provided quantitative variables as mean±SD and categorical variables as number (%). The maternal cardiometabolic markers as exposure variables (triglycerides, TC, LDL-c, HDL-c, glucose, HOMA-IR, systolic-BP, and diastolic-BP) were divided into quartiles, and the lowest category was defined as the reference. Multivariate linear regression analyses were performed to explore the association between each maternal cardiometabolic marker separately as continuous exposure variables in both the first and third trimesters and each newborn anthropometric measurement as a continuous outcome (birth weight and HC). Based on the scientific literature and biological plausibility, we considered the following a priori selected covariates as possible

confounders: Age, BMI, GWG, educational level, social class, smoking status, physical activity, rMedDiet score, planned pregnancy, parity, and sex of the infant. Estimates were presented as β coefficients (β) with 95% confidence intervals (CIs).

Multiple logistic regression models were also used to estimate odds ratios (ORs) and 95% CIs for LGA and SGA at birth linked to each maternal cardiometabolic markers (in separate models), assessed as both continuous and categorical exposure variables (based on two groups: normal-low (<75th percentile as reference) and high (≥75th percentile)) levels. These analyses included the same covariates as the linear models. Statistical significance was set at p <0.05.

Results

The characteristics of the study participants are provided in **Table 1**. Overall, the mean age was 29.6 years old, the mean BMI was 24.12 kg/m^2, 32% of the women had a university education, 19% had a high SES, and 14% of women smoked during pregnancy. The mean levels of lipid biomarkers, glucose, HOMA-IR, systolic-BP, and diastolic-BP in early and later pregnancy are shown in **Table 2**. With the exception of glucose, all of these markers increased throughout the third trimester. The average values are within normal limits.

The results from multivariate-adjusted linear regression analyses for the associations between each maternal cardiometabolic marker in the first and third trimesters of pregnancy and the anthropometric outcomes of the newborns are shown in **Table 3** and **Table 4,** respectively. After adjustment for confounders, maternal triglyceride levels modeled either in their continuous form (β: 2.01; 95% CI: 0.59, 3.44, p= 0.006) or categorically ($\beta_{Q4\ vs.\ Q1}$: 175.98; 95% CI: 24.58, 327.38, p-trend= 0.023) in the first trimester showed a significant positive association with birth weight. In the first trimester, we did not find any correlation between other maternal cardiometabolic factors and neonatal anthropometry measurements **(Table 3)**. In the third trimester, diastolic-BP was shown to be inversely related to birth weight, modeled either in its continuous form (β: -10.86; 95% CI: -19.09, -2.62; p= 0.010) or categorically ($\beta_{Q4\ vs.\ Q1}$: -245.49; 95% CI: -431.54, -59.45, p-trend= 0.018). Similarly, for birth HC, diastolic-BP levels showed a negative association in the continuous analysis (β: -0.04 95% CI: -0.07, -0.01, p= 0.008). Compared with newborns of mothers in the lowest quartile, newborns of mothers in the third ($\beta_{Q3\ vs.\ Q1}$: -0.63; 95% CI: -1.26, -

0.01, p= 0.047) and four quartiles ($\beta_{Q4\ vs.\ Q1}$: -0.87; 95% CI: -1.49, -0.24, p=0.007) of diastolic-BP had lower HC values (**Table 4**).

Overall, there were 10.5% (n=27) and 6.4% (n=13) SGA infants based on birth weight and HC, respectively; while there were 8.1% (n=21) and 16.7% (n=34) LGA infants based on birth weight and HC, respectively. When a logistic regression analysis was applied to assess the odds ratios of SGA or LGA, first-trimester triglyceride levels were negatively associated with a lower risk of birthweight-based SGA (OR:0.98; 95% CI: 0.96, 0.99, p= 0.010), adjusting for confounders. The odds ratio for triglyceride at the ≥75th percentile was 0.21 (95% CI: 0.04, 0.95, p= 0.043). At the same time, maternal LDL-c levels were associated with increased ORs for LGA in terms of birthweight (OR:1.02; 95% CI: 1.00, 1.04, p= 0.046), while diastolic-BP levels were associated with increased ORs for SGA in terms of HC (OR:1.13; 95% CI: 1.02, 1.24, p= 0.015) (**Table 5**). In the third trimester, diastolic-BP levels were still associated with an increased likelihood of HC-SGA newborns (OR=1.21, 95% CI: 1.04, 1.42, p= 0.016). In addition, diastolic-BP was also a significant predictor of birthweight-SGA newborns (OR:1.09; 95% CI: 1.03, 1.17, p= 0.007). Compared to the <75th percentile, the diastolic-BP ≥75th percentile was associated with a higher risk of birthweight-SGA (OR:3.54; 95% CI: 1.20, 10.42, p= 0.022). We did not find any association between maternal glucose parameters, lipids, or systolic-BP at the end of pregnancy with risk of either SGA or LGA at birth (**Table 6**).

Discussion

This prospective cohort study, which focuses on healthy pregnant women residing in the Mediterranean area, shows that maternal lipids, specifically circulating triglyceride and LDL-c levels early in pregnancy (first trimester), were significantly associated with newborn weight, as well as the risk of LGA at birth. We also found that a moderately elevated maternal diastolic-BP throughout pregnancy was associated with an increased risk of giving birth to SGA neonates in terms of both birth weight and HC.

Supporting our findings, a progressive increase has been documented in maternal circulating triglycerides, TC and LDL-c levels with advancing gestational age during normal pregnancy, while HDL-c peaks towards mid-pregnancy [33]. However, of clinical relevance, our study

indicates that even slightly disordered maternal triglyceride levels within a physiological range in early pregnancy may result in fetal overgrowth. This suggests maternal triglycerides play an important role as energy sources during this sensitive and critical period of early embryonic development [34]. This is also supported by earlier data from the Generation R study on normal pregnancy, in Rotterdam, which demonstrated a positive association between maternal triglycerides and embryonic size in early pregnancy [15]. Furthermore, our results are also consistent with observations in other samples, the vast majority in the Chinese population, which suggest that high maternal triglyceride levels in the first trimester in normal pregnancy are associated with increased birth weight and may be an early predictor of LGA [13, 14, 35]. Similarly, other studies in Japan and Italy, involving nondiabetic women with positive diabetic screens but normal glucose tolerance tests, have also confirmed the link between elevated fasting triglyceride levels at mid-gestation and increased neonatal birth weight [36, 37]. These studies also found that maternal hypertriglyceridemia, defined as the 75th cut-off point, was associated with a higher risk of LGA infants [36, 37]. Interestingly, in the aforementioned studies, the cut-off values used correspond to triglyceride concentrations of over 203 [36] and 259 mg/dL [37], while our study, which employs a lower cut-off value (over 105 mg/dL), revealed a predictive independent effect on the baby being born LGA. Since elevated lipids in early pregnancy may predict a more severe hyperlipidemia later in pregnancy, and considering the vulnerability of pregnant women, we suggest that the 75th cut-off point of triglycerides in our study could be helpful for screening high-risk pregnant women in early pregnancy and for predicting higher risks of large infants.

