Obesity and Overweight: Impact on Maternal and Milk Microbiome and their Role for Infant Health and Nutrition

Izaskun Garcia-Mantrana[1]; Maria Carmen Collado[1,*]

1. Institute of Agrochemistry and Food Technology, Spanish National Research Council (IATA-CSIC), Department of Biotechnology.

*Correspondence: Dra. Maria Carmen Collado, Institute of Agrochemistry and Food Technology, Spanish National Research Council (IATA-CSIC), Department of Biotechnology. Av. Agustin Escardino 7, 46980 Valencia, Spain.

E-mail: mcolam@iata.csic.es

Author disclosures: I. Garcia-Mantrana and M.C. Collado, no conflicts of interest.

No financial support is acknowledged

Abbreviations: **BMI**, body mass index; **C-section**, caesarean section delivery; **DM**, diabetes mellitus; **HDL-cholesterol**, high-density lipoprotein cholesterol

Key words: breast milk / diversity / microbiota / obesity / overweight.

Abstract

Obesity, particularly in infants, is becoming a significant public health problem that has reached “epidemic” status worldwide. Obese children have an increased risk of developing obesity related diseases, such as metabolic syndromes and diabetes, as well as increased risk of mortality and adverse health outcomes later in life. Experimental data show that maternal obesity has negative effects on the offspring’s health in the short and long term. Increasing evidence suggests a key role for microbiota in host metabolism and energy harvest, providing novel tools for obesity prevention and management. The maternal environment, including nutrition and microbes, influences the likelihood of developing childhood diseases, which may persist and be exacerbated in adulthood. Maternal obesity and weight gain also influence microbiota composition and activity during pregnancy and lactation. They affect microbial diversity in the gut and breast milk. Such microbial changes may be transferred to the offspring during delivery and also during lactation, affecting infant microbial colonisation and immune system maturation. Thus, an adequate nutritional and microbial environment during the peri-natal period may provide a window of opportunity to reduce the risk of obesity and overweight in our infants using targeted strategies aimed at modulating the microbiota during early life.

1 Introduction

1.1 Obesity, over-nutrition and microbes

Obesity and overweight is becoming a significant public health problem that has reached "epidemic" status worldwide. There are around 475 million obese adults and over 200 million school-age children with overweight [1]. These children are more likely to be obese later in life and they have an increased risk of developing obesity-related diseases, such as metabolic syndromes and diabetes, as well as adverse health outcomes later in life and premature death [2].

Globally, overweight and obesity are the fifth leading cause of death, resulting in the deaths of at least 2.8 million adults annually [3]. The origins of obesity are multifactorial with complex interactions between genetic, behavioural, social and environmental factors causing an imbalance between energy intake and energy expenditure, and low-grade inflammation.

The development of obesity and also, metabolic syndrome has been linked to specific pathways connecting metabolism with the immune system [4–6]. However, a novel factor identified as playing a role in human obesity and associated metabolic risks is gut microbiota. Gut microbiota is involved in nutrient absorption, digestion, protection and metabolic activities, but also recent evidence suggests that there is a link between gut microbiota and energy homeostasis, including energy harvest and host adiposity [7, 8]. Studies in animals and humans have demonstrated that human gut microbial communities differ between obese and lean individuals; more specifically, obese subjects showed an increased ratio of Firmicutes to Bacteroidetes, as well as lower microbial diversity, when compared to lean subjects [9, 10]. However, there are conflicting results regarding these microbial shifts, including the ratio of Firmicutes to Bacteroidetes in relation to obesity risk [10].

In a germ-free mouse model, obesogenic microbiome transplantation significantly increased body fat percentage and insulin resistance after two weeks. A recent animal study [10] reported that the microbiota from obese and lean subjects induced analogous phenotypes, and microbiota associated with lean subjects reduced adiposity in obese recipients when combined with an appropriate diet. Furthermore, dietary strategies such as calorie restriction and exercise have been shown to modulate obesogenic microbiota [11–13].

1.2 Perinatal environment and effects on infant health

Epidemiological studies suggest that an adverse preconception, gestational and post-natal environment affects programming of the infant for later health. Maternal unbalanced dietary intake, weight status (under- or over-nutrition) and breast milk composition have an important effect on the developing embryo [14].

The maternal metabolism is adjusted during pregnancy to afford the foetus an optimal intrauterine environment and both under- and over-nutrition may increase the risk of non-communicable diseases (NCDs) later in life [15]. Maternal pre-gestational weight correlates with birth weight, and maternal obesity has been linked to foetal overgrowth and macrosomia, congenital defects, neural tube defects, stillbirth, neonatal Apgar score, pre-term delivery, child morbidity, respiratory problems such as asthma and neonatal mortality [16–19]. The nutritional environment during pregnancy shapes foetal development, often manifesting in persistent changes in blood pressure, cholesterol metabolism, insulin response to glucose and other metabolic and endocrine parameters [20].

