Diploma Thesis

Metabolic programming by maternal obesity

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Graz, am 26.05.2018 *Silber Isabella eh.*

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Abstract

Background:

Obesity is a worldwide problem and its prevalence is increasing rapidly. Maternal obesity is considered to be one of the influencing factors by affecting the offspring during pregnancy. The exact pathophysiology of how maternal obesity influences the offspring *in utero* and thus, long-term, is still unclear, but metabolic imprinting has been suggested to play an important role. Maternal obesity is associated with different adverse consequences for the offspring, for instance, increased risk at adiposity, adverse cardiovascular outcomes and insulin resistance. The aim of this review was to give a comprehensive overview of the association between maternal obesity and long-term adverse outcomes in the offspring.

Methods:

This review was conducted by researching the online data base PubMed for human-orientated publications. All in all, 73 publications, published between 2005 and 2017, were used. Basic information was found in books, the WHO website and PubMed.

Results:

Maternal obesity is associated with a lot of adverse outcomes in the offspring. The results were grouped according to the affected organ systems or phenotype. The most impressive result was the impact of maternal obesity on the offspring's risk at obesity in later life.

Conclusion:

Obesity does not only influence the expecting mother, but also affects the offspring tremendously. Thus, a healthy lifestyle, especially during the periconceptional period, is important to ensure a healthy pregnancy and reduce the offspring's risk at later life disease.

Zusammenfassung

Hintergrund:
Adipositas ist ein weltweites Problem und die Prävalenz steigt rapide. Mütterliche Adipositas ist einer der Faktoren, die diesen Anstieg beeinflussen und dadurch wird der Nachwuchs während der Schwangerschaft beeinflusst. Die genaue Pathophysiologie, wie mütterliche Adipositas den Nachwuchs *in utero* und langfristig beeinflusst, ist noch unklar aber verschiedene Prozesse, wie zum Beispiel die Epigenetik, sind beitragende Faktoren. Mütterliche Adipositas ist mit verschiedenen Konsequenzen für den Nachwuchs assoziiert, zu denen ein erhöhtes Risiko für Adipositas, kardiovaskuläre Erkrankungen und Insulinresistenz zählen. In dieser Arbeit wird der Zusammenhang zwischen mütterlicher Adipositas und langfristiger ungünstiger Auswirkungen auf den Nachwuchs näher beleuchtet und zusammengefasst.

Methoden:
Zur Durchführung der Arbeit wurde die Online Datenbank PubMed recherchiert. Es wurden 73 Publikationen, die zwischen 2005 und 2017 veröffentlicht wurden, verwendet. Weiters wurden Bücher, die WHO Webseite und PubMed für Basisinformationen verwendet.

Ergebnisse:
Mütterliche Adipositas ist mit verschiedenen Auswirkungen, die den Nachwuchs betreffen, vergesellschaftet. Die Ergebnisse wurden in verschiedene Kapitel je nach betroffenem Organsystem oder Körperteilen eingeteilt. Das am meisten herausstechende Ergebnis ist, dass der mütterliche metabolische Status Auswirkungen auf das Adipositas-Risiko des Nachwuchses im späteren Leben hat.

Schlussfolgerung:
Adipositas beeinflusst nicht nur die Mutter selbst sondern auch den Nachwuchs. Aus diesem Grund ist ein gesunder Lebensstil, vor allem in der Perikonzeptionsperiode, wichtig, da dieser eine gesunde Schwangerschaft und das Risiko für spätere Erkrankungen für den Nachwuchs minimiert.

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Abbreviations

5-HT	serotoninergic
α-MSH	α-melanocyte-stimulating hormone
aBW	birthweight, adjusted for gestational age at delivery
AC	abdominal circumference
ADHD	attention deficit hyperactivity disorder
AgRP	agouti-related peptide
AGA	average for gestational age
AMPK	adenosine monophosphate-activated protein kinase
ANP	atrial natriuretic peptide
ASD	autism spectrum disorders
BAC	birthweight and abdominal circumference at birth
BAT	brown adipose tissue
BMI	body mass index
CART	cocaine- and amphetamine-regulated transcript
CNS	central nervous system
CpG	cytosine-guanine (dinucleotides)
CRP	C-reactive protein
C-section	Caesarean section
CT	computer tomography
CVD	cardiovascular disease
DA	dopaminergic
DBP	diastolic blood pressure
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DoHAD	developmental origins of health and disease
ECG	electrocardiography
e.g.	exempli gratia; for example
ER	endoplasmic reticulum
ET-1	endothelin-1
FFA	free fatty acid
FMI	fat mass index

GDM	gestational diabetes mellitus
GWG	gestational weight gain
HDL	high-density lipoprotein
HR	heart rate
IGF	insulin-like growth factor
IL	interleukin
IQ	intelligence quotient
IR	insulin resistance
IRS	insulin receptor substrate family
IUGR	intrauterine growth restriction
IVF	*in vitro* fertilization
JNK	c-Jun-NH2 terminal kinase
kg	kilogram
LEP	leptin gene
LGA	large for gestational age
LRTI	lower respiratory tract infection
m	meter
MC	melanocortin
MC 4-R	melanocortin 4-receptor
MCP-1	monocyte chemotactic protein-1
mpp	maternal pre-pregnancy
mRNA	messenger RNA
NO	nitric oxide
NPY	neuropeptide Y
ω-3/6	omega-3/6
OGTT	oral glucose tolerance test
OR	odds ratio
PEP	pre-ejection period
PGI_2	prostacyclin
PI_3K	phosphatidylinositol-3-kinase
PKB	protein kinase B
PPA	preperitoneal adipose tissue
PPARγ	peroxisome proliferator-activated receptor γ
POMC	pro-opiomelanocortin

PUFA	polyunsaturated fatty acid
RER	rough endoplasmic reticulum
RNA	ribonucleic acid
RR	relative risk
RSA	respiratory sinus arrhythmia
s	second
SBP	systolic blood pressure
SCA	subcutaneous adipose tissue
SCFA	short-chain fatty acid
SD	standard deviation
SFT	skinfold thickness
SGA	small for gestational age
sICAM-1	soluble intracellular cell adhesion molecule
T2DM	type two diabetes mellitus
T_3	tri-iodo-L-thyronine
TNFα	tumor necrosis factor-α
UCP1	uncoupling protein-1
UPR	unfolded protein response
VLDL	very-low-density lipoprotein
vs.	versus
WAT	white adipose tissue
WC	waist circumference
WHO	World Health Organization

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1 Introduction

This paper will discuss the effects of intrauterine overnutrition caused by maternal obesity on the offspring. How can metabolic programming effect the offspring's long-term health?

1.1 Definition

Obesity is a medical condition and a global health epidemic. By the World Health Organization (WHO), obesity is defined as an abnormal and excessive fat accumulation (1).

The body mass index (BMI) is a standard measure for obesity, based on the overall body weight (1). It is calculated by dividing the weight in kilograms (kg) by their height in meters (m) raised to the second power. The BMI classification ranges from underweight to obese. Being obese means having a BMI greater than 30 kg/m^2 (2) [Table 1].

Table 1. Classification of body weight according to BMI (2).

BMI (kg/m^2)	Classification
≤ 18.4	underweight
18.5 - 24.9	normal weight
25 - 29.9	overweight
30 - 34.9	obesity grade 1 (obese)
35 - 39.9	obesity grade 2 (severely obese)
≥ 40	obesity grade 3 (extremely obese)

Due to differences in body composition, the BMI is not the best method to detect adiposity as it does not differentiate between distributions of fat or lean mass (3).

1.2 Epidemiology

The obesity prevalence increases tremendously in people of all ages (4). Since 1980 the prevalence has doubled. Not only developed but also developing countries are affected (5). In 2016, over 1.9 billion individuals (18 years and older) were overweight. Out of those more than 650 million were obese. However, this epidemic does not only affect adults. There were about 41 million overweight or obese children under the age of 5 (6). Therefore obesity is an intergenerational problem (5).

1.3 Causes, consequences and costs of obesity

Obesity is a global epidemic. It is a problematic condition in both developed and developing countries and its incidence is rising (5).

The obesity epidemic is caused by many different factors. These include genetic or behavioral factors. However, metabolic, environmental and even cultural factors also play a role. Additionally, the socioeconomic status and even the parents' education determine the risk to become obese. Socioeconomics is usually underestimated (7) because it plays a significantly bigger role before, during and even after birth than it was intended to be (1,7). Behavioral factors such as low physical activity and an unhealthy lifestyle also influence the risk of becoming obese (4) [Figure 1].