Interestingly, unlike other studies [16–18], we did not find an association between maternal triglycerides in late pregnancy and newborn size. Based on previous studies, it is possible to postulate that only very high triglyceride levels in late pregnancy are related to fetal and newborn size. In a study demonstrating a negative association between fasting maternal third-trimester triglycerides with newborn birthweight and risk for LGA [16, 17], the median of triglycerides was 271 mg/dl (IQR: 210-345) (3.1 mmol/L) and the optimal cut-off point for third-trimester triglycerides in predicting LGA was ≥313 mg/dl (≥3.5 mmol/L). In contrast, the median in this study population was 189 mg/dl (IQR: 130-240) (2.1 mmol/L (IQR: 1.5-2.7)). This could explain

the absence of an association at the end of pregnancy in our population. The lifestyle factors such as diet, exercise, and adequate gestational weight gain are crucial aspects for managing any lipid disorder regardless of pregnancy status. Unlike our study, previous studies did not take into account these potential confounders [16–18]. Consequently, residual confounding cannot be ruled out, and it often leads to results that are too high or too low. This could also explain the discrepancy.

It is known that fetal growth is influenced by maternal lipid metabolism [38]; however, the underlying mechanisms behind the observed positive relationship with triglycerides in early pregnancy are not completely understood, as maternal triglycerides do not appear to cross the placenta. It is hypothesized, therefore, that hydrolysis of circulating maternal triglycerides by placental lipoprotein lipase increases in early pregnancy, resulting in the release of free fatty acids that cross the placenta. These free fatty acids are then taken up and processed by trophoblast cells to meet metabolic demands, produce hormones required for maintaining pregnancy, and transferring them to the developing fetus. Thus, excessive mother-to-fetus fatty acid transfer can induce fetal overgrowth and lipid overaccumulation in fetal tissues [39].

During pregnancy, LDL-c and HDL-c are enriched in triglycerides [40], which may explain our findings regarding the association between LDL-c levels in the first trimester and large birthweight. Similarly to our study, other researchers have reported positive associations between early pregnancy LDL-c and macrosomia and LGA newborns [14, 41, 42]. However, a recently published meta-analysis by Mahindra et al. involving only healthy women or women who had no confounding factors, such as obesity, hypertension or GD, that could alter lipid levels [43] did not observe any effect during early to late pregnancy, and suggested that LDL-c and VLDL-c cannot be used as predictors of LGA. In this study, we were unable to demonstrate any significant association in the third trimester. Further rigorous research in which maternal lipids are measured at various points throughout gestation in a wide-ranging population, may provide additional insight to be able to either confirm or refute this hypothesis. Meanwhile, our results emphasize the importance of monitoring serum lipid levels, especially before conception or during the initial obstetrical visit, particularly if a woman hasn't been screened before pregnancy.

In line with most earlier studies we did not find a significant association between HDL-c levels and fetal growth [14, 15, 35, 44]; however, some studies have found an association. There are studies that suggest that increases in HDL-c levels during pregnancy, especially in the second and third trimesters, predict SGA [45, 46]. Conversely, low levels of maternal HDL-c were significantly and independently associated with a higher risk of LGA neonates for women with GD with co-existent preeclampsia [47]. This perhaps indicates that HDL could have protective qualities mainly in complicated pregnancies.

In our study, we did not find the expected positive association between increases in maternal glucose levels during pregnancy and fetal overgrowth. Neither first- nor third-trimester fasting maternal glycemia levels were associated with the neonatal size at birth. These results are not consistent with previous studies [8, 9, 48, 49]. Nevertheless, the absence of evidence does not always mean that there is no effect in real life. In our relatively healthy population, fasting mean glucose levels of 70 and 68 mg/dL in early and late pregnancy represent values from the normal range, which might have reduced associations toward the null, contributing to the discrepancy between our study and others. Unfortunately, this study population therefore did not allow us to research the associations with elevated fasting glycemia levels or extreme hyperglycemia. In addition, we were also unable to find any significant association with IR during pregnancy. This could be related to the indirect method used for assessing HOMA-IR-based IR. A more specific study that uses the euglycemic hyperinsulinemic clamp, which is considered the gold standard for measuring IR directly [50], could establish a relationship, which we were not able to verify in this study.

Regarding maternal BP, we detected associations between elevations in diastolic-BP at the beginning and end of pregnancy and an increased risk of SGA in terms of both weight and HC at birth. The associations were independent of other relevant maternal obesogenic confounders, such as BMI, diet, physical activity, and gestational weight gain, which were rarely controlled in studies on this topic. Our results, based on a cohort of healthy Mediterranean women whose BP was below the threshold for hypertensive disorders of pregnancy, confirm and expand upon previous reports [20, 21]. For instance, in the Avon Longitudinal Study of Parents and Children (ALSPAC) involving 9697 normotensive pregnant women with a higher 1st-trimester systolic-

BP, but not diastolic-BP, and greater increases in systolic and diastolic-BP between the second and third trimester, an association was found between lower weight at birth and SGA, considering confounders, but not those mentioned in this study [22]. In another large population-based study (n=157 446) of Swedish women, maternal prehypertension (diastolic-BP 80–89 mm Hg) in late pregnancy (36th weeks) was predictive of an SGA birth [51]. A few studies have found an inverted U-shaped association in non-hypertensive pregnant women, so that both lower and higher diastolic-BP during pregnancy were associated with SGA babies [52]. Our results are further supported by recent studies that focus on 24-hour ambulatory BP in late pregnancy in both normotensive [53] and hypertensive (blood pressure >/=140/90 mm Hg) [54] pregnant women, reporting an association with lower birthweight and a higher risk of SGA. Interestingly, in our study, high diastolic-BP was a better predictor of infant birthweight than high systolic-BP. This aligns with the perspective of other authors [53], who argued that diastolic-BP is often found to be a stable marker during pregnancy and a better predictor of birthweight than systolic-BP, with the latter being more responsive to moment-to-moment stimuli.

We have also added to the previous literature by examining the HC instead of just the birth weight alone. We found a strong relationship between higher maternal diastolic-BP in late pregnancy and the risk of SGA in terms of HC. Lower neonatal HC may not only represent a reduced brain size, but could also indicate the possibility of later physical, neurological, cognitive and psychological abnormalities [55]. Taken together, this evidence emphasizes the importance of closely monitoring BP as early as possible in pregnancy until delivery, even in normotensive women, to ensure adequate fetal growth. Pregnant women with healthy pregnancies often have higher than normal blood pressure levels, although they are still within the accepted physiological range of BP variability [56], as observed in our study. Overall, it has been hypothesized that slightly increased BP levels may impair the development of the placental villous tree and reduce the placental functional capacity, impairing fetal growth [57].

This longitudinal study, which spans from early pregnancy through to delivery, has some strengths that deserve to be mentioned. Our analyses use a large dataset from the ECLIPSES study, which had rigorous prospective data collection and included critical maternal information for correcting confounding factors. Notably, this study is one of the first to explore the effects of most

maternal cardiometabolic markers on neonatal growth in both early and late pregnancy. Furthermore, our study also contributes to the existing literature by examining HC at birth rather than just birthweight, which is generally the only parameter analyzed in most previous studies. Our study also had a few limitations. First, our study population comprised apparently healthy Mediterranean pregnant women, so our results may not be generalizable to other populations. Second, the cardiometabolic risk markers were limited to a single measurement during each trimester, which could affect their reliability due to possible fluctuations. Third, it's important to note that BP measurements were not acquired through 24-hour ambulatory BP monitoring, which potentially impacts our findings. Fourth, as this is an observational study, causality cannot be claimed. And lastly, the possibility of residual confounding cannot be ruled out.