Maternal gestational environment may create long-lasting and/or permanent modifications in foetal physiology and these can lead to increased risk of developing

obesity, diabetes and cardiovascular diseases in adulthood [21, 22]. Several studies have shown an association between birth weight and the increased risk of certain diseases in adulthood. Low birth weight is also commonly taken to be a reflection of poor intrauterine nutritional environment with subsequent long-term health effects. Epidemiological data on specific prenatal circumstances such as undernutrition have generated convincing evidence of programming taking place in humans [23]. Increasingly, evidence suggests the impact of maternal under- and over-nutrition in the early programming of obesity [24, 25]. If this is the case, maternal nutritional status during pregnancy and lactation plays an important role for programming the health of our infants. Experimental and animal studies suggest that maternal obesity during pregnancy and lactation have negative effects on offspring health, increasing the risk of metabolic disease [26–28]. Furthermore, maternal obesity is a well-known factor contributing to pre-eclampsia and impaired glucose response, both of which increase the risk of non-insulin-dependent diabetes and metabolic syndrome later in life [29]. It has also been found that maternal overweight and obesity before pregnancy are associated with increased neonatal oxidative stress [30]. Maternal obesity and highmaternal pre-pregnancy body mass index (BMI) are linked to higher rates of C-section [18]. In a recent longitudinal study of 436 mother-child pairs that were followed until the children reached seven years of age, C-section and maternal pre-natal exposure to antibiotics during the last trimester of pregnancy were related to a higher risk of childhood obesity [31]. Other studies of pre-natal exposure to antibiotics also demonstrated a link with increased risk of obesity related problems in children aged from 7 to 16 years [32]. However, there is a biological/physiological relationship between maternal overweight and breastfeeding success. Rasmussen and colleagues [33] reported that overweight and obese mothers had a diminished prolactin response in the first post-partum week. Taken

127 together, these data suggest that maternal obesity promotes an obesogenic environment
128 during infancy, which results in an increased risk of obesity.
129 Recent data suggest the role of microbes and gut microbiota in the metabolic and
130 immunological programming [34]. Microbes are one of the most important
131 environmental factors that support the signals involved in immune system development
132 and maturation [35, 36]. The first microbial contact of neonates is the maternal
133 microbiota during pregnancy, birth and then through lactation. Thus, a healthy nutritional
134 and microbial environment during the peri-natal period may provide a window of
135 opportunity to diminish obesity and overweight development (Fig. 1). Obesity caused by
136 infants inheriting altered microbiota has been described as a vicious circle [34]. In light
137 of this it is relevant to develop new strategies to modulate the nutritional and microbial
138 environment during the peri-natal period, which may reduce the risk of obesity and
139 overweight both early in life and in the long-term.
140 Therefore, it is essential to identify which early life events
141 are related to key environmental exposures to develop new dietary strategies to modulate
142 the microbial and nutritional parameters associated with the risk of being overweight in
143 childhood.
144

145 **2 Microbiota during the peri-natal period and obesity**

146 Recent reviews highlight how the disruption of maternal microbial transfer caused by
147 maternal obesity, C-section and also peri-natal exposure to antibiotics may result in
148 abnormal infant microbial colonisation increasing the risk of obesity in the offspring
149 [37–41]. Thus, obesity and weight gain during pregnancy, delivery, and lactation
150 influence infant microbial exposure guiding infant gut colonisation.

Specific gut microbiota changes during pregnancy favouring proinflammatory status had been reported [42]. Although this inflammatory status has been associated with metabolic diseases, the changes during pregnancy could be beneficial for pregnant women and their babies. In the context, all these changes in gut microbiota andmetabolismmay be beneficial for the foetus by promotion of energy storage to support the foetus growth [42]. Furthermore, pregnancy also influences the vaginal microbiome which is modified in terms of structure and composition with a possible relationship with pregnancy outcomes [43]. Lactobacillus spp. are predominant in the vaginal microbiome during pregnancy. Differences in the composition and stability of the microbial community between pregnant and non-pregnant women have been observed [44]. There is also increasing evidence associating abnormalities in vaginal microbiota during pregnancy with pre-term deliveries. Thus, studying the vaginal ecosystem and detection of pathogens is a key instrument in the prevention of pre-term delivery and peri-natal infections [45, 46].

Pregnancy also influences the subgingival microbiota [47] and is linked to high risk of oral inflammatory-related problems, such as periodontal diseases where microbes play an important role in the pathogenesis [48]. Research shows periodontal disease and systemic health are closely linked. Obesity is a significant predictor of periodontal disease mediated through insulin resistance [49]. Obesity is associated with high plasma levels of proinflammatory cytokines, which promote inflammatory status increasing the risk of several diseases.