A healthy lifestyle is important to avoid being affected by numerous consequences overweight/obese individuals have to endure. Obesity is a major risk factor for non-communicable diseases (1). Consequences (or comorbidities) of obesity are an increased risk for type two diabetes mellitus (T2DM), hypertension, myocardial infarction, colon cancer, angina, gall bladder disease and ovarian cancer. Moreover, to a lesser extent, stroke and osteoarthritis are also associated with obesity (8) [Figure 1].

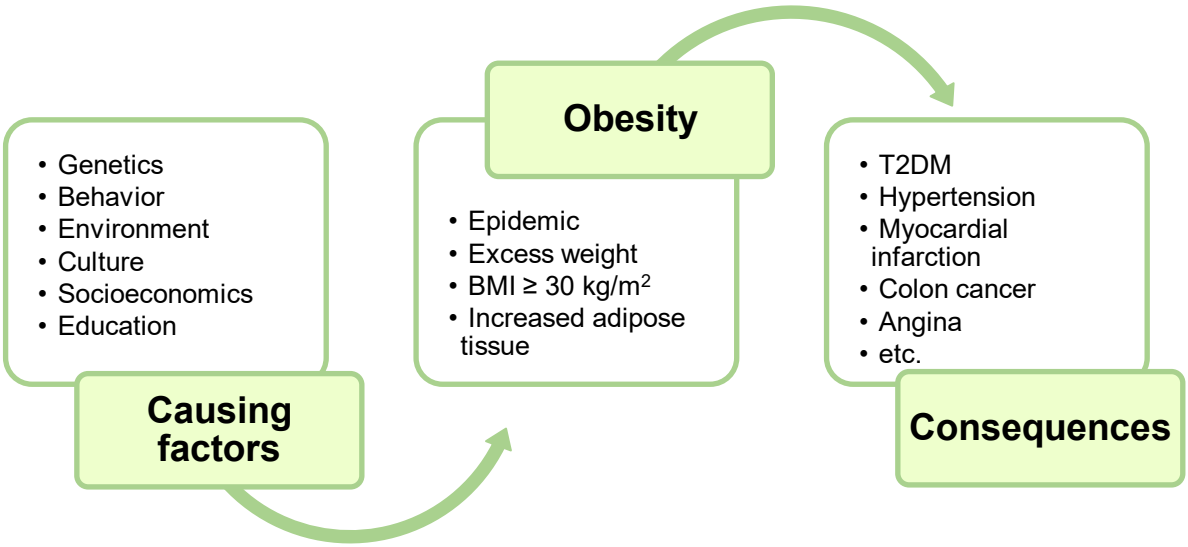

Figure 1. Causes and consequences of obesity.

Obesity and its comorbidities are a great burden for public health care systems and represent about 2-7% of health care costs in developed countries (5,9).

1.4 Pathophysiology of obesity

Excess weight is a result of increased adipose tissue, which is composed of visceral and subcutaneous depots. The visceral depots are mainly located in the intraabdominal area. The subcutaneous depots are distributed all over the body and form a continuous layer underneath the skin (1). These two kinds of fat possess different gene expression, macrophage infiltration, interleukin-6 (IL-6) and leptin production (10). Quantification of the two fat depots is also different. Visceral fat can be quantified by measuring the waist circumference (WC) (only useable during the preconception period or in early pregnancy) or by imaging techniques (e.g. computer tomography (CT)) (1). The location and form of the visceral fat depot can vary between obese people (1). Obese women with increased visceral adiposity are at a higher risk for metabolic abnormalities, for example insulin resistance (IR) (1,10), dyslipidemia (10), inadequate fibrinolysis (1), higher susceptibility to thrombosis (1) and are constantly in a chronic inflammatory state (1). IR results in an increased level of free fatty acids (FFA) and a higher secretion of triglyceride rich lipoproteins (1). How subcutaneous depots influence metabolic dysfunctions is still

not fully understood. However, they may be related to the FFA concentration and thus, influence insulin sensitivity (11).

Clinically, obesity is characterized by a pro-inflammatory environment. The inflammatory response in obese individuals, termed “metinflammation” (12), differs from a classical inflammation. It is a chronic and low-grade inflammation characterized by the production of abnormal cytokines, an altered adipokine profile and activated inflammatory pathways. In pregnancy, this metinflammation can also induce inflammation in the fetus’ tissues (12) [Figure 2].

1.5 Adverse consequences and obese pregnancy

Obesity is considered a risk factor in pregnancy and for obese pregnant women complications arise in about 20% (1). Also in pregnancy, obesity bears risk factors, not only for the unborn baby but also for the mothers (12).

Obese women might be confronted with infertility issues. A study showed that women with a BMI higher than 35 kg/m^2 have a 26-49% lower chance to conceive naturally than women with a BMI of 21-29 kg/m^2. Reducing weight increases the likelihood for natural conception without assisted reproductive techniques (e.g. *in vitro* fertilization (IVF)) (10) [Figure 3].

Once pregnancy has established, obesity has immediate influences on pregnancy as well. It is a risk factor for (viral) infections prenatally, i.e. rubella, cytomegalovirus, influenza and herpes simplex virus. This is not only dangerous for the women, but can have consequences for the fetus and may induce adverse cardio-metabolic and neurobehavioral outcomes. The possibility of a vertical, mother-to-child-transmission may also be increased in obese pregnant women. The reason for the higher susceptibility is still unknown but the altered inflammatory status may play a role, and pregnancy furthermore increases this predisposition (13).

Due to the affected metabolic and inflammatory state, obese pregnant women tend to have altered levels of insulin, leptin, cytokines and hormones and are at higher risk to develop hypertension, hyperlipidemia, glucose intolerance and coagulation disorder, which are all associated with “metabolic syndrome”. Obese pregnant women also tend to have a higher IR than normal weight women.

As already mentioned, obesity is an inflammatory state itself (1). Maternal obesity is linked to metabolic inflammation. An underlying cause is the increased adipose tissue, which produces higher systemic pro-inflammatory cytokine levels and elevates adipose tissue macrophage accumulation (12). Certain pro-inflammatory cytokines (e.g. tumor necrosis factor-α (TNFα), ILs, monocyte chemotactic protein-1 (MCP-1)) are also increased in obese, non-pregnant individuals (1,14). In general, baseline pro-inflammatory mediators and inflammatory markers (e.g. IL-6, soluble intracellular cell adhesion molecule 1 (sICAM-1), C-reactive protein (CRP) and TNFα) are increased in obese pregnant women (11). Additionally, the adipose tissue itself secretes inflammatory cytokines, such as TNFα, IL-6, leptin and adiponectin (11). These mediators predispose the mother and baby to some harmful effects, for example preeclampsia and neonatal complications (1). Furthermore, the changes accompanying the metabolic inflammation also include the placenta and thus, directly affect the fetus (1,11,12,15,16) and according to the "developmental origins of health and disease" model (DoHAD), the offspring later in life. In fact, evidence indicates that early changes in inflammatory markers can predict the offspring's later risk for cardiovascular and metabolic diseases. Therefore, analyzing the offspring's early inflammatory profile can show certain changes and even be used as a biomarker for later life metabolic diseases (12) [Figure 2].

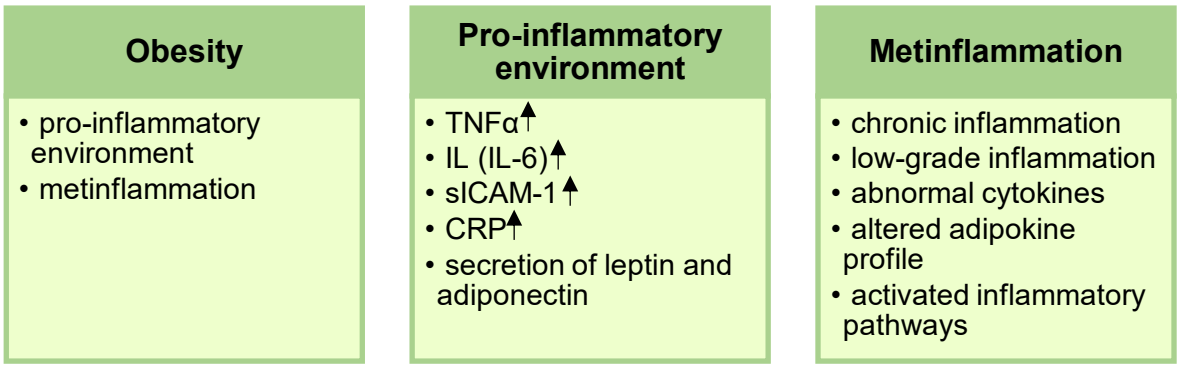

Figure 2. Pathophysiology of obesity in pregnant women.