Conclusion

In summary, this prospective cohort study found a link between maternal metabolic biomarkers in the first and third trimesters of pregnancy and newborn size. Increases in triglyceride and LDL-c levels at the beginning of pregnancy were positively associated with neonatal birthweight and a higher risk of LGA for weight. In addition, BP during pregnancy, especially diastolic-BP was an independent predictor of SGA for both weight and HC at birth. Thus, it would be beneficial to provide health education before pregnancy and to screen women early for lipid and blood pressure disorders as well as actively monitor these maternal cardiometabolic risk factors throughout pregnancy to ensure normal fetal development and the future health of the child.

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Author Contributions

VA designed and conducted the research. VA performed data curation. AD and EM analyzed the data and wrote the article. CJ, CR-R and FM contributed to the collection and management of data. All authors revised the manuscript for important intellectual content and read and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no one who meets the criteria has been omitted. VA is the guarantor of this work, as such, she has had full access to all study data and takes responsibility for their integrity and for the accuracy of the data analysis.

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Data Availability and materials

The datasets generated and/or analyzed during the current study are not publicly available due to subject confidentiality but are available from the corresponding author at a reasonable request.

Declarations

Conflict of interest: The authors declare that they have no conflict of interest.

Ethics Approval: The ECLIPSES study was registered at www.clinicaltrialsregister.eu (ID: EUCTR-2012-005480-28) and at www.clinicaltrials.gov (ID: NCT03196882). The study was approved by the Ethical Committee of the Jordi Gol Institute for Primary Care Research and the

Pere Virgili Institute for Health Research. The research complies with the tenets of the Helsinki Declaration.

Informed consent: Informed consent was obtained from all participants included in the study.

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Table 1. Sociodemographic and lifestyle characteristics of pregnant women (n=264).

General Characteristics	Summary Statistics
Age (years)	29.64 ± 4.71
Age categories (years)	
<25	40 (15.2)
25-29	73 (27.7)
≥30	151 (57.2)
Weight (kg)	63.26 ± 9.65
BMI (kg/m^2)	24.12 ± 3.53
BMI categories	
18.5–24.9 (normal weight)	169 (64.0)
25.0–29.9 (overweight)	81 (30.7)
≥30 (obesity)	14 (5.3)
GWG (kg)	10.56 ± 3.69
IOM GWG recommendations†	
Insufficient	114 (43.2)
Adequate	103 (39.0)
Excessive	47 (17.8)
Educational level	
Low (primary or below)	83 (31.4)
Medium (secondary)	97 (36.7)
High (university or above)	84 (31.8)
Social class	
Low	35 (13.3)
Medium	180 (68.2)
High	49 (18.6)
Smoking status	
Never/ Former smoker	227 (86.0)
Current smoker	37 (14.0)
Alcohol consumption	
No	222 (87.1)
Yes	33 (12.9)
Physical Activity (METs-min/week)	
T1 (<1070)	90 (34.1)
T2 (1070-3336)	114 (43.2)
T3 (≥3336)	60 (22.7)
rMedDiet score (point)	
T1 (<9)	92 (36.1)
T2 (9-12)	107 (42.0)
T3 (≥12)	56 (22.0)
Planned pregnancy	
No	62 (23.5)
Yes	202 (76.5)
Parity	
No	112 (42.4)
Yes	152 (57.6)

Values are expressed in means ± SD (standard deviation) or number (%, percentage). Abbreviations: BMI, body mass index; GWG, gestational weight gain; IOM, Institute of Medicine; METs, metabolic equivalents; T, tertile; rMedDiet, Mediterranean diet; †Recommendations for GWG according to IOM guidelines are: initial BMI <18.5 kg/m^2, total weight gain 12.5–18 kg; BMI 18.5–24.9 kg/m^2, total weight gain 11.5–16 kg; BMI 25.0–29.9 kg/m2, total weight gain 7–11.5 kg; and BMI ≥30 kg/m^2 total weight gain 5–9 kg.

Table 2. Maternal cardiometabolic markers levels during pregnancy according to the different quartile.

		Quartiles			
Cardiometabolic markers	All	Q1	Q2	Q3	Q4
First trimester	mean ± SD				
Triglycerides (mg/dL)	89.23 ± 37.16	54.30 ±7.50	71.71 ± 4.74	91.09 ± 6.59	140.61 ± 34.46
Total cholesterol (mg/dL)	167.28 ± 34.01	132.97 ± 8.84	154.14 ± 5.07	171.94 ± 6.46	211.26 ± 34.73
LDL-c (mg/dL)	88.18 ± 25.49	63.56 ± 6.60	78.13 ± 3.76	90.78 ± 3.80	120.23 ± 28.09
HDL-c (mg/dL)	61.28 ± 13.04	46.95 ± 4.05	56.20 ± 1.97	64.12 ± 2.96	79.17 ± 8.74
Glucose (mg/dL)	70.23 ± 10.73	57.87 ± 8.99	67.95 ± 1.45	72.95 ± 1.45	82.68 ± 6.71
HOMA-IR	1.63 ± 1.20	0.65 ± 0.17	1.10 ± 0.12	1.52 ± 0.15	3.26 ± 1.35
SBP (mm Hg)	112.34 ± 11.85	98.99 ± 5.72	109.17 ± 1.90	116.88 ± 2.46	129.04 ± 5.81
DBP (mm Hg)	66.44 ± 7.75	57.49 ± 3.25	64.72 ± 1.69	69.66 ± 1.01	77.09 ± 4.13
Third trimester					
Triglycerides (mg/dL)	**188.86 ± 76.93***	90.4 ± 26.32	166.82 ± 17.23	214.77 ± 15.26	286.93 ± 43.06
Total cholesterol (mg/dL)	**237.81 ± 45.24****	185.70 ± 18.73	219.28 ± 7.85	248.53 ± 9.04	299.88 ± 27.51
LDL-c (mg/dL)	**131.19 ± 35.85****	91.96 ± 14.78	115.69 ± 5.54	137.47 ± 7.44	180.40 ± 24.82
HDL-c (mg/dL)	**66.33 ± 14.13****	50.48 ± 5.81	62.00 ± 2.17	70.29 ± 3.13	86.91 ± 10.51
Glucose (mg/dL)	**67.40 ± 10.07***	55.23 ± 7.56	65.19 ± 1.46	70.33 ± 1.80	80.02 ± 5.61
HOMA-IR	1.84 ± 1.63	0.67 ± 0.21	1.23 ± 0.15	1.69 ± 0.15	3.78 ± 2.27
SBP (mm Hg)	**115.82 ± 11.15****	101.52 ± 4.39	112.56 ± 2.02	120.66 ± 2.69	130.59 ± 4.05
DBP (mm Hg)	**70.66 ± 7.94****	60.82 ± 3.42	68.38 ± 1.52	73.73 ± 1.80	81.39 ± 3.57

Values are expressed in means ± SD (standard deviation). Abbreviations: LDL-c, low density lipoprotein cholesterol; HDL-c, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure. Reference values in the first/third trimester: triglycerides 40–159 /131–453 mg/dL; total cholesterol 141–210/219–349 mg/dL; LDL-c 60–153/101–224 mg/dL, HDL-c 40–78/48–87 mg/dL [58]; glucose 81.59/79.52 mg/dL; HOMA-IR 1.25/1.81 [59]; SBP - DBP 112.1– 65.4/ 116.0 – 70.0 [60]. The significance of the numbers in bold as * p-value < 0.05, and ** p-value <0.001 compared with first trimester were calculated with the paired Student's t-test.