An association between salivary microbiota and obesity in adolescents and in adult women has been reported [50,51]. Maternal weight, BMI, and weight gain over gestation have been related to specific gut microbial shifts [52–54] and major changes have been reported between the first and third trimester. There is evidence that

concentrations of Bifidobacterium spp. are lower in obese and overweight mothers and in mothers with excessive weight gain than in healthy mothers [52]. Another study reported similar findings: lower Bifidobacterium spp. and Bacteroides spp. but increased levels of Staphylococcus, and Escherichia coli spp. in overweight women compared with lean pregnant mothers [53]. It has been reported an increase in Proteobacteria and Actinobacteria and also, a reduced bacterial richness at the end of pregnancy [42]. Specific immune andmetabolic changes during pregnancy have been also reported, including metabolic syndrome characteristics and these affect microbiota composition and activity. It appears that microbiota type during the third trimester is related to inflammation and when isolated and transferred to germ-free mice, adiposity and insulin insensitivity were increased in the mouse model [42].

This sequence of events creates a repetitive circle in obese pregnant women in which the metabolic, immunologic and microbial environments associated with obesity together affect infant health and development and this would increase their risk for obesity [54]. Maternal nutritional status also influences gut microbiome during pregnancy and breastfeeding [53]. Features of faecal microbiota in pregnant women have been associated with alterations in biochemical parameters.

Parameters such as folic acid, ferritin, transferrin and cholesterol have a special relevance to the nutritional and maternal health status during gestation. Negative iron balance throughout pregnancy, may lead to maternal iron-deficiency anaemia during the third trimester. Folate is a methyl donor that is required to methylate DNA, a critical epigenetic modification to normal genome and cellular function. The cells'ability to methylate compounds such as proteins, myelin, etc., will be compromised by a deficiency of folate. In addition, deficiencies of iron and folic acid during pregnancy can impact foetal development. A positive relationship between Bacteroides spp. and

Bifidobacterium spp. and folic acid levels has been reported. Bacteroides levels were also related to high-density lipoprotein-cholesterol and lower triglycerides.

On the other hand, lower Bifidobacterium spp. and higher Enterobacteriaceae spp. levels including E. coli, were linked to high ferritin and low transferrin [53]. Some studies have examined the association of dietary variables and gut microbiota but further studies are needed to find out the impact of nutrients in our gut microbes and also, in our health. Although only long-term diet was correlated with enterotype clustering [55], other studies observed remarkable differences. In a recent study, Carrothers and colleagues [56] reported that variation in dietary components, nutrient and energy intake would be related to the relative abundance of specific bacterial groups. They observed that in terms of abundant bacterial taxa the gut microbiota of healthy lactating women is similar to that found in other healthy adult individuals, although other significant differences could also be observed. Increased intake of some micronutrients such as pantothenic acid, riboflavin, vitamin B6 and B12 resulted in an increased abundance of Prevotella and a decreased abundance of Bacteroides. Mineral intakes such as copper, magnesium, manganese and molybdenum were positively correlated with Firmicutes and negatively correlated with Bacteroidetes.

Furthermore, the consumption of a calorie-rich diet was positively correlated to Firmicutes concentrations. Wu and colleagues described a positive association of Bacteroides with fat and protein consumption, whereas a higher carbohydrate intake was associated with a relative abundance of Prevotella [55]. However, other studies reported opposite correlations between specific microbes and macronutrient intake [56]. One study showed an inverse trend between protein intake and the relative abundance of Bacteroides while Prevotella was not associated with carbohydrate intake [56]. Further

studies are needed to examine how dietary variables, and which ones, might affect an individual´s gut microbiome composition [56].

3 Beyond nutrition: the impact of obesity in breast milk composition

Human breast milk (HM) is the best option for infant nutrition and it is considered the most important post-natal link between infants and mothers. Breast milk is a complex biological fluid that provides energy, nutrients, and other bioactive compounds such as enzymes, hormones, proteins, polyamines, microbes and oligosaccharides, for the development of newborn infants. The biodiversity of microbiota in breast milk has been assessed recently [57–60] and it was found that Staphylococcus spp., Streptococcus spp. and some lactic acid bacteria were the most common groups. The breast milk microbiome is influenced by lactation stage and shaped by maternal health status, maternal BMI, and weight gain during pregnancy, as well as the mode of delivery and gestational age of the infant [57, 58, 61–63]. Obese mothers have lower diversity and a distinct microbiota composition in their breast milk compared to normal-weight mothers [58].