(Obesity is characterized by a pro-inflammatory environment. The inflammatory response in obese individuals is called metinflammation. The listed characteristics are typical for either the pro-inflammatory environment or metinflammation in obese pregnant women.)

Obese pregnant women are at a higher risk for miscarriages (5,10,14,17), stillbirth (odds ratio (OR) for late antepartum death is 2.4-3.1 compared to normal weight women (10)) (11), neonatal mortality (11) and metabolic and cardiovascular dysfunctions. They are more likely to develop gestational diabetes mellitus (GDM) (OR increases from obese (OR 3.56) to severely obese (OR 8.56) (10)) (1,5,8,11-14,16,17), gestational hypertension (relative risk (RR) 1.09 for each unit increase in maternal pre-pregnancy (mpp) BMI (10); obese OR 2.5, severely/extremely OR 3.2 (17)) (5,14,17) and preeclampsia (increased blood pressure de novo or additionally to chronic hypertension plus one or more dysfunctions such as proteinuria (18); risk ratio 2.47 (10); risk doubles for every 6 unit increase in mpp BMI (10); obese OR 1.6, severely/extremely obese OR 3.3 (17)) (1,5,8,11-14,17) [Figure 3].

Some studies report that maternal obesity is linked to preterm delivery, but whilst others show no link. A large study including about 300 000 births found that obese women were less likely to give birth before 32 weeks of gestation. However, differentiating between actual preterm deliveries because of obesity from preterm deliveries due to obesity-related comorbidities is difficult. Nevertheless, even after adjusting for maternal confounders, there was no association between maternal obesity and preterm birth (10). However, other studies found different results. Due to all the mentioned obese pregnancy-related problems, severely and extremely obese women are at a higher risk (OR 1.5) to deliver preterm (before 37 weeks of gestation) (17). Additionally, another study also showed higher rates of induced and spontaneous preterm births. They also showed that women with a mpp BMI over 35 kg/m^2 are also likely to go beyond term. Obese women often experience a failed induction of labor and dysfunctional labor (failure to progress) (5) [Figure 3].

Being obese increases complication rates during delivery. Obese women more often require a Caesarean section (C-section) (5,8,10,14) and operative vaginal delivery (5,8). If an operative delivery is required, obesity overcomplicates these methods (8). About 33.8% of obese women and about 47.4% of severely obese women deliver by C-section (10) and emergency C-section is way more risky in obese women (8). There is also an increased risk for shoulder dystocia (8) [Figure 3].

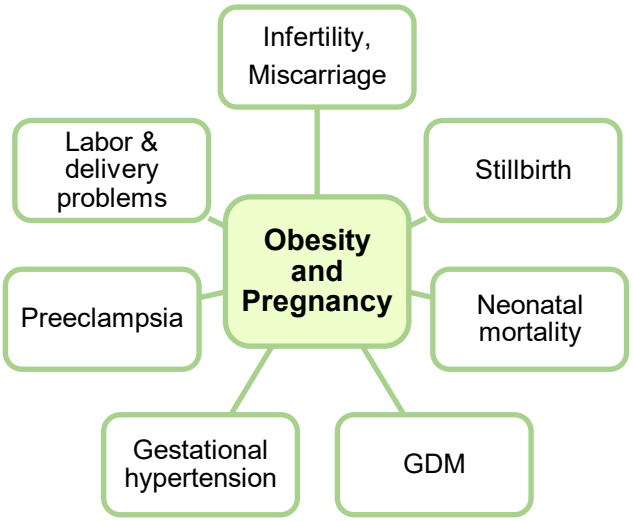

Figure 3. Problems in obese pregnancy.

Besides delivery complications, local and general anesthesia is more complicated. The placement of an epidural or spinal anesthesia might be difficult. Even general anesthesia might be more complicated due to difficult intubation and an increased risk of postpartum sleep apnea (17).

After and during delivery, there are some other minor and major adverse outcomes, which have an increased risk in obese pregnant women. Minor complications, for example heartburn, chest infection and symphysis pubis discomfort, occur more often. Major outcomes include maternal postpartum hemorrhage/excessive blood loss, (wound) infection and longer hospital stay (8). They are at a higher risk for maternal death (8,11,12). Underlying reasons include thromboembolism and cardiac causes (8). These complications and diseases are definitely reasonable with pathophysiology, but detection of potential life-threatening conditions, including the measurement of blood pressure, and transport is difficult (8).

After birth, lactation might fail in these women (18). In general, obese women are less likely to start and continue breastfeeding. When comparing them to normal weight women, the OR for breastfeeding at discharge from hospital is 0.86 (10).

1.6 Hypotheses for programming

Hypotheses for programming have been present for a while. It started with Freinkel in 1980 (“fuel-mediated teratogenesis”) and continued with many more the following years. In recent years, the relation between environmental influences during intrauterine development and the long-term health of the offspring has emerged and led to the DoHAD model (13). The DoHAD approach bases on the Barker hypothesis, which was first reported in 1993 by Barker et al. This approach describes an association between low birthweight and the susceptibility for developing certain diseases in later life (19). The DoHAD model describes that environmental stimuli, such as maternal over- or undernutrition, can induce alterations during a critical developmental period in the organogenesis, tissue development and metabolism. Thus, environmental stimuli increase the offspring’s susceptibility to dysfunctions later on (12), such as changes in the metabolism, behavior, appetite regulation, with a higher chance of becoming obese and having metabolic and behavioral problems (11). Similar models have been independently developed by different authors, such as the “thrifty phenotype” concept (19), the “fetal programming hypothesis” (1), the “fuel-mediated hypothesis” (19) and the “developmental plasticity hypothesis” (20).

1.7 Metabolic imprinting and epigenetics

1.7.1 Metabolic imprinting

Metabolic imprinting is a process explaining that certain environmental stimuli, which occur during a critical developmental period, can have long-term effects on the offspring. This critical developmental period includes pregnancy and lactation. The purpose of metabolic imprinting is a better adaption of the offspring to postnatal life (15).

The involved mediators and signaling pathways, which transmit signals from the mother to the offspring, are not fully understood yet. It has been discussed that hormones (leptin, insulin), nutrients (glucose, FFA, triglycerides) and inflammatory cytokines are involved. As mentioned, inflammatory cytokines are increased in

obese pregnant females and they are discussed as important mediators for metabolic imprinting (15).

1.7.2 Introduction into epigenetics

Early life exposure to certain nutritional states, such as maternal overnutrition and metabolic factors (e.g. glucose, lipids, amino acids), causes specific changes and may predispose the fetus to diseases. One cause is that intrauterine malnutrition alters fetal organogenesis leading to a life-long impact on the morphology and physiology (19). Another cause are epigenetic changes based on DNA (deoxyribonucleic acid) methylation, which have been discussed as one of the key underlying mechanisms (13,15).

Epigenetics describe mechanisms how gene expression can be affected globally. Different epigenetic mechanisms include histone modifications, non-coding RNAs (ribonucleic acid) and DNA methylation (13,20).

DNA methylation is a covalent modification of the DNA and determines to which extent a gene can be expressed (21). Target of methylation are cytosine residues in cytosine-guanine (CpG) dinucleotides (13) by DNA methyltransferases (20). CpG dinucleotides are found all over the genome with the majority being methylated. Regions with a high abundance of CpG are called CpG-islands, and regions up- and downstream of these islands are called CpG-shores. The shores are in charge of about 80% of the tissue-specific methylation (20). DNA methylation represents a stable modification which is maintained even during cell cycle (mitotic inheritance (20)) (19). Thus, via DNA methylation, changes persist even if the triggering factor is a not present any more. They might even be passed on to the next generation (meiotic inheritance (20)) (19,20). Passing on those epigenetic modifications to the next generations is called the “transgenerational cycle” (20) and allows future generations to better adapt to their environment (16,20,22). Mechanisms affecting DNA methylation include maternal perinatal nutrition, energy status, endocrine status and oxidative stress (15). Additionally, epigenetics vary in different tissues. They are regulated in a tissue- and developmental stage-specific manner. Especially during early development, the plasticity of the epigenome is high and thus, also the susceptibility to adverse environments (19).

1.7.3 Epigenetic modifications

Many DNA methylation patterns are tissue- and cell-specific (13), develop during embryogenesis and fetal development and are sensitive to nutrition (16).