Table 3. Multivariate-adjusted linear regression models for the associations of maternal cardiometabolic markers in the first trimester, and birth outcomes.

	Birth weight		Birth HC	
Cardiometabolic markers	**β (95% CI)**	***p***	**β (95% CI)**	***p***
Triglycerides (mg/dL)				
Continuous	**2.01 (0.59, 3.44)**	**0.006***	0.00 (-0.00, 0.00)	0.343
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	20.94 (-127.27, 169.15)	0.781	-0.19 (-0.71, 0.32)	0.455
Q3	39.66 (-106.02, 185.33)	0.592	-0.19 (-0.71, 0.31)	0.445
Q4	**175.98 (24.58, 327.38)**	**0.023***	0.16 (-0.39, 0.74)	0.539
p-trend	**0.029***		0.675	
Total cholesterol (mg/dL)				
Continuous	1.51 (-0.05, 3.06)	0.057	0.00 (-0.00, 0.00)	0.616
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	51.74 (-97.52, 201.01)	0.495	0.22 (-0.29, 0.73)	0.400
Q3	-14.42 (-167.82, 138.98)	0.853	0.09 (-0.46, 0.64)	0.755
Q4	75.18 (-76.41, 226.79)	0.330	0.06 (-0.48, 0.59)	0.841
p-trend	0.655		0.993	
LDL-c (mg/dL)				
Continuous	1.39 (-0.70, 3.49)	0.191	0.00 (-0.01, 0.01)	0.719
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	31.67 (-117.43, 180.77)	0.676	0.22 (-0.29, 0.74)	0.392
Q3	46.25 (-106.53, 199.04)	0.551	0.12 (-0.41, 0.65)	0.661
Q4	29.73 (-124.72, 184.18)	0.705	0.03 (-0.49, 0.56)	0.902
p-trend	0.666		0.956	
HDL-c (mg/dL)				
Continuous	1.76 (-2.34, 5.85)	0.399	0.00 (-0.01, 0.01)	0.977
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	105.09 (-46.42, 256.58)	0.173	0.54 (-0.01, 1.09)	0.056
Q3	104.50 (-43.37, 252.37)	0.165	0.29 (-0.24, 0.82)	0.284
Q4	114.68 (-36.11, 265.48)	0.135	0.19 (-0.35, 0.74)	0.478
p-trend	0.147		0.701	
Glucose (mg/dL)				
Continuous	1.38 (-3.46, 6.22)	0.574	-0.01 (-0.03, 0.01)	0.288
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	21.85 (-125.97, 171.65)	0.774	-0.28 (-0.81, 0.25)	0.298
Q3	97.69 (-52.56, 247.93)	0.201	0.16 (-0.37, 0.69)	0.551
Q4	27.47 (-122.23, 177.17)	0.718	-0.32 (0.83, 0.20)	0.230
p-trend	0.515		0.528	
HOMA-IR				
Continuous	23.06 (-21.65, 67.76)	0.311	0.06 (-0.12, 0.24)	0.507
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	55.07 (-95.94, 206.08)	0.473	-0.16 (-0.68, 0.37)	0.550
Q3	129.13 (-24.81, 283.07)	0.100	-0.21 (-0.75, 0.34)	0.451
Q4	67.83 (-85.12, 220.78)	0.383	-0.21 (-0.76, 0.34)	0.457
p-trend	0.285		0.449	
SBP (mm Hg)				
Continuous	0.53 (-4.23, 5.29)	0.828	-0.01 (-0.02, 0.01)	0.481
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	33.78 (-116.72, 184.28)	0.659	-0.06 (-0.58, 0.45)	0.808
Q3	64.63 (-76.04, 205.30)	0.366	0.09 (-0.40, 0.58)	0.716
Q4	-20.52 (-175.19, 134.17)	0794	-0.33 (-0.88, 0.22)	0.243
p-trend	0.955		0.441	
DBP (mm Hg)				
Continuous	0.89 (-6.16, 7.95)	0.802	-0.00 (-0.03, 0.02)	0.816
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	120.07 (-21.98, 262.12)	0.097	0.370 (-0.12, 0.86)	0.136
Q3	42.57 (-103.65, 188.79)	0.567	0.03 (-0.49, 0.54)	0.920
Q4	-6.61 (-158.25, 145.03)	0.932	-0.04 (-0.56, 0.49)	0.892
p-trend	0.812		0.730	

Linear regression models were used to calculate the β coefficient (β) and 95% confidence interval (95% CI). Adjusted for age categories (<25 (ref.), 25-29, ≥30 years), physical activity tertile (T1: ≤1070 (ref.), T2:1071-3335, T3: ≥3336 METs-min/week), Mediterranean diet score tertile (T1: ≤8 (ref.), T2: 9-11, T3: ≥12 points), GWG (insufficient (ref), adequate, excessive), BMI categories (normal weight (ref.), overweight/obesity), parity (nulliparous (ref.), multiparous), educational level (low/medium (ref.), high), smoking status (never/former smoker (ref.), current smoker), planned pregnancy (no (ref.), yes), social class (low/medium (ref.), high), sex infant. Abbreviations: HC, head circumference; LDL-c, low density lipoprotein cholesterol; HDL-c, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure. The significance of the numbers in bold as * *p*-value < 0.05, and ** *p*-value <0.001 compared with the reference category. The *p*-value for the trend is based on the birth outcomes as a continuous variable.

Table 4. Multivariate-adjusted linear regression models for the associations of maternal cardiometabolic markers in the third trimester, and birth outcomes.