Lower counts of Bifidobacterium and higher counts of Staphylococcus were detected in the milk samples of obese mothers than in normal-weight mothers [63]. The higher presence of Bifidobacterium group in healthy infants also suggests a protective role against developing specific diseases later in life attributed to breastfeeding [64], as does the higher abundance of bifidobacteria in breastfed infant gut [65]. Kalliomaki and co-workers reported lower levels of Bifidobacterium spp. In infants who were overweight by the age of seven years old compared with normal-weight children [66]. They characterised faecal samples from 25 overweight or obese children and compared these with samples from 24 normal-weight children. They observed that Bifidobacteria counts in faecal samples during infancy were significantly higher in children remaining at a

normal weight at age seven years, whereas significantly greater numbers of Staphylococcus aureus in infancy were detected in children who subsequently became overweight [66]. Human milk contains a complex of growth promoting substances, led by human milk oligosaccharides (HMOs) which promote and support specific microbial establishment [67]. The presence of Bifidobacterium spp. in breast milk is also encouraged by these human milk oligosaccharides. HMOs have a clearly "bifidogenic effect" among other potential benefits attributed to them. Thus, promoting higher presence of Bifidobacterium supp. early in life may provide protection against overweight and obesity and exclusive breastfeeding encourages a microbiota dominated by Bifidobacterium spp. that differs from those who follow other infant feeding strategies. Nevertheless, the potential impact of microbes on infant health has not yet been clarified, although it is currently a key challenge in research.

Breast milk also provides immunological components, bioactive compounds and metabolic hormones that would play a role on the infant's immune system development and metabolism during the neonatal period; these compounds would be influenced by perinatal factors. In a previous study, we have reported that maternal obesity, overweight, and weight gain over pregnancy guide the immunomodulatory and bioactive breast milk compounds not only in terms of microbes, but also in terms of TGF-2, sCD14, and cytokines. It has been reported lower TGF-and sCD14 in overweight and obese breast milk [63]. Although larger studies using more adequate methods of sample collection and preparation need to be conducted, a positive association between maternal BMI and breast milk leptin concentration

has been consistently found in 26 studies included in a systematic review [68]. Leptin is a hormone present in breast milk, but not in infant formula. Leptin seems to give infants moderate protection from excessive weight gain, perhaps because it has additional

downstream effects on infant appetite regulatory pathways, thereby preventing overweight and obesity development. In some animal studies neonate rats supplemented with leptin during the suckling period were more resistant to increase of body weight in adulthood [69, 70], and also more resistant to dietary obesity induced by consumption of an increased calorie diet [69]. In a recent study, Khodabakhshi and colleagues investigated differences in the concentrations of leptin, ghrelin and adiponectin, hormones are involved in appetite and energy balance, in breastmilk samples frommothers with obese and non-obese children [71]. They reported higher ghrelin concentrations in the breast milk from mothers with normal-weight children than those detected in mothers with obese children [71].

Polyamines are also biologically active compounds present in breastmilk. They play a key role in the immune system development. Recent studies investigating levels of polyamines in breast milk samples of obese and lean mothers concluded that obesity was associated with low concentrations of polyamines in breast milk [72]. In a prospective, case control study, breastmilk from obese mothers had increased levels of fatty acids with proinflammatory properties such as palmitic, docosatetraenoic, and stearidonic acids and also increased levels of fatty acids with lower presence of anti-inflammatory properties such as gondoic, erucic, nervonic acids, compared to the fatty acid composition profile observed in lean mothers [73]. All of these studies show the influence of obesity and nutrition on human breast milk composition.

Taking into account that human breastmilk is the best choice for infant feeding during early development and that there are several factors that can affect its composition, a continued basic and clinical research in the field of breastfeeding is needed.

4 Relevance of infant microbial colonisation in the risk of obesity

Gut microbiota colonisation process in infants is a key for later health as alterations in this process have been linked to a high risk of specific diseases, including obesity and allergic diseases [74]. Infant microbial colonisation has an impact on the immune and endocrine systems [75]. Early infant excessive weight gain has been linked to obesity at three years of age [76]. These data is associated to other findings regarding early microbiota composition traits in infants who become obese by seven years of age [66]. Infants from obese mothers had temporal accelerated cognition and language development, but these acceleration stops at 18 months of age. This novel observation would need further studies to identify the potential mechanisms involved [77].

Mothers with high BMI are more likely to have infants developing overweight than lean mothers. The maternal microbiota is the most important microbial origin for the infant gut. Thus maternal obesity could be considered a predictor of child overweight. Several studies demonstrate that infants born to obese mothers have a different bacterial colonisation pattern than those born to lean mothers [54, 78] and differences are maintained during the first years of life. Familial socioeconomic status has also been shown to have an impact on infant microbiome where differences in levels of Blautia spp. Eubacterium spp., Oscillibacter spp., and Faecalibacterium spp. were reported in the infants of obese mothers compared to lean mothers [78]. A recent review showed that the presence of higher concentrations of Lactobacillus spp. and lower concentrations of Bacteroides spp. in the infant gut during the first three months of life may predict the risk of child obesity and overweight [40]. The same review highlighted the role of Bifidobacteria and Staphylococci in tendency towards overweight, together with faecal immunoglobulin A levels, which were acquired from breast milk and secreted later by the gut epithelia. However, the development of overweight may begin