As mentioned above, epigenetic changes can be maintained during cell cycle. This way the changes can be transmitted to daughter cells after dividing them (19). Epigenetic marks are more or less perpetuating depending on their response to environmental and other signals (20). Unfortunately, there is only little evidence showing persistent changes from early development on until adulthood (19). Looking at siblings born before and after their mother underwent bariatric surgery, confirmed the theory about DNA-methylation as CpG sites in peripheral blood cells were differentially methylated (13). It has also been discussed that DNA methylation changes over time. However, other studies suggest that DNA methylation is stable over time, but might differ in individuals due to inheritance (20).

The fact that genetic predisposition to epigenetic alterations exists as well, makes this whole process of creating a phenotype even more challenging. Not only the environment (diet, physical activity, etc.), the genotype (gene polymorphism, etc.), the epigenotype (DNA methylation, histone modifications, etc.), but also stochasticity (which influences the epigenotype) plays an important role in creating the phenotype. Thus, epigenetic modifications are sensitive to the environment, chance and genetic predisposition (20) [Figure 4].

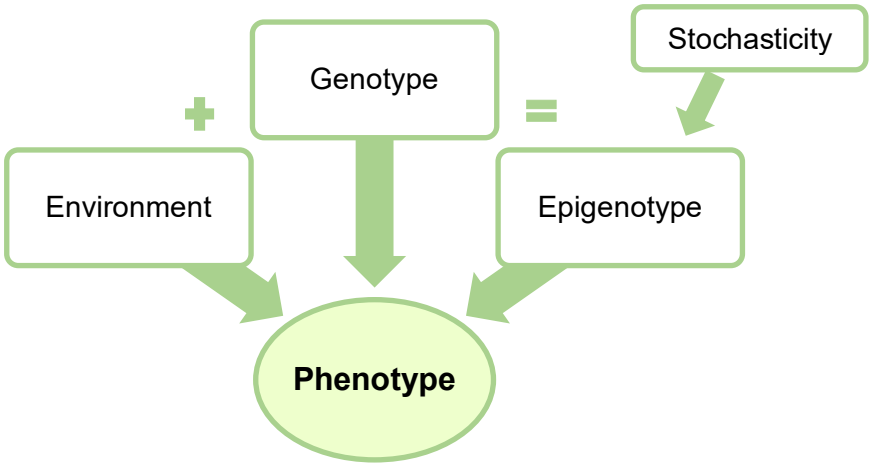

Figure 4. Impact of environment, genotype and stochasticity on phenotype.

Despite the fact that the intrauterine environment seems likely to be one of the determining factors, becoming obese might be due to the “obesogenic” genes and shared postnatal environment between mother and child. However, some studies have shown a higher correlation between the maternal and offspring BMI and body composition than the paternal BMI (23). Thus, there might be a paternal influence on an offspring’s long-term health but studies have shown a stronger connection with the mother’s unhealthy lifestyle (9,10).

Do genetics really play a big role? Children, who were born to ovum recipients, had a more similar BMI to the recipient than their donor. This fact leads to the thought that the genetic component plays a lesser role in obesity development (23).

Another fact supporting this idea is that children born to women after they underwent bariatric surgery and lost weight, had not only differently methylated DNA, but also reduced birthweight and obesity rates than their siblings born before surgery. The children’s cardio-metabolic risk improved as well (example for the “developmental plasticity hypothesis”) (23).

It is still unknown whether or not epigenetic changes have a definitive effect on the development of later life diseases in the offspring. The fact that DNA methylations were still present three years after they have been detected, makes it more plausible that they are persistent (13).

As mentioned above, DNA methylation patterns are specific for certain cells and tissues. However, it is controversial whether DNA methylation in blood leucocytes, which were extracted from peripheral veins or the cord, represent relevant data to draw conclusions on programming of obesity. Studies suggest that levels of DNA methylation for a few non-imprinted genes (imprinted genes are = genes, which are expressed in a parent-specific manner (19)) in the blood are the same as in buccal cells (13).

Testing for causal effects of maternal obesity on DNA methylation in the offspring in humans is difficult. However, by using paternal obese patients as a negative control group, studies have shown that maternal obesity is more associated with offspring’s epigenetic changes than paternal obesity (13).

1.7.4 DNA methylation changes in obese adults

There is a big variance in energy consumption and the effect of diet on BMI between individuals, indicating that weight and energy homeostasis are subjects to variable regulation. For instance, genetic factors and adult environment are huge contributors to obesity. Certain genes are associated with a higher obesity risk. A few of them have already been detected ("identified obesity-susceptible loci"). Thus, the genetic variation in the *FTO* gene might have the largest effect on BMI by increasing it only by 0.26 – 0.66 kg/m^2 per risk-allele, which is less than it was thought to be (9). Offspring of obese mothers have a 2.1% higher DNA methylation of the *AHRR* gene (13).

CpGs outside CpG islands and cytosines in non-CpG sites are also linked to the metabolism-related phenotype due to their variation in DNA methylation (20).

As mentioned above, there might be some stable genetic marks. Some of those have been detected in a study, which was conducted over a period of 11 years. 50% of genetic marks remained stable over the years. The other half represented non-stable marks and thus, likely to be influenced by the environment. 4 of the stable epigenetic marks showed a correlation with BMI at two time points during those 11 years, and nearby genes included *MMP9* and *PRKG1* (20).

1.7.5 Adverse effects on children

Programming of later life diseases starts *in utero*. Maternal nutrition is being discussed as one of the predisposing factors for certain diseases of children born to obese mothers. To what extent does the mother's obesity influence the offspring's long-term health?

2 Materials and Methods

The purpose of this paper was to summarize and review available literature about the effects of maternal obesity on the offspring by using the online data base PubMed. This was best possible by summarizing information in the form of a review.

Firstly, general information about adiposity, digestion, regulating pathways and epigenetic mechanisms was obtained in several physiology, pathophysiology and biochemistry books. The World Health Organization (WHO) website was also accessed for worldwide obesity information in February 2018.

Secondly, PubMed was searched with three different search terms (“maternal obesity”, “offspring” and “long-term”) from May 2017 until October 2017. 423 publications were found (347 Medline articles, 126 reviews). From these articles, only articles and reviews investigating human data were used (228 articles). All the articles were looked through and sorted. After all, 60 publications from 2005-2017 were regarded as relevant for the present theses and used (42 reviews and 18 studies). Due to the lack of original studies in chapters “Cardiovascular disease”, “Pancreatic changes” and “Respiratory, atopic outcomes and autoimmune diseases” the bibliographies of available publications were further searched. Additionally, 13 more articles were acquired this way (“Cardiovascular disease”: 6 studies, “Pancreatic changes”: two studies, “Respiratory, atopic outcomes and autoimmune diseases”: 5 studies).

Lastly, information about the Western Diet was again obtained with PubMed research in January 2018.

3 Results

3.1 Leptin and energy homeostasis

3.1.1 General information

3.1.1.1 What is Leptin?

Leptin is a hydrophilic peptide hormone secreted by adipocytes which circulates in the bloodstream in free form. Its half-life period ranges from a few minutes to hours, its receptors are located in the cell membrane and it is activated by a second-messenger system (24). Leptin plasma concentration correlates with the fat cell mass in an individual's body (25).

3.1.1.2 Physiology

It is important for the body to maintain its weight. Satiety and hunger regulate food intake and therefore the body's energy resources (2). Energy homeostasis is regulated by internal and external environments and the brain. The brain senses various signals, e.g. hormonal, metabolic and hard wired neural signals from the periphery, and integrates these signals to regulate food intake and to balance intake and energy consumption (26). This complex process is controlled by several structures, mainly located in the hypothalamus and the medulla oblongata. Several areas in the hypothalamus are in charge of regulating satiety and hunger. The solitary nucleus, which is located in the medulla oblongata, is also a part of this complex system. The nucleus integrates peripheral signals and responds to these (2).

Leptin regulates appetite and energy balance (10). The fat depots are the biggest energy resource in the human body. To maintain a certain body weight, the size of fat depots has to be regulated. Together with insulin, leptin controls fat storage (2). Leptin signals in an afferent way to the hypothalamus. If the fat cell mass is high, the leptin concentrations are high too and vice versa (25) [Figure 5]. Efferent hypothalamic signals sense high leptin concentrations, reduce food intake and increase energy expenditure (25). This is a tonic, negative feedback acting on

the anabolic circuit and a positive feedback acting on the catabolic neural circuit (26). On the other hand, low leptin plasma concentrations lead to an increase in food intake and reduction of energy consumption (25).