	Birth weight		Birth HC	
Cardiometabolic markers	**β (95% CI)**	***p***	**β (95% CI)**	***p***
Triglycerides (mg/dL)				
Continuous	-0.03 (-0.79, 0.73)	0.943	0.00 (-0.00, 0.00)	0.825
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	-15.25 (-175.25, 144.77)	0.851	-0.05 (-0.62, 0.52)	0.856
Q3	-83.72 (-243.37, 75.93)	0.302	-0.18 (-0.74, 0.38)	0.523
Q4	28.89 (-134.33, 192.12)	0.727	-0.06 (-0.64, 0.51)	0.833
p-trend	0.983		0.702	
Total cholesterol (mg/dL)				
Continuous	-0.41 (-1.58, 0.77)	0.498	-0.00 (-0.01, 0.00)	0.245
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	-46.73 (-194.95, 101.49)	0.535	-0.21 (-0.72, 0.31)	0.429
Q3	1.88 (-148.00, 151.76)	0.980	-0.11 (-0.64, 0.41)	0.667
Q4	-61.18 (-214.71, 92.36)	0.433	-0.31 (-0.85, 0.23)	0.258
p-trend	0.590		0.336	
LDL-c (mg/dL)				
Continuous	-1.03 (-2.53, 0.47)	0.178	-0.00 (-0.01, 0.00)	0.249
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	-26.00 (-177.55, 125.55)	0.736	-0.01(-0.55, 0.52)	0.962
Q3	8.60 (-142.77, 159.98)	0.911	-0.02 (-0.56, 0.52)	0.945
Q4	-79.65 (-236.04, 76.73)	0.317	-0.14 (-0.69, 0.42)	0.619
p-trend	0.428		0.629	
HDL-c (mg/dL)				
Continuous	-0.82 (-4.55, 2.92)	0.667	-0.00 (-0.01, 0.01)	0.834
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	42.90 (-100.11, 185.91)	0.555	-0.02 (-0.53, 0.48)	0.929
Q3	-60.98 (-208.95, 86.99)	0.418	-0.13 (-0.64, 0.38)	0.6313
Q4	-22.11 (-177.96, 133.73)	0.780	0.09 (-0.46, 0.62)	0.757
p-trend	0.490		0.917	
Glucose (mg/dL)				
Continuous	4.16 (-1.45, 9.76)	0.145	0.00 (-0.02, 0.03)	0.714
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	-4.55(-170.84, 161.74)	0.957	-0.39 (-0.97, 0.18)	0.176
Q3	83.02 (-74.73, 240.77)	0.301	-0.03 (-0.61, 0.56)	0.936
Q4	67.51 (-98.07, 233.08)	0.422	-0.19 (-0.78, 0.39)	0.504
p-trend	0.251		0.846	
HOMA-IR				
Continuous	-3.31 (-37.48, 30.86)	0.849	-0.05 (-0.18, 0.08)	0.437
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	7.59 (-156.72, 171.91)	0.927	0.07 (-0.51, 0.65)	0.820
Q3	-21.68 (-184.17, 140.80)	0.763	-0.27 (-0.84, 0.29)	0.337
Q4	-52.28 (-217.20, 112.65)	0.533	-0.39 (-1.01, 0.22)	0.203
p-trend	0.476		0.118	
SBP (mm Hg)				
Continuous	-4.89 (-11.02, 1.24)	0.117	-0.01 (-0.04, 0.01)	0.184
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	-55.26 (-231.09, 120.65)	0.536	-0.02 (-0.61, 0.57)	0.945
Q3	-108.09 (-294.39, 78.14)	0.253	-0.19 (-0.83, 0.45)	0.551
Q4	-133.18 (-325.65, 59.28)	0.174	-0.31 (-0.98, 0.36)	0.365
p-trend	0.143		0.318	
DBP (mm Hg)				
Continuous	**-10.86 (-19.09, -2.62)**	**0.010***	**-0.04 (-0.07, -0.01)**	**0.008***
Q1	0.0 (ref.)		0.0 (ref.)	
Q2	-91.75 (-270.44, 86.94)	0.312	-0.42 (-1.02, 0.18)	0.165
Q3	-73.67 (-253.24, 105.89)	0.419	**-0.63 (-1.26, -0.01)**	**0.047***
Q4	**-245.49 (-431.54, -59.45)**	**0.010***	**-0.87 (-1.49, -0.24)**	**0.007***
p-trend	**0.018***		**0.005***	

Linear regression models were used to calculate the β coefficient (β) and 95% confidence interval (95% CI). Adjusted for age categories (<25 (ref.), 25-29, ≥30 years), physical activity tertile (T1: ≤1070 (ref.), T2:1071-3335, T3: ≥3336 METs-min/week), Mediterranean diet score tertile (T1: ≤8 (ref.), T2: 9-11, T3: ≥12 points), GWG (insufficient (ref), adequate, excessive), BMI categories (normal weight (ref.), overweight/obesity), parity (nulliparous (ref.), multiparous), educational level (low/medium (ref.), high), smoking status (never/former smoker (ref.), current smoker), planned pregnancy (no (ref.), yes), social class (low/medium (ref.), high), sex infant. Abbreviations: HC, head circumference; LDL-c, low density lipoprotein cholesterol; HDL-c, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure. The significance of the numbers in bold as * *p*-value < 0.05, and ** *p*-value <0.001 compared with the reference category. The *p*-value for the trend is based on the birth outcomes as a continuous variable.

Table 5. Multivariate-adjusted Odds Ratio and 95% confidence interval, for the associations of maternal cardiometabolic markers in the first trimester, and birth outcomes.

	Birth weight				Birth HC			
	SGA		LGA		SGA		LGA	
Cardiometabolic markers	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Triglycerides (mg/dL)								
Continuous	27 (10.5)	**0.98 (0.96, 0.99)** *	21 (8.1)	1.01 (0.99, 1.02)	13 (6.4)	0.99 (0.97, 1.02)	34 (16.7)	1.00 (0.99, 1.01)
Normal (<75th Pctl)	25 (12.9)	1 Ref.	12 (6.2)	1 Ref.	12 (7.6)	1 Ref.	25 (15.8)	1 Ref.
High (≥75th Pctl)	2 (3.1)	**0.21 (0.04, 0.95)** *	9 (14.1)	2.49 (0.85, 7.32)	1 (2.2)	0.43 (0.05, 4.05)	9 (19.6)	0.75 (0.27, 2.03)
Total cholesterol (mg/dL)								
Continuous	27 (10.5)	0.99 (0.97, 1.00)	21 (8.1)	1.01 (0.99, 1.02)	13 (6.4)	0.99 (0.97, 1.02)	34 (16.7)	1.00 (0.99, 1.01)
Normal (<75th Pctl)	20 (10.6)	1 Ref.	12 (6.4)	1 Ref.	11 (7.3)	1 Ref.	26 (17.3)	1 Ref.
High (≥75th Pctl)	7 (10.0)	0.85 (0.32, 2.25)	9 (12.9)	2.69 (0.94, 7.75)	2 (3.7)	0.59 (0.10, 3.46)	8 (14.8)	0.68 (0.26, 1.75)
LDL-c (mg/dL)								
Continuous	27 (10.5)	0.99 (0.97, 1.01)	21 (8.1)	**1.02 (1.00, 1.04)** *	13 (6.4)	0.98 (0.95, 1.02)	34 (16.7)	1.00 (0.99, 1.02)
Normal (<75th Pctl)	20 (10.4)	1 Ref.	14 (7.3)	1 Ref.	11 (7.2)	1 Ref.	26 (17.0)	1 Ref.
High (≥75th Pctl)	7 (10.8)	0.82 (0.29, 2.32)	7 (10.8)	1.55 (0.52, 4.61)	2 (3.9)	1.04 (0.16, 6.66)	8 (15.7)	0.59 (0.22, 1.58)
HDL-c (mg/dL)								
Continuous	27 (10.5)	0.99 (0.96, 1.03)	21 (8.1)	0.98 (0.94, 1.02)	13 (6.4)	0.99 (0.95, 1.05)	34 (16.7)	0.99 (0.96, 1.03)
Normal (<75th Pctl)	21 (11.1)	1 Ref.	17 (8.9)	1 Ref.	10 (6.8)	1 Ref.	26 (17.6)	1 Ref.
High (≥75th Pctl)	6 (8.8)	0.74 (0.26, 2.14)	4 (5.9)	0.60 (0.17, 2.13)	3 (5.4)	0.88 (0.19, 4.16)	8 (14.3)	1.12 (0.42, 2.99)
Glucose (mg/dL)								
Continuous	27 (10.5)	1.00 (0.96, 1.05)	21 (8.1)	0.99 (0.95, 1.03)	13 (6.4)	1.03 (0.96, 1.11)	34 (16.7)	0.99 (0.96, 1.03)
Normal (<75th Pctl)	18 (9.3)	1 Ref.	16 (8.3)	1 Ref.	9 (6.0)	1 Ref.	26 (17.3)	1 Ref.
High (≥75th Pctl)	9 (13.8)	1.76 (0.69, 4.52)	5 (7.7)	0.87 (0.27, 2.79)	4 (7.4)	1.37 (0.33, 5.71)	8 (14.8)	0.67 (0.26, 1.75)
HOMA-IR								
Continuous	27 (10.5)	0.86 (0.58, 1.28)	21 (8.1)	0.81 (0.47, 1.41)	13 (6.4)	0.88 (0.45, 1.72)	34 (16.7)	0.97 (0.65, 1.44)
Normal (<75th Pctl)	20 (10.4)	1 Ref.	16 (8.3)	1 Ref.	10 (6.4)	1 Ref.	25 (15.9)	1 Ref.
High (≥75th Pctl)	7 (10.8)	1.02 (0.38, 2.76)	5 (7.7)	0.97 (0.29, 3.17)	3 (6.4)	1.52 (0.27, 5.87)	9 (19.1)	0.77 (0.28, 2.09)
SBP (mm Hg)								
Continuous	27 (10.5)	0.98 (0.94, 1.02)	21 (8.1)	1.01 (0.96, 1.05)	13 (6.4)	1.02 (0.97, 1.08)	34 (16.7)	0.98 (0.94, 1.02)
Normal (<75th Pctl)	22 (11.8)	1 Ref.	14 (7.5)	1 Ref.	9 (5.9)	1 Ref.	25 (16.3)	1 Ref.
High (≥75th Pctl)	5 (7.0)	0.56 (0.19, 1.67)	7 (9.9)	1.04 (0.35, 3.14)	4 (7.8)	1.74 (0.42, 7.12)	9 (17.6)	0.87 (0.32, 2.36)
DBP (mm Hg)								
Continuous	27 (10.5)	1.01 (0.95, 1.07)	21 (8.1)	1.01 (0.94, 1.08)	13 (6.4)	**1.13 (1.02, 1.24)** *	34 (16.7)	1.01 (0.96, 1.07)
Normal (<75th Pctl)	18 (9.7)	1 Ref.	15 (8.1)	1 Ref.	7 (4.6)	1 Ref.	27 (17.9)	1 Ref.
High (>75th Pctl)	9 (12.5)	1.08 (0.43, 2.73)	6 (8.3)	0.87 (0.29, 2.63)	6 (11.3)	3.28 (0.84, 12.76)	7 (13.2)	0.62 (0.23, 1.68)