during the in utero period due to an obesogenic maternal environment providing an inflammatory and obesogenic environment to the foetus, which in turn affects the development of the infant from childhood to adulthood [14, 79]. In addition, it has been demonstrated that the human microbiome's development begins prior to birth as specific microbes and microbial DNA have been detected in the placenta, umbilical cord, amniotic fluid (prior to delivery), and infant meconium [24, 80, 81]. Thus, shifts in maternal microbiota depending on the mother's diet, health status and lifestyle may be transferred to the infant, while in utero and during birth. Recent studies show that maternal health, such as allergic problems as atopic disease and also, type-2 diabetes mellitus (DM) affects meconium microbiota [82, 83]. As already mentioned, obesity in mother is linked to C-section, and it has been shown that infants born via C-section have an increased risk of developing asthma, allergies, respiratory problems, type-1 diabetes and obesity [84–87] compared to vaginally born infants. In addition, C-section is associated with child adiposity and also, is associated with increased BMI in infancy, childhood and later in life [88]. C-section infants are colonised by different and less diverse bacterial community spectra [89], even containing microbes present in the skin, oral cavity and and hospital environment [89–92].

Peri-natal antibiotic administration is related to C-section deliveries and it strongly affects the initial establishment of neo-natal microbiota [92, 93]. In a large cohort of 6114 boys and 5948 girls, early post-natal antibiotic exposure has been linked with later obesity and overweight [94]. This study reported that early antibiotic administration (<6 months of life) was related to an increased infant body mass. In addition, the same authors reported a distinct body mass increase associated with cephalosporins and macrolides, especially in boys. Those studies suggest a potential effect of antibiotics on

metabolic and microbiological programming that increases the risk of obesity and overweight.

Using an animal model, it has been demonstrated that low doses of antibiotics at birth are sufficient to modify early microbiota during maturation and also alter host metabolism, adiposity, and the expression of immune genes [37]. Furthermore, the phenotype was transferred to germ-free hosts, showing that microbial composition changes, not antibiotics per se, play a causal role in metabolism and weight gain. Therefore, a potential link is suggested between microbiota exposure and colonisation patterns and C-section, antibiotic use, and the risk of obesity.

Several differences have been observed between gut and upper respiratory tract microbiota of exclusively breast-fed and formula-fed infants [95–100]. Bifidobacterium group is more frequent in breastfed but other compositions are also common. Among breastfed infants, the maternal transmission of specific intestinal bacterial strains has been described [99–101], supporting the maternal microbial transfer hypothesis and suggesting unique family-specific strains in each mother-infant dyad. Additionally, human milk contains milk glycans such as oligosaccharides, glycoproteins, and glycolipids, which have also been recognised as modulators and drivers of infant microbiota development that promote the growth and activity of specific bacterial populations, in particular Bifidobacterium and Bacteroides spp. [102, 103].

5 Strategies to modulate maternal microbiota

Diet has an important effect on gut microbiota composition. This suggests the possibility of using dietary intervention strategies to induce modifications that can have an impact on human physiology. In a recent study [104] with Macaca fuscata (Japanese macaque), the role of a high-fat maternal diet on the neonatal microbiome, which in turn

affects the intestinal maintenance of metabolic health in the offspring, has been demonstrated. Consequently, the contribution of specific gut bacteria, together with nutrition and lifestyle counselling, may provide health benefits and may also help to alleviate the disorders associated with an aberrant gut microbiota composition. Increasing evidence suggests that early dietary interventions with probiotics may result in programming effects on adult health.

In recent years, several bacterial strains have been evaluated to understand their possible role in these disorders. Maternal dietary intervention using specific probiotics may be beneficial for metabolic status and also, affects foetal physiology [105]. Probiotics during pregnancy would benefit certain clinical conditions. A recent review of 37 pre-natal probiotics studies demonstrated that probiotics modulate immune markers in the serum and breast milk, improve maternal glucose metabolism, and reduce the incidence of gestational diabetes and pre-eclampsia [106]. It is also reported that probiotics were able to reduce the central adiposity during the first six months postpartum [107]. Probiotics pre-natally and post-natally affected plasma glucose and insulin sensitivity [108]. In addition, in a randomised, prospective, parallel group, combining dietary counselling and probiotics resulted in better glucose regulation during and after pregnancy due to the intervention. Therefore, dietary and probiotic interventions may be a good tool for preventing and alleviating metabolic disorders in late pregnancies [109], when many metabolic imbalances occur. Nutrition counselling combined with probiotic interventions has been shown to have a beneficial impact on gestational diabetes and also, reduce the foetal overgrowth associated with maternal diabetes [110]. Peri-natal probiotic intervention ameliorated weight gain in infants who developed overweight during infancy, and the effect was most pronounced in infants at the age of four years [111]. The same study reported that intervention reduced the birth-weight-adjusted