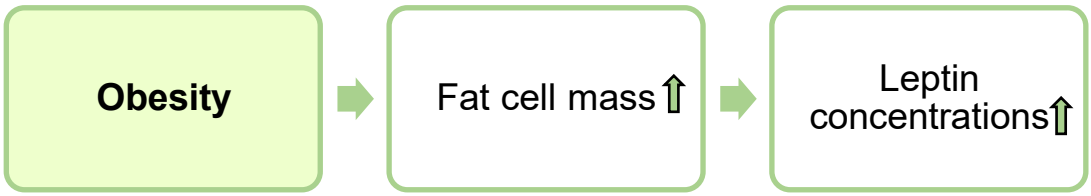

Figure 5. Association between fat mass and leptin concentrations.

Leptin binds to specific leptin receptors (type b; LRb = Ob-Rb) in the hypothalamus, which are mainly located in the arcuate and paraventricular nuclei. Low leptin concentrations cause reduced receptor signaling mainly sensed by the neurotransmitters in the arcuate nucleus (25). On one hand, leptin is stimulating the release of the cocaine- and amphetamine-regulated transcript (CART) and α-melanocyte-stimulating hormone (α-MSH), which belongs to the category of pro-opiomelanocortin (POMC) produced melanocortins (MC). α-MSH inhibits food intake by binding MC 4-receptors (MC 4-R) in a few hypothalamic areas and in the dorsal nucleus of the vagus nerve. It is also increasing the sympathetic nervous system and energy expenditure. The latter one increases due to a daily increase in skeletal muscle activity and muscle tone (25). On the other hand, leptin, α-MSH and also insulin inhibit the release of neuropeptide Y (NPY) and agouti-related peptide (AgRP) in the arcuate nucleus. This increases hunger, appetite and the parasympathetic nervous system, and decreases the energy expenditure (25).

As a growth hormone and especially in combination with insulin, leptin is in charge of regulating the hypothalamic development (16). Both leptin and insulin have skills to affect not only neural survival (neurotropic), but also the outgrowth (neurotrophic) of developing neurons (26). As a neurotrophic factor, leptin is important during a certain time period for developing certain pathways and formations. However, this role is less investigated in humans than in animals (4).

Maintaining a certain body weight is important for health. Studies suggest that some people are predisposed to developing and maintaining an elevated body weight even when calory intake is similar to normal weight people. The neural

network, which controls energy homeostasis, mediates the amount of calories which leads to the development of overweight (26). If someone has a higher food intake than energy expenditure, this excess is stored as adipose tissue. This storage is being mobilized and used in times of energy deficits (26).

3.1.1.3 Leptin and obesity

Obese people have increased levels of leptin, which can lead to leptin resistance maintaining the state of obesity, inflammation and even metabolic disease (12). This causes a dysregulated energy balance (9) [Figure 6].

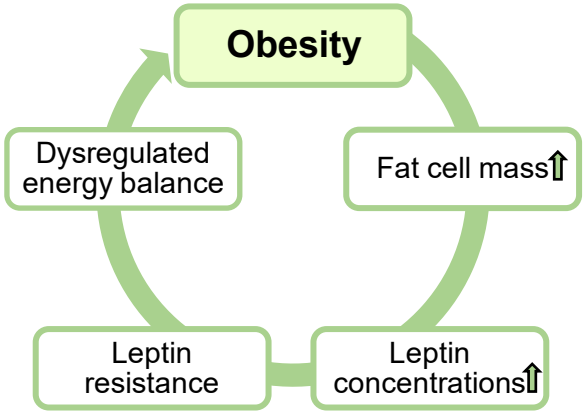

Figure 6. Leptin and obesity.

For a normal appetite system, it is crucial for all pathways between all brain regions and other organs to work, especially while these connections are still developing. It is still unknown how maternal obesity influences the baby's brain so early on but leptin is thought to have major influences (27).

Leptin does not only regulate appetite and saturation. It also contributes to the development of these regulatory pathways between central nervous system (CNS), metabolism and body composition during development (1) and high or low leptin concentrations during fetal development can affect these pathways. The communicating/connecting pathways involved in satiety, feeding regulation and metabolism are already fully developed at 21 weeks of gestation in humans (9). Therefore, exposing the fetuses to high leptin levels, as in obese mothers, even before the pathways are fully developed, might lead to an insufficient way of

responding to a leptin surge (9). (A surge is when the offspring experiences temporarily rising leptin concentrations during the normal developmental time period (27)). The placenta is a source of leptin during fetal *in utero* development, whilst in newborns, leptin concentrations are explained by adiposity (9). Many studies have shown that altered levels of leptin have a major impact on brain development in animals. In humans, if this occurs during the developmental period of brain cell networks, certain conditions like metabolic syndrome and neurologic disorders could arise. Insulin plays a big role in this context as well (1).

Studies have shown that at the end of the third trimester of gestation leptin starts to rise after the hypothalamic development is finished (15,26).

3.1.1.4 (Epi)Genetics of leptin and obesity

Some obese people are missing the leptin gene. However, most people carry defective signaling pathways. Some mutations are, for example, a homozygote leptin receptor-defect, a heterozygote loss-of-function mutation of MC 4-R and a mutation of the POMC-gene (25). If mutations are found in the leptin gene, an obese phenotype might occur (28).

Leptin is also influenced by epigenetics, and maternal glycaemia is one trigger of this epigenetic regulation (13), which is again, based on CpG methylation. A tissue-specific DNA-methylation of leptin exists, which is altered in obesity (20). These modifications result, which is again, based on organized hypothalamic feeding pathways as well and even the leptin sensitivity is affected in a negative way (18). Specific CpG sites in the leptin gene (LEP) promoter are demethylated during the adipocyte differentiation period, which is ultimately important for the upcoming leptin expression (29).

3.1.2 Leptin changes in the obese mother

Leptin levels correlate with body fat mass in pregnant and non-pregnant women. Regulation during pregnancy is more complex. The placenta is a rich source of leptin for mother and fetus. Leptin concentrations almost double during pregnancy and the placenta is thought to be the reason for the increase. Elevated leptin levels will mobilize maternal fat stores and thus, make substrates better available for the fetus (30). When increased placental inflammation occurs, leptin levels are high.

Therefore, keeping stable leptin levels during early pregnancy is important to ensure normal early development without any alterations in maturation of tissues and pathways involved in metabolic homeostasis (12).

When comparing obese women to non-obese women, leptin profiles differ across pregnancy. In a study by Misra et al. the serum leptin concentrations were measured 5 times during pregnancy (6-10, 10-14, 16-20, 22-26, 32-36 weeks of gestation). At each time point they were higher in overweight/obese women. The concentration also increased with advancing pregnancy, but the increase was lower in obese women than in non-obese (30).

The influence of leptin levels on birthweight adjusted for gestational age at delivery (aBW) was also part of Misra et al.'s study. In obese women during the second half of pregnancy, an increase in the rate of change of maternal serum leptin concentrations is associated with a reduction in the offspring's birthweight. However, after excluding women with hypertension and diabetes, results were similar but no longer statistically significant (30).

Leptin plays an important role in controlling placental growth and function and impacts fetal growth and development. There is a link between maternal obesity/hyperleptinemia and other markers of placental insufficiency and dysfunction. In the second trimester leptin is reduced in pregnancies with a growth restricted fetus. If serum leptin concentrations are elevated in obese women over a longer period, late pregnancy expression of placental leptin, which is desperately needed for placental development and fetal growth, might be suppressed. This also correlates with the finding that overweight/obese women do not show such a high increase in leptin production per unit of body mass (30).

3.1.3 Leptin changes in the offspring

A reduction or increase of leptin can be found in offspring. A reduction of leptin can be found in intrauterine growth restricted (IUGR) babies (15). Leptin levels are increased in offspring of obese mothers. These offspring experience a prolonged leptin surge meaning that leptin concentrations are temporarily rising during this normal developmental time period (27).

Elevated umbilical cord blood leptin concentrations were associated with slower infant weight gain during early life (6 months, two years and three years)

(31). They also have been associated with overeating in pregnancy and the risk to get T2DM in later life is higher (27).

Studies found that babies with leptin deficiency, who become obese in their childhood, will not deviate from the normal growth trajectory until they are about two years old. This suggests a minor influence of leptin on food intake and energy in early life (4). A study by Catalano et al. showed that 8 year old offspring of obese mothers had increased leptin levels (28). In general, young adults born to obese mothers have higher leptin levels than those born to non-obese mothers. In this scenario mainly male offspring were affected (10).