Logistic regression models were used to calculate the Odds Ratio (OR) and 95% confidence interval (95% CI). Adjusted for age categories (<25 (ref.), 25-29, ≥30 years), physical activity tertile (T1: ≤1070 (ref.), T2:1071-3335, T3: ≥3336 METs-min/week), Mediterranean diet score tertile (T1: ≤8 (ref.), T2: 9-11, T3: ≥12 points), GWG (insufficient (ref), adequate, excessive), BMI categories (normal weight (ref.), overweight/obesity), parity (nulliparous (ref.), multiparous), educational level (low/medium (ref.), high), smoking status (never/former smoker (ref.), current smoker), planned pregnancy (no (ref.), yes), social class (low/medium (ref.), high), sex infant. Abbreviations: HC, head circumference; LDL-c, low density lipoprotein cholesterol; HDL-c, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure. The significance of the numbers in bold as * p-value < 0.05, and ** p-value <0.001 compared with the reference category.

Table 6. Multivariate-adjusted Odds Ratio and 95% confidence interval, for the associations of maternal cardiometabolic markers in the third trimester, and birth outcomes.

	Birth weight				Birth HC			
	SGA		LGA		SGA		LGA	
Cardiometabolic markers	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Triglycerides (mg/dL)								
Continuous	19 (9.0)	0.99 (0.99, 1.01)	18 (8.5)	0.99 (0.99, 1.00)	10 (5.9)	0.99 (0.99, 1.01)	29 (17.1)	0.99 (0.99, 1.00)
Normal (<75th Pctl)	14 (8.6)	1 Ref.	14 (8.6)	1 Ref.	8 (6.1)	1 Ref.	23 (17.4)	1 Ref.
High (≥75th Pctl)	5 (10.0)	1.05 (0.34, 3.24)	4 (8.0)	0.85 (0.21, 3.52)	2 (5.3)	1.09 (0.15, 8.12)	6 (15.8)	1.10 (0.33, 3.66)
Total cholesterol (mg/dL)								
Continuous	26 (10.1)	0.99 (0.99, 1.01)	21 (8.2)	0.99 (0.98, 1.01)	13 (6.4)	0.99 (0.97, 1.01)	34 (16.7)	0.99 (0.98, 1.00)
Normal (<75th Pctl)	20 (10.4)	1 Ref.	17 (8.9)	1 Ref.	13 (8.3)	1 Ref.	29 (18.6)	1 Ref.
High (≥75th Pctl)	6 (9.2)	0.84 (0.30, 2.35)	4 (6.2)	0.58 (0.17, 1.98)	0 (0.0)	0.00 (0.00, 0.00)	5 (10.6)	0.46 (0.15, 1.44)
LDL-c (mg/dL)								
Continuous	26 (10.1)	0.99 (0.98, 1.01)	21 (8.2)	0.99 (0.98, 1.01)	13 (6.4)	0.98 (0.96, 1.00)	34 (16.7)	0.99 (0.98, 1.01)
Normal (<75th Pctl)	20 (10.3)	1 Ref.	16 (8.2)	1 Ref.	13 (8.3)	1 Ref.	28 (17.9)	1 Ref.
High (≥75th Pctl)	6 (9.7)	0.81 (0.28, 2.29)	5 (8.1)	0.96 (0.31, 3.01)	0 (0.0)	0.00 (0.00, 0.00)	6 (12.8)	0.72 (0.25, 2.04)
HDL-c (mg/dL)								
Continuous	26 (10.1)	0.99 (0.96, 1.02)	21 (8.2)	0.99 (0.96, 1.03)	13 (6.4)	1.00 (0.96, 1.05)	34 (16.7)	0.99 (0.96, 1.02)
Normal (<75th Pctl)	19 (9.9)	1 Ref.	17 (8.9)	1 Ref.	10 (6.6)	1 Ref.	28 (18.5)	1 Ref.
High (≥75th Pctl)	7 (10.8)	1.08 (0.39, 3.01)	4 (6.2)	0.65 (0.19, 2.19)	3 (5.8)	1.05 (0.24, 4.66)	6 (11.5)	0.54 (0.19, 1.56)
Glucose (mg/dL)								
Continuous	19 (9.0)	0.99 (0.95, 1.05)	18 (8.5)	1.02 (0.96, 1.07)	10 (5.9)	0.97 (0.89, 1.05)	29 (17.1)	0.99 (0.95, 1.04)
Normal (<75th Pctl)	14 (9.1)	1 Ref.	10 (6.5)	1 Ref.	7 (5.8)	1 Ref.	17 (14.2)	1 Ref.
High (≥75th Pctl)	5 (8.6)	0.90 (0.29, 2.81)	8 (13.8)	2.49 (0.78, 7.96)	3 (6.0)	1.06 (0.17, 6.81)	12 (24.0)	1.54 (0.59, 3.99)
HOMA-IR								
Continuous	26 (10.1)	1.14 (0.91, 1.44)	21 (8.2)	0.92 (0.64, 1.32)	13 (6.4)	1.21 (0.91, 1.62)	34 (16.7)	0.88 (0.62, 1.24)
Normal (<75th Pctl)	17 (8.8)	1 Ref.	16 (8.3)	1 Ref.	9 (5.6)	1 Ref.	27 (16.9)	1 Ref.
High (≥75th Pctl)	9 (14.1)	1.94 (0.69, 5.39)	5 (7.8)	0.74 (0.19, 2.82)	4 (9.3)	1.99 (0.37, 10.49)	7 (16.3)	0.52 (0.14, 1.93)
SBP (mm Hg)								
Continuous	21 (11.1)	1.03 (0.98, 1.08)	19 (10.1)	0.96 (0.91, 1.02)	10 (6.3)	1.06 (0.97, 1.17)	30 (18.8)	0.98 (0.93, 1.02)
Normal (<75th Pctl)	15 (10.6)	1 Ref.	15 (10.6)	1 Ref.	7 (5.8)	1 Ref.	23 (19.0)	1 Ref.
High (≥75th Pctl)	6 (12.8)	1.82 (0.57, 5.74)	4 (8.5)	0.41 (0.10, 1.69)	3 (7.7)	6.27 (0.75, 52.64)	7 (17.9)	0.58 (0.18, 1.80)
DBP (mm Hg)								
Continuous	21 (11.1)	**1.09 (1.03, 1.17)** *	19 (10.1)	0.94 (0.87, 1.01)	10 (6.3)	**1.21 (1.04, 1.42)** *	30 (18.8)	0.96 (0.90, 1.03)
Normal (<75th Pctl)	10 (7.5)	1 Ref.	14 (10.4)	1 Ref.	6 (5.4)	1 Ref.	23 (20.5)	1 Ref.
High (≥75th Pctl)	11 (20.0)	**3.54 (1.20, 10.42)** *	5 (9.1)	0.58 (0.17, 2.02)	4 (8.3)	5.47 (0.72, 41.73)	7 (14.6)	0.67 (0.22, 2.07)