399 mean BMI at the age of four years. Impaired glucose regulation and other metabolic
400 disorders in the mother during pregnancy and breastfeeding can affect the offspring's
401 health in early and later life [34]. Taking probiotics during gestation and lactation has
402 been reported to modulate the infant Bifidobacterium spp. colonisation and also to
403 influence breast milk microbiota composition compared with placebo group [112].
404 Recently it has been reported the effects of peri-natal probiotic supplementation on
405 breast milk composition, including Bifidobacterium spp. and Lactobacillus spp. and also
406 functional components such as HMOs and lactoferrin [113]. The same study only
407 benefitted mothers with vaginal deliveries while no differences were noted in milk
408 samples from women who delivered by C-section suggesting a probiotic-dependent
409 milk microbiota modulation in mothers with vaginal delivery.
410 In addition to all these nutritional strategies to modulate the microbiota there are other
411 interventions such as exercise, faecal transplantation (not during pregnancy) and
412 bariatric surgery that have demonstrated an impact on the gut microbiome. Exercise
413 could be able to modulate the gut microbiota composition and may potentially benefit
414 the host. Recent animal studies showed that exercise increased Bifidobacterium spp. and
415 Lactobacillus spp. and significantly altered overall microbial composition and also
416 increased n-butyrate concentrations [114–116]. In a recent review, Mika and colleagues
417 reported that early-life exercise increases gut bacterial species involved in promoting
418 physiological and metabolic health [117]. However, no data is available for pregnant
419 mothers although the great benefits of exercise during pregnancy on maternal health and
420 peri-natal outcomes are well known [118]. Further studies should cover the impact of
421 maternal exercise on microbiome and the impact on their offspring's health.
422 Another recent approach is faecal transplantation. In recent years, there is an incredible
423 increase of the use of microbial replacement therapy named "faecal microbiota

424 transplantation" which has been shown to be effective in Clostridium difficile
425 infections, and other problems as ulcerative colitis and irritable bowel syndrome [119,
426 120]. This type of intervention remains experimental in cases of recurrent Clostridium
427 difficile infections, where no alternative effective treatments exist, and never in the case
428 of pregnancy [121]. However, several aspects such as safety and therapeutic evidence
429 should be considered and no information about its use during pregnancy and lactation
430 have been reported. Bariatric surgery has been shown to be an effective tool for long-
431 term weight loss in individuals affected by severe obesity. Bariatric surgery helps to
432 improve obesity-related conditions such as type-2 diabetes (T2D), high blood pressure,
433 cholesterol levels and the risk of cardiovascular diseases. Given the role of gut
434 microbiota in host metabolism, a recent study investigated the long-term effects of two
435 different types of bariatric surgery on the microbiome of these patients. It showed that
436 both procedures induced similar and long lasting effects on their gut microbiomes
437 compared with obese controls [122]. Transfer of gut microbiota from post-surgical to
438 intact germ-free mice resulted in a decrease in the weight and fat mass of the recipient
439 animals. These studies suggest that changes in gut microbiota contribute to reduce
440 weight and adiposity after bariatric surgery [122,123]. In a recent meta-analysis and
441 systematic review, including 17 non-randomised or case-control studies, has been
442 reported that bariatric surgery improved some pregnancy outcomes as a significant
443 lower incidence of preeclampsia, gestational diabetes and large neonates, however high
444 prevalence of small neonates, preterm birth, admission in NICU among others, have
445 been reported [124]. Same study showed that laparoscopic adjustable gastric banding
446 has not effect on small neonates compared to the other gastric surgeries. These
447 operations are becoming more frequent among women during their reproductive years.
448 We have discussed the benefits of bariatric surgery, but there is a risk of adverse

449 pregnancy outcomes after bariatric surgery and obese women undergoing surgery need
450 to be aware of these potential outcomes. Malabsorptive gastric surgery is associated
451 with an increased risk of foetal growth restriction. Although bariatric surgery decreases
452 the risk of gestational diabetes, it is strongly associated with small for gestational age
453 [125]. Moreover, adverse pregnancy outcomes including a higher rate of stillbirths are
454 observed in pregnancies occurring during the first year after bariatric surgery. Then,
455 pregnancies should be delayed at least one year after bariatric surgery [126].
456 Considering all the information provided in the review, there is a window of
457 opportunity during early infant life in which maternal microbes and nutrition play a key
458 role in long-term health benefits mothers-infant dyads.
459

460 **6 Conclusions**

461 The deviated maternal environment including nutrition, hygiene and microbes is
462 associated with the development of childhood diseases such as obesity that may persist
463 to adulthood. Maternal obesity and weight gain influence the microbiota present during
464 pregnancy and lactation, which in turn affect microbial composition and diversity.
465 Breast milk from obese mothers shows a distinct microbial composition and lower
466 bacterial diversity and a reduction in immunomodulatory factors. These shifts are
467 transferred to their offspring during delivery and also during lactation, providing the
468 neonate with an obesogenic environment driving infant microbial colonisation and
469 immune system maturation. Increasing our understanding of the role of maternal
470 bacteria in infant microbiota would help develop new dietary strategies based on
471 microbial modulation and aimed at the beneficial early programing of child health.
472

473 **Acknowledgments**

Both authors read and approved the final manuscript. The authors have declared that they have no conflicts of interest. This review has been written within the topic developed in the European Research Council ERC-starting grant, MAMI project under grant agreement No. 639226. M.C. Collado is involved in the "ISCH COST Action-IS1405" entitled "Building Intrapartum Research Through Health -an interdisciplinary whole system approach to understanding and contextualising physiological labour and birth (BIRTH)".