3.2 Adiposity

3.2.1 General information

Maternal overnutrition represented by mpp BMI and gestational weight gain (GWG) is associated with offspring adiposity throughout life (32). In general, offspring born to obese mothers are at a higher risk for obesity. For example, maternal obesity influences the fetal development, which is shown by elevated birthweight and body fat. In fact, for those two outcomes, mpp obesity is an independent risk factor (31). As already discussed in the introduction, longitudinal changes in obesity and other cardiovascular risk factors are also related to genetic factors, which are increasingly recognized as influencing and determining contributors (32).

3.2.1.1 Adipose tissue

The adipose tissue consists of different cell types including adipocytes (fat cells), preadipocytes, fibroblasts, endothelial cells and immune cells. In healthy individuals, major cell types are adipocytes, preadipocytes and inflammatory leukocytes. Adipose tissue is in charge of secreting factors, so-called adipokines (12), such as adiponectin, which is secreted by fat cells (25) [Figure 7]. In general, adipokines are responsible for adipocyte differentiation, glucose and lipid metabolism, satiety, neuroendocrine function, immune regulation and cardiovascular functions (12). If adipokine secretion is not properly regulated, this can cause altered interactions

with other organs and may lead to obesity-mediated diseases such as IR and metabolic syndrome (12). Adiponectin acts via adenosine monophosphate-activated protein kinase (AMPK) to promote insulin sensitivity in muscle tissue (10).

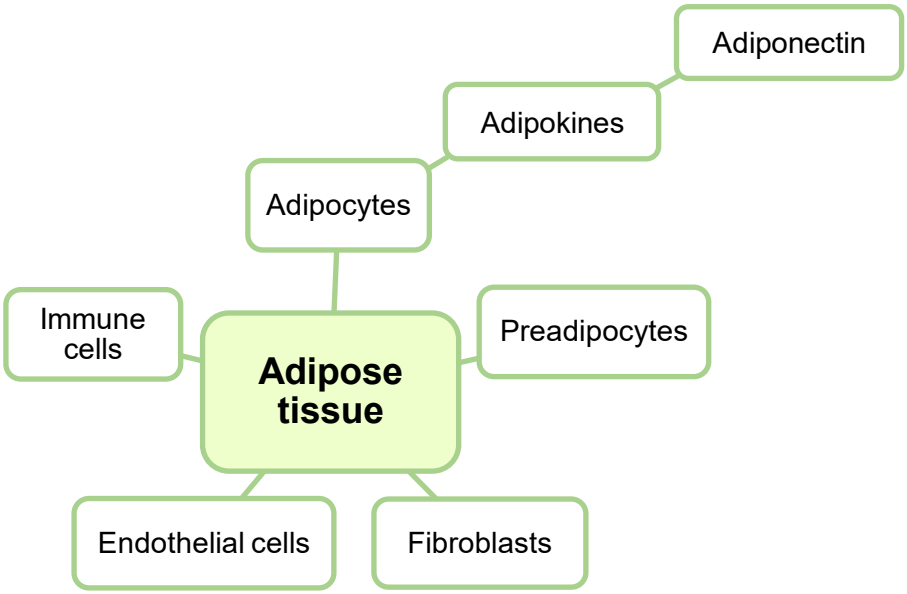

Figure 7. Cellular components of adipose tissue. Adipocytes secrete adipokines, such as adiponectin.

Obesity changes composition and phenotype of adipose tissue (12). For instance, plasma adiponectin concentrations are low in obese people as it is negatively correlated with BMI (25). Due to high energy intake, adipocytes increase their volume, which is called adipocyte hypertrophy. As a consequence, adverse processes such as hypoxia, adipocyte necrosis and chemokine secretion can arise. An altered balance of adipose tissue-derived cytokines and adipokines may also induce a pro-inflammatory state. Different mediators, such as IL-6 and CRP, are elevated and may be the link between (maternal) obesity and the development of later life disease (12). Additionally, obesity is characterized by high adipose tissue expansion. As a consequence blood supply declines, hypoxia arises and adipocyte dysfunctions follow. The downregulation of adiponectin mRNA (messenger RNA) expression is one of these dysfunctions, which lead to more inflammation (12).

3.2.1.1.1 Development of adipose tissue

Adipogenesis begins *in utero*. Stem cell precursors are the origin of the adipose lineage, which can develop in either brown (BAT) or white adipose tissue (WAT). These two have different functions (33). BAT is mainly located around central organs and can generate heat in a short amount of time (34). WAT is used as energy storage (33) in situations when the body needs energy and food is limited (34). Furthermore, WAT is able to secrete hormones, which regulate appetite and energy homeostasis (see chapter “Leptin and energy homeostasis” for more information) (33). In general, adipose tissue presents itself for the first time during mid gestation. The total amount of adipose tissue increases mainly in late gestation, especially during the last few weeks. It is then composed of BAT and WAT. A large amount of subcutaneous adipose tissue (SCA) is placed in late gestation as well (34).

Fetal adipose tissue resembles BAT morphologically and biochemically. It is also rich in mitochondria and fat droplets. The uncoupling protein-1 (UCP1), which is specific for BAT, is also present. During fetal development UCP1 is highly expressed to prepare the fetus for the extrauterine environment by enabling heat production. Different endocrine stimulatory factors such as cortisol and insulin-like growth factors (IGF) and the development of the sympathetic nervous system are important for the peripartum deposition of adipose tissue and UCP1 excess at birth. After birth the UCP1 expression rapidly drops (33). Postnatally, parts of BAT are replaced by WAT. One BAT depot, which gets replaced, is located around central organs. If the abundance of BAT is reduced or the amount of WAT is increased in early life, an interference with life can occur and maybe suppress energy consumption. Thus, this individual is at a higher risk of becoming obese (34).

The distribution of fat depots in the offspring is important because it predicts the offspring’s metabolic and cardiovascular risk. The distribution is even more pivotal than the total amount of fat. Visceral fat is one of the major predictors. For instance, decreased adiponectin, hypertriglyceridemia and also hyperinsulinemia are associated with an increase in visceral fat (31). Increased abdominal fat depots exist in offspring, which are at higher risk to develop metabolic diseases (13).

3.2.1.1.2 Effects of maternal obesity on fetal adipose tissue development

The amount of fat cells of an individual is already determined in early life. Thus, if the programming of adipose tissue development is influenced by maternal obesity, the consequences, including a predisposition for higher lipid accumulation, might persist throughout the offspring's life (27).

In fact, there are a few aspects in adipogenesis which are influenced by maternal obesity. One of them is peroxisome proliferator-activated receptor γ (PPARγ), which is a nuclear transcription factor important for adipocyte differentiation. PPARγ is elevated in skeletal muscle and adipose tissue in sheep and rats, which were born to obese mothers. Another protein affected by maternal obesity, is the AMPK. Its activity is low in fetal skeletal muscle and heart tissue of offspring born to obese mothers. Inhibition of AMPK causes an impairment of fatty acid biosynthesis. Furthermore, AMPK is associated with the suppression of PPARγ transcriptional activity. PPARγ and AMPK have important roles in the development of offspring obesity when mothers were obese. Another influencing factor is maternal inflammation. Due to inflammation, the number of adipocytes can increase which increases lipid storage. The offspring's risk to become obese is even higher. A reduction of UCP1 activity might play a role as well. This results in a decrease of mobilization of fatty acids for oxidation. As a result, lipids are being stored. Due to all the mentioned alterations, offspring have an increased birthweight, a higher adiposity, an elevated intramuscular lipid depot and experience a decrease in muscle fiber development. However, it is still unknown how this process influences the development of obesity in humans (27).

3.2.2 Results of several parameters

3.2.2.1 Birthweight

Birthweight is an easy accessible measure and reflects fetal growth (35). Mpp BMI is an indicator for higher birthweight in offspring (12,17): higher birthweight is mainly associated with maternal overeating (27), higher maternal BMI (27,34,35), adverse maternal metabolic profile (11) and high cord blood levels of leptin (29). Children

born large for gestational age (LGA), small for gestational age (SGA) and with IUGR have all been linked to maternal adiposity (12) [Figure 8].

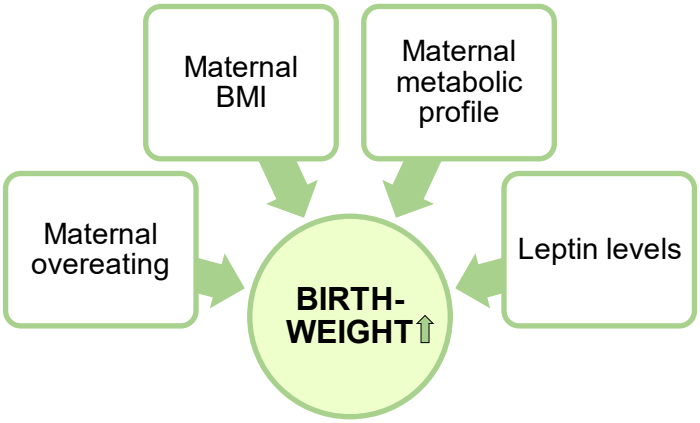

Figure 8. Maternal characteristics causing elevated birthweight.