Logistic regression models were used to calculate the Odds Ratio (OR) and 95% confidence interval (95% CI). Adjusted for age categories (<25 (ref.), 25-29, ≥30 years), physical activity tertile (T1: ≤1070 (ref.), T2:1071-3335, T3: ≥3336 METs-min/week), Mediterranean diet score tertile (T1: ≤8 (ref.), T2: 9-11, T3: ≥12 points), GWG (insufficient (ref), adequate, excessive), BMI categories (normal weight (ref.), overweight/obesity), parity (nulliparous (ref.), multiparous), educational level (low/medium (ref.), high), smoking status (never/former smoker (ref.), current smoker), planned pregnancy (no (ref.), yes), social class (low/medium (ref.), high), sex infant. Abbreviations: HC, head circumference; LDL-c, low density lipoprotein cholesterol; HDL-c, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure. The significance of the numbers in bold as * p-value < 0.05, and ** p-value <0.001 compared with the reference category.

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Discussion

The discussion section encompasses key topics, limitations, and areas warranting further research. It also elucidates the significance and potential interpretations of the primary findings while raising awareness of the numerous factors that influence changes in maternal cardiometabolic markers during pregnancy and their subsequent impact on fetal growth.

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GENERAL DISCUSSION

Pregnancy is a time-limited condition during which women experience significant cardiometabolic changes. Prenatal maternal risk factors, varying in their influence, can exacerbate these changes, leading to considerable short- and long-term health implications for both mother and child. This dissertation investigates the associations between prenatal maternal sociodemographic, lifestyle, and clinical characteristics and CCR and its components throughout pregnancy. Additionally, it examines whether an abnormal maternal cardiometabolic profile influences inappropriate fetal growth, as assessed by newborn size.

In relation to the influence of prenatal environmental factors, we have observed that having a normal early pregnancy weight, lower GWG, and increased PA, as well as higher education and social class, were significantly linked to a more favorable maternal cardiometabolic profile throughout pregnancy, assessed as a CCR score. Conversely, smoking and drinking alcohol during pregnancy showed a non-significant trend towards a worse cardiometabolic phenotype. Interestingly, our study also supported a significant association between first- and third-trimester CCR scores, which suggests early pregnancy cardiometabolic disturbances are a harbinger of women's future cardiometabolic health in late pregnancy, as Catalano argues [279]. In this context, it is noteworthy that a cluster of cardiometabolic factors has been reported to be more strongly associated with adverse pregnancy outcomes than just one factor [197].

In our study, one in three pregnant women who live in the Mediterranean region had overweight/obesity in early pregnancy. This figure is supported by previous epidemiological studies in Europe, where the prevalence of pre-pregnancy overweight/obesity is estimated to be as high as 30% [280,281]. Given the importance of maternal overweight/obesity for the development of cardiometabolic abnormalities during pregnancy [282,283], we have described this relationship in pregnant women using a composite risk score. A novel finding was that early pregnancy overweight/obesity was the strongest predictor of the CCR score in both early and late pregnancy. Women who begin pregnancy with a BMI>25 kg/m^2 exhibited a worse cardiometabolic profile during the T1, characterized by elevated SBP, DBP, and LDL-c compared to their normal-weight counterparts. Furthermore, our data demonstrated higher insulin and HOMA-IR-based IR, particularly in the T1, among overweight/obese pregnant women. This supports a heightened risk of early pregnancy IR, potentially driven by increased maternal adiposity [284,285]. From our findings and the above evidence, it is imperative

that overweight/obese women of reproductive age be encouraged to undertake preconception-intensive behavioral lifestyle interventions for weight loss and improve their metabolic status before and during very early pregnancy.

Insufficient GWG was associated with a decrease in SBP and DBP during T3, while those with excessive GWG exhibited a significant increase in HDL-c levels during the same period. These findings are consistent with the literature [286,287]. The observed decrease in blood glucose levels among women with insufficient GWG in the T3 suggests a potential protective effect against hyperglycemia and IR. However, the impact of GWG on glucose metabolism remains relatively understudied and contradictory. Overall, regarding maternal adiposity, we can hypothesize from our findings that BMI at pregnancy baseline is more relevant than GWG when predicting cardiometabolic risk during pregnancy.

Research confirms that pregnant smokers have less favorable lipid profiles compared to non-smokers [179,180]. In our study, we also found that exposure to tobacco smoke during pregnancy adversely affects lipid profiles. Pregnant smokers had higher third-trimester levels of TG and LDL-c, even when adjusted for BMI and GWG, and faced an increased cardiometabolic risk. This may be due to increased lipoprotein lipase activity, impaired LDL-c clearance caused by nicotine, and elevated free fatty acids from enhanced lipolysis [288,289]. These lipid disorders can contribute to detrimental cardiovascular effects during pregnancy.

Socio-environmental factors, especially higher levels of education (in relation to lower BMI and SBP), social class (in relation to lower fasting glucose, insulin, and HOMA-IR), and regular PA, were also strongly associated with better cardiometabolic markers and lower CCRs during pregnancy.

In addition to weight-related factors, our research emphasized the critical role of parity in influencing IR. Multiparous women exhibited significantly higher IR in early pregnancy, with the risk escalation in proportion to the number of previous pregnancies. This relationship likely involves a multifactorial interplay of hormonal, inflammatory, and adiposity-related mechanisms that worsen with each subsequent pregnancy [290–292]. The cumulative effect of these factors may lead to a progressive increase in IR, underscoring the complex nature of the relationship between parity and maternal metabolism.

A novel aspect of this study is the identified positive correlation between parity, overweight/obesity, and an increased risk of insulin resistance (IR) in early pregnancy, a

relationship not previously explored. Remarkably, overweight/obese multiparous pregnant women exhibited a six-fold higher risk of IR.