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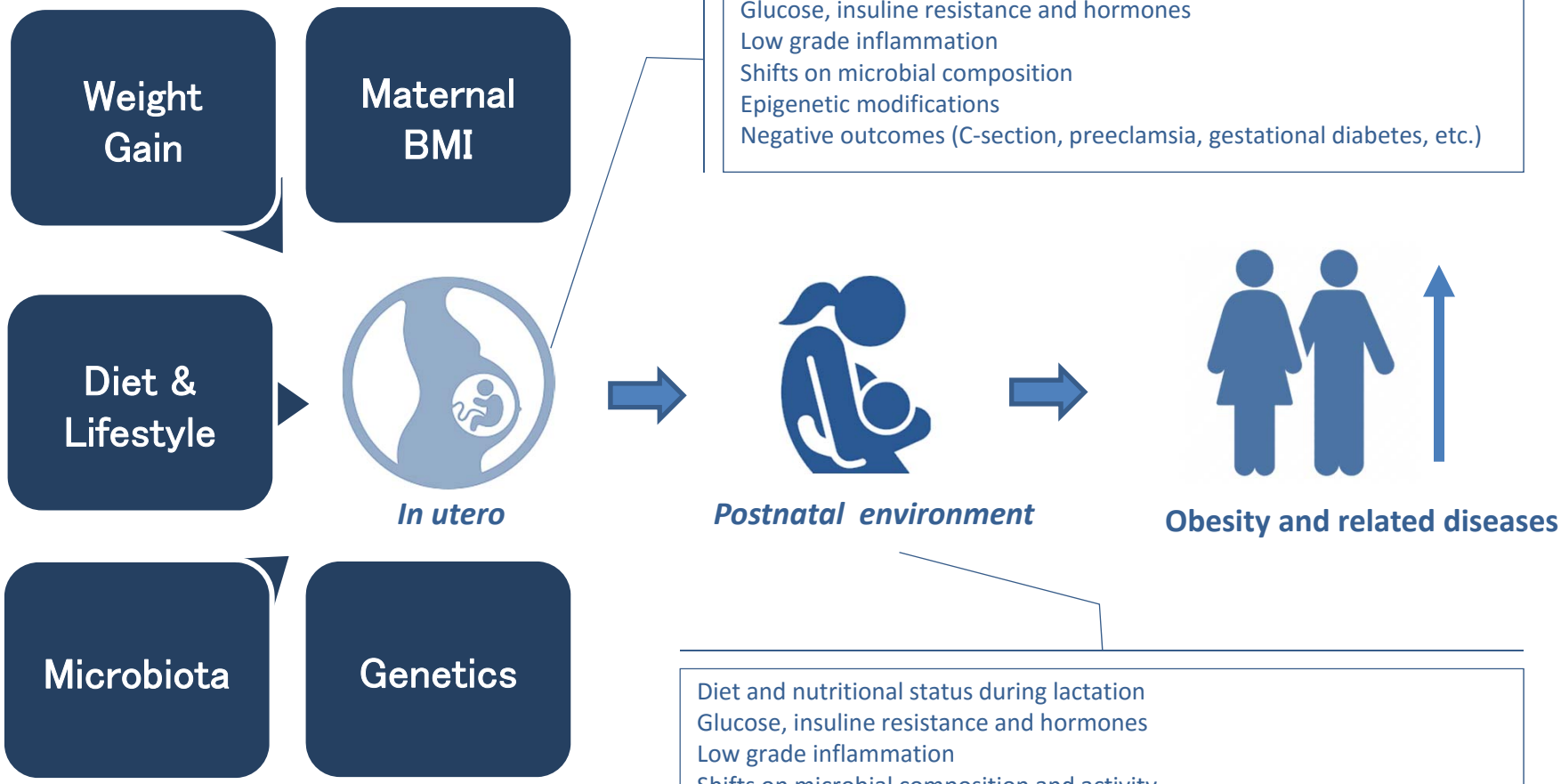
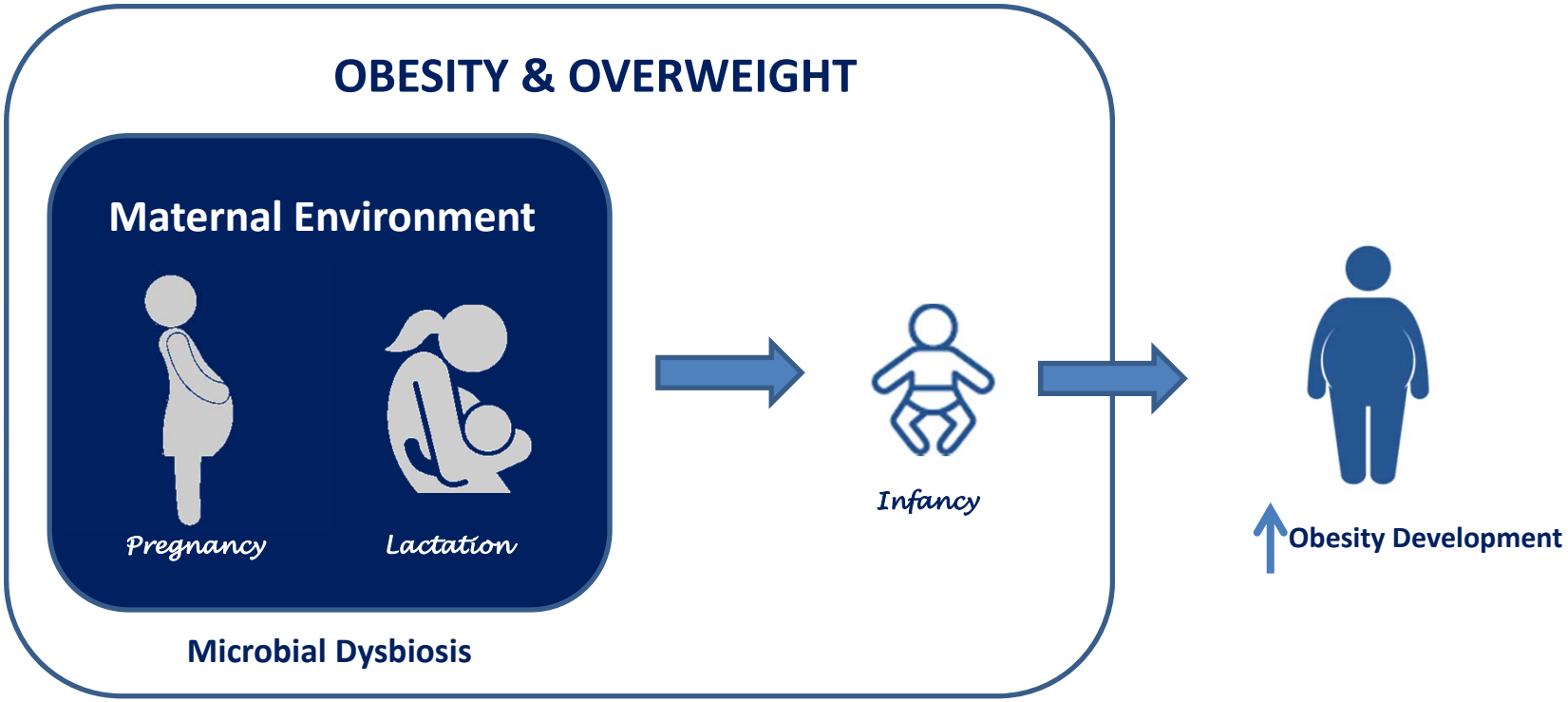
Figure Legends