The obese mother's lipid profile differs from a normal weight mother and shows increased levels of lipids. High triglyceride, FFA and low high-density lipoprotein (HDL) levels in late gestation are linked to a higher birthweight (11).

In the first few months of life, birthweight doubles and thus, these months represent the greatest phase of postnatal weight gain. Therefore, this period might be important for energy balance mechanisms (7).

Due to high birthweight the offspring is at risk for later life obesity and metabolic syndrome (28). Different associations, e.g. U-shaped or J-shaped, were found between birthweight and later life metabolic disease (8,17,33,36) [Figure 9]. A U-shaped association indicates that both, high and low birthweight, are linked to a higher later life metabolic disease risk (33,36). A J-shaped association indicates that the prevalence for a greater BMI is higher in individuals born LGA (17). A systematic review has further shown that the association between increased birthweight and adult obesity is linear (36). Rooney et al. found a direct association between birthweight and obesity risk, but obesity risk was two times higher in babies, whose birthweight was more than 3.86 kg. Below a birthweight of 3.18 kg, the risk of obesity was slightly reduced (7) [Table 2].

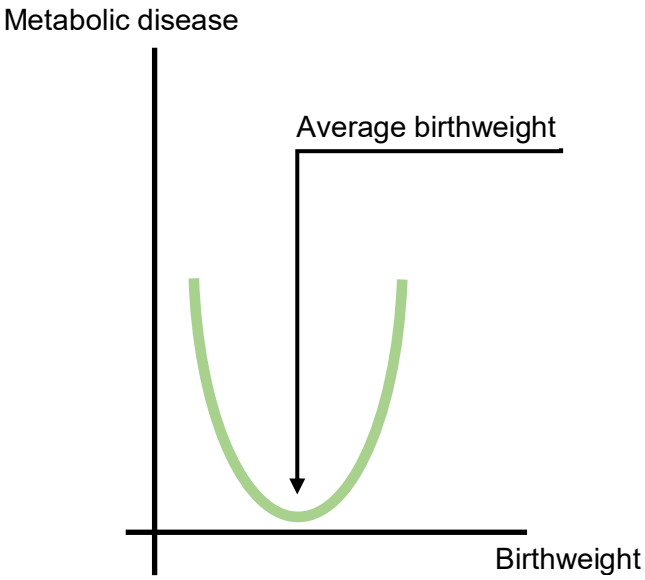

Figure 9. Association between metabolic disease risk and offspring's birthweight. Maternal metabolic disease can induce both, increased or reduced birthweight.

Another factor influencing the offspring's birthweight is leptin. Allard et al. found that high cord blood leptin concentrations are associated with an increased birthweight (232 g per log increase of cord blood leptin concentration) (29).

3.2.2.1.1 Fetal overgrowth

The term 'fetal overgrowth' includes both, LGA (birthweight above the 90th percentile) and macrosomia (birthweight over 4000g) (10). Maternal obesity is linked to both (1).

Fetal overgrowth was present in women with high pre-pregnancy weight (OR 2.08-3.36 (27)), obese women (OR 2.0 (10); OR 1.6 (17)) and extremely obese women (OR 2.4 (10)). Only for women with GDM, the OR is higher (OR 4.4) (17). The rising prevalence of LGA babies parallels the rising prevalence of maternal obesity (28). Ensenauer et al. revealed that obese women (with an $HbA_{1c} \geq 5.7\%$ at delivery) gave birth to offspring, whose birthweight was higher by a mean of 186 g. Those mothers were also more likely to give birth to a LGA offspring (OR 3.48) (37).

Due to the higher birthweight, offspring of obese mothers are at risk for some complications which can arise immediately after birth, such as hyaline membrane

disease (OR 2.14), extended assisted ventilation (OR 1.71), birth injury (OR 1.58) and meconium aspiration (OR 1.42) (1).

If birth- and infant weight are above average, they positively associate with a higher adult BMI/adult obesity (27) with an OR of 2.07 (8). The offspring's BMI/obesity can be predicted with higher birthweight depending on the respective age. For example, the higher BMI at the age of one is predicted by a higher birthweight (> 4000g) (11). Rooney et al. revealed that the state of obesity in childhood (4-5 years) and early adulthood (18-20 years) can be described the same way (7). BMI at the age of one can predict the weight at age 5-8 (11) [Table 2].

3.2.2.1.2 Small for gestational age

SGA is defined as the birthweight below the 10th percentile. This is based on growth curves, which are standardized to gestational age and the infant's sex. Causes may be genetic, environmental or due to IUGR (36). SGA is also linked to a high maternal BMI (10,27). For instance, a Dutch study showed that about 18.8% of obese women delivered SGA babies and stillborn babies were smaller as well (10).

3.2.2.2 Body size

3.2.2.2.1 Body composition

Macrosomic babies have a bigger amount of adipose tissue (36). Considering their body weight, they have a higher fat mass than SGA and average for gestational age (AGA) offspring (10). In further consequence they are at a higher risk for (childhood) obesity and diabetes (36).

Uebel et al. found neonatal preperitoneal adipose tissue (PPA) at week one being an independent predictor for the PPA at age one. This might reflect the influence of intrauterine environment on the fetus' adipose tissue development, which can have long lasting effects (31).

3.2.2.2.2 Body fat percentage

There are several causes for developing higher body fat percentages. Two causes are mpp BMI (17,28) and a higher first antenatal maternal BMI (38). A strong

correlation was shown between mpp BMI and the offspring's body fat percentage (17). An elevation in percentage was found in 8 year old children (28). Reynolds et al. showed a link between higher antenatal BMIs and a rise in body fat percentage in 30 year old offspring. They found a rise of 0.35% per kg/m^2 antenatal BMI (38).

Another cause is an altered maternal lipid profile during gestation. The body fat percentage is elevated if the mother's triglyceride and FFA levels are high during the last few weeks of gestation and low HDL cholesterol levels are present (11).

3.2.2.2.3 Fat mass and skinfold thickness

Mpp BMI strongly associates with an elevated offspring fat mass (17). Fat mass is usually estimated by skinfold thickness (SFT). SFT can be measured on the non-dominant side in a few different areas of the body, e.g. at the biceps, triceps, and at subscapular and suprailiac regions using calipers (38).

An increase in birthweight of offspring born to obese mothers, was mostly related to the offspring's elevated fat mass (35). This leads to an increased fat mass during the neonatal period, during childhood and at the age of 24 years (38).

Increased skinfolds were associated with cord blood leptin levels in the offspring in a study by Allard et al. More precisely, the SFT at birth was increased 1.75 mm per log of cord blood leptin concentration (29).

3.2.2.2.4 Fat free mass

Birthweight positively associates with fat free mass at age 15 (10). Specifically, one kg increase in birthweight increased the amount of fat free mass in adult men and women by 2.2 kg and 2.7 kg, respectively (27).

3.2.2.3 Circumferences

Abdominal birth circumference (AC) and birthweight ratio helps rating the obesity of a baby in relation to the weight. The ratio decreased with an increase in maternal BMI meaning that intrauterine overnutrition results in fetal weight gain in general and not only in accumulation of fat. The methods used to measure the AC or birthweight might be another reason why the ratio decreases: AC is usually rounded in whole

centimeters whilst birthweight is rounded in smaller units, making the measurement of birthweight is more accurate (23).

A high maternal early pregnancy BMI is associated with an increase in fetal WC. Reynolds et al. found out that a higher mpp BMI independently predicts the offspring's WC (38). An increase in WC in childhood at age 8 was linked to an obese mpp BMI (28). Another link was shown between birthweight and WC at age 15 (10).

3.2.2.4 Body Mass Index/Fat mass index

It is thought that the BMI is heritable for about 40 to 70%. However, only about two percent of genetic loci related to obesity have yet been detected (9). In general, the mpp BMI predicts the offspring's BMI (39). It is also the strongest predictor for a high BMI in the offspring's childhood (18). A study by Reynolds et al. revealed that higher mpp BMI can independently predict the offspring's BMI and FMI (fat mass index; is calculated by dividing fat mass (kg) by height (m)) (38). Besides a higher maternal (pre-) pregnancy BMI, the offspring's birth- (11,28)/infant- (10)/childhood- (10) weight and excessive GWG are also associated with a higher offspring's BMI/obesity (11).