To date, only three studies have investigated the relationship between parity and maternal IR. However, their findings are inconsistent [222–224]. Two studies have found a positive association between IR in middle pregnancy (20–30 weeks' gestation) and parity [223,224], which was not confirmed by the study by Seghieri et al [222]. In this context, previous researchers have also indicated that women with high HOMA-IR in early to mid-pregnancy have an increased risk of subsequent preeclampsia, excessive weight gain during pregnancy, and giving birth to macrosomic and large-for-gestational-age neonates [258,293,294].

In this dissertation, we also explored the impact of maternal cardiometabolic factors on fetal development. Elevated TG and LDL-c levels in early pregnancy were associated with increased neonatal weight and a higher risk of LGA at delivery.

Of clinical relevance, our study indicates that even mildly elevated maternal TG levels within a physiological range in early pregnancy can lead to fetal overgrowth, emphasizing their crucial role as energy sources during early embryonic development [295,296]. This is further supported by the Generation R study in Rotterdam, which found a positive association between maternal TG and embryonic size in early pregnancy [263]. Our results also support findings from various studies, predominantly in the Chinese population, indicating that elevated maternal first-trimester TG is associated with increased birth weight and may be an early predictor of LGA [261,262,297,298]. Other studies in Japan and Italy, focused on women with positive diabetic screens but normal glucose tolerance tests, confirmed that maternal hypertriglyceridemia at mid-gestation, defined as the 75th percentile cutoff, was associated with a higher risk of LGA infants [299,300].

Notably, their cutoff values of TG were over 203 [299] and 259 mg/dL [300], respectively, while our study, with a lower cutoff value (over 105 mg/dL), revealed an independent predictive effect on the likelihood of the baby being born LGA. We propose using the 75th percentile cutoff of TG from our study in early pregnancy to screen high-risk pregnancies and predict larger infants. It is hypothesized that the hydrolysis of maternal TG by placental lipoprotein lipase in early pregnancy leads to the release of free fatty acids that cross the placenta, contributing to fetal overgrowth and lipid accumulation in fetal tissues [301].

Several studies, like ours, have identified a relationship between early pregnancy LDL-c levels, macrosomia, and LGA infants [262,302–304]. However, we were unable to demonstrate any significant association in T3. Similarly, consistent with previous research [262,263,297,305], we did not observe any correlation between maternal HDL-c levels throughout pregnancy and fetal growth. While previous studies have linked elevated maternal glucose levels during pregnancy to increased fetal growth and a heightened risk of macrosomia, or LGA, in infants [256,257,306–309], our investigation did not support these associations. This was true for both T1 and T3 fasting glucose levels. Furthermore, our study did not uncover significant associations with IR during pregnancy, potentially due to the indirect method used to assess HOMA-IR-based IR. Future studies utilizing more direct measures, such as the euglycemic hyperinsulinemic clamp [310], may offer clearer insights into these relationships.

Our study found that elevated maternal DBP throughout pregnancy is associated with an increased risk of SGA in neonates, affecting both birth weight and HC. Our results confirm and expand upon previous reports [267,268]. It has been hypothesized that slightly increased BP levels may impair the development of the placental villous tree and reduce the placental functional capacity, impairing fetal growth as an underlying mechanism [311,312]. High DBP was a better predictor of infant birth weight than high SBP.

Strengths and limitations

The present doctoral dissertation has several strengths and limitations that deserve to be addressed.

Among the strengths are the relatively large sample size and the longitudinal design of the studies comprising this dissertation, as well as the use of a large dataset from the ECLIPSES study, which had rigorous prospective data collection and included critical maternal information for correcting confounding factors, allowing for observation from early pregnancy through delivery. Analyzing maternal cardiometabolic health during pregnancy through the clustering of cardiometabolic risk factors is novel and provides greater overall risk than any individual factor on its own. Another notable strength is the investigation into the impact of multiparity on maternal IR in early pregnancy and subsequent pregnancies. Lastly, our study is one of the first to explore the effects of most maternal cardiometabolic markers on neonatal growth in both early and late pregnancy.

The current studies also have limitations that should be considered when inferring findings from this dissertation. To begin with, our study population comprised apparently healthy Mediterranean pregnant women, so our results may not be generalizable to other populations. Also, the CCR score utilized in the study is specific to the sample population, and we assumed that each component has equal weight in predicting metabolic risk, which may limit its generalizability. Furthermore, due to resource constraints, the hyperinsulinemic-euglycemic clamp test was not utilized for assessing IR, which could affect the accuracy of the results obtained using the HOMA-IR. Previous findings also support the importance of other potential factors mediating the recurrence of GDM, such as the interpregnancy interval and percentage of body fat or fat distribution pattern through successive pregnancies; not having these data is, therefore, another potential weakness. Furthermore, limitations in the study include reliance on the use of a standard mercury sphygmomanometer for blood pressure measurements instead of 24-hour ambulatory monitoring, which might impact the findings. Finally, as an observational study, causal relationships cannot be elucidated.

In summary, our integrated analysis highlights the complex interplay of weight status, GWG, parity, lipid metabolism, PA, education, and SES in determining cardiometabolic health during pregnancy. These findings emphasize the importance of a holistic approach to maternal health that includes preconception lifestyle modifications, regular monitoring of metabolic markers, and support for healthy behaviors throughout pregnancy to optimize outcomes for both mother and child.

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Conclusion

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CONCLUSIONS

The conclusions from the three original research articles conducted among a Mediterranean cohort of pregnant women are elaborated upon.

- Potentially modifiable prenatal factors, such as having a normal weight, more physical activity, higher education and social class levels, and lower gestational weight gain, were independently associated with a lower cardiometabolic risk score during the gestation. The results of each cardiometabolic marker—body mass index, systolic blood pressure, and low-density lipoprotein cholesterol—also maintained the same relationship.

- Smoking and drinking alcohol during pregnancy showed a trend towards a higher cardiometabolic risk score at the end of pregnancy, especially influencing the lipid profile.

- Multiparity was positively associated with insulin resistance, as determined by the HOMA-IR index as assessed in the first trimester.

- Pregnant women with one or more parities exhibited a 1.59-fold higher risk of experiencing elevated insulin resistance in comparison to their nulliparous counterparts. The association between parity and an augmented risk of insulin resistance was further accentuated when women were also overweight and/or obese.

- Early pregnancy levels of circulating triglycerides were significantly associated with the risk of small-for-gestational-age newborns, while LDL-c levels were linked to large-for-gestational-age newborn weight. In contrast, circulating total cholesterol, HDL-c levels, and fasting glycemia levels during pregnancy showed no association with newborn weight outcomes.

- Moderately elevated maternal diastolic blood pressure throughout pregnancy, but not systolic blood pressure, was associated with an increased risk of giving birth to small-for-gestational-age neonates in terms of both birth weight and head circumference.

In general, to mitigate harmful maternal cardiometabolic risk factors, it's crucial to implement preventive measures before and during pregnancy, and these insights underscore the importance of monitoring and managing maternal health to ensure optimal fetal growth.

Future insights

Future research should specifically study the mechanisms linking maternal cardiometabolic and fetal outcomes. Longitudinal studies with diverse populations can provide insights into genetic, environmental, and lifestyle factors. Additionally, investigating dietary interventions, physical activity, and stress management during pregnancy could offer practical guidelines for expectant mothers.

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