Figure 1. Early nutritional and microbial environment determines adult health. Immune and metabolic deviation later in life may be the consequence of inadequate bacterial exposure in early life. Maternal environment, including microbiota composition and activity, may be transferred to the infant during pregnancy, at delivery and also during breastfeeding providing the basis for infant development and creating a fingerprint for short- and long-term effects on health.


Weight Gain
Maternal BMI
Diet & Lifestyle
Microbiota
Genetics
In utero
Maternal Diet and nutritional status
Glucose, insuline resistance and hormones
Low grade inflammation
Shifts on microbial composition
Epigenetic modifications
Negative outcomes (C-section, preeclamsia, gestational diabetes, etc.)
Postnatal environment
Obesity and related diseases
Diet and nutritional status during lactation
Glucose, insuline resistance and hormones
Low grade inflammation
Shifts on microbial composition and activity
Negative outcomes for infants (high size and weight; prematurity; metabolic response; etc)



The maternal environment, including nutrition and microbes, influences the likelihood of developing childhood diseases, which may persist and be exacerbated in adulthood. Maternal obesity and weight gain also influence microbiota composition and activity during pregnancy and lactation. They affect microbial diversity in the gut and breast milk. Such microbial changes may be transferred to the offspring during delivery and also during lactation, affecting infant microbial colonisation and immune system maturation. Thus, an adequate nutritional and microbial environment during the peri-natal period may provide a window of opportunity to reduce the risk of obesity and overweight in our infants using targeted strategies aimed at modulating the microbiota during early life.