Macrosomia and excessive GWG are strong predictors of a higher BMI at one year of age. The BMI at one year of age then predicts the weight status for age 5-8 (11). If infants are overweight, they are also likely to be overweight in preschool years. Specifically, childhood obesity predicts adult obesity (10) [Table 2].

Table 2. Different influential effects of maternal BMI on offspring's BMI/adiposity.

Influence of maternal (pre-) pregnancy BMI on the offspring	
Offspring's age	**Details about adiposity**
early childhood	• two-fold increase (28)
4-5 years	• 52% obese (7)
6-11 years	• highest BMI tertile (18)
9-14 years	• 62% obese (7)
18-20 years	• 44% obese (7)

21 years	• three times more likely to become overweight (39)
	• 5-times more likely to become obese (39)
60 years	• positive association (13)
offspring any age	• BMI increase of 1.8 kg/m^2 per increase of one standard deviation (SD) in mpp BMI (13)
offspring any age	• 6.2-6.4 times more likely to be obese (7)
Influence of birthweight on infancy/childhood/adolescence/ adulthood	
4-5 years	• birthweight ↑→ likely to be obese (7)
9-14 years	• one kg increase in birthweight → risk at obesity/overweight increased by 50% (after adjustment for maternal BMI risk is still increased by 30%) (28)
15 years	• birthweight ↑ → positive association between BMI and FMI (10)
18-20 years	• birthweight ↑→ likely to be obese (7)
21 years	• one kg increase in birthweight → BMI increases by 1.102 kg/m^2 in women and 0.645 kg/m^2 in men at 21 years (27)
18-26 years	• correlation with birthweight (28)
adult women	• birthweight ↓ (lower than 2300 g) → OR 1.67 to become obese (27)
adult women	• birthweight ↑ (≥ 4500 g) → OR 1.99 to become obese (27)
Influence of offspring's BMI during infancy/childhood/adolescence/ adulthood on later life	
4-5 years	• 22.6% obese (7)
	• 12.3 times more likely to be obese adults (RR) (7)

9-14 years	• 29.6% obese (7)
	• 45.1 times more likely to be obese adults (RR) (7)
12 years	• 5-times more likely to be obese at 12 years if overweight in pre-/elementary school (7)
	• OR 2-10 for childhood to adulthood obesity (7)
18-20 years	• 14% obese (7)

The RRs for the different time points show that obese children are more likely to be obese adults. This shows a very strong link between childhood obesity and adult obesity (7).

3.2.2.5 Longitudinal change in offspring's BMI

Many studies have focused on specific time points but only few investigated the longitudinal change in BMI (32). Ziyab et al. revealed that the so-called "change in path" occurred between one and 4 years of age. In the following years no directional changes have been found meaning that the first 4 years of life are crucial for later BMI. Therefore, this time period is called "critical developmental window". Long-term changes in the offspring's BMI might have a major impact (40).

A study done by Lawrence et al. showed that a mpp BMI greater 26.2 kg/m^2 was associated with an increase in the offspring's BMI from age 17 to 32 years of nearly two kg/m^2. This mpp BMI was compared to a mpp BMI less than 20.8 kg/m^2 (32).

3.2.2.6 Adverse cardio-metabolic profile

An association between maternal obesity and an adverse offspring metabolic profile is supposed (41). It was shown that high mpp BMI is linked to an unfavorable metabolic profile at the newborn and young adult age (11) and a metabolic dysregulation at age 6-11 years (18).

A study by Ferreira et al. demonstrated that maternal BMI is associated with about 49% of offspring's metabolic traits. Paternal BMI was associated with around 44%. Both of them showed very similar links (41).

This study also revealed that an offspring's adverse metabolic profile is associated with an elevation in maternal and paternal BMI. The offspring's metabolic profile was positively associated with very-low-density lipoprotein (VLDL)-lipoproteins/-cholesterol/-diameter, branched/aromatic amino acids, glycoprotein acetyls and triglycerides. It was negatively linked to HDL, HDL-diameter and all different HDL-cholesterols. Latter ones showed an inverse relationship (41). These links between parental BMIs and the offspring's metabolic profile have been found again at a follow-up 16-17 years later leading to the idea that the association is due to a shared environment, genetics, socioeconomics and lifestyle rather than an intrauterine influence. They also found similar traits 31 years later, but this time only maternal BMI was assessed (41).

3.2.2.7 Metabolic syndrome

Metabolic syndrome describes the presence of several adverse metabolic conditions such as obesity, hypertension, glucose intolerance and dyslipidemia (17) [Figure 10].

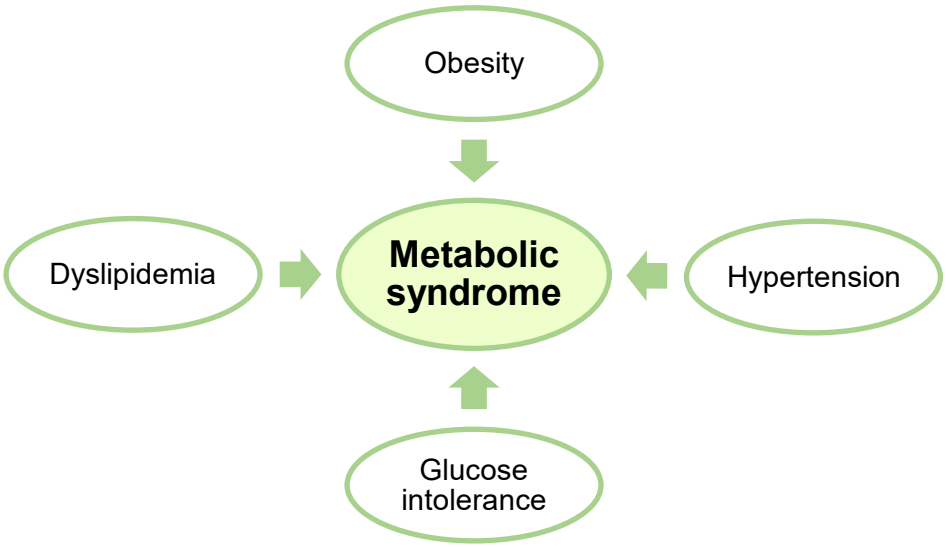

Figure 10. Metabolic conditions describing metabolic syndrome.

It is defined as concurrence of at least three metabolic risk factors. These risk factors are abdominal obesity, high triglycerides, low HDL, high blood pressure and elevated fasting blood sugar. This syndrome is a risk factor for diabetes (especially

T2DM) and cardiovascular disease (CVD) (36). It is usually present in middle aged individuals and not children, but due to the increasing obesity incidence, the number of younger individuals being affected is rising (10,17). Different environmental exposures, such as poor nutrition during adolescence and adulthood, increase the individual's susceptibility. However, evidence shows also the involvement of intrauterine exposure (36).

Offspring born to obese mothers are at a higher risk for developing metabolic syndrome, regardless of their birthweight. However, if they were LGA or their mothers were obese, a two-fold increase is found in their risk of developing this disease (10).

3.3 Cardiovascular disease

3.3.1 General information about cardiovascular diseases

CVD and obesity are two major health concerns and highly impact adult morbidity and mortality (42). Evidence has shown an association between maternal obesity and adverse cardiovascular/-metabolic outcomes (42) such as hypertension (43). The etiology of cardio-metabolic disease is still unclear, but some studies indicate that genetics and lifestyle play a role (44).

3.3.1.1 Cardiovascular changes in obesity

Obesity causes structural alterations in the vascular system (45). One of these occurs in the microcvascular system, which consists of small resistance arteries, arterioles, capillaries and venules with a diameter below 150 µm. The microvascular bed can be found within the parenchyma of each tissue. Its vessels are in charge of the exchange of gases, nutrients and metabolites. Moreover, arterioles limit fluctuations in hydrostatic pressure through regulation of the vascular tone. The vascular tone is regulated by endothelial cells, which secrete vasoconstrictors (e.g. thromboxane A_2 and endothelin-1 (ET-1)) and vasodilators (nitric oxide (NO) and prostacyclin (PGI_2)) (44). Vasodilation is a process in which endothelial cells and

smooth muscle cells act together and reduce vascular resistance (45). Thus, the microvascular bed regulates peripheral resistance and blood pressure (44).

There are different changes in obese individuals, which are related to CVD risk, such as adverse central fat accumulation (42), structural alterations in blood vessels (45), microvascular dysfunction (44) and endothelial dysfunction (45) [Figure 11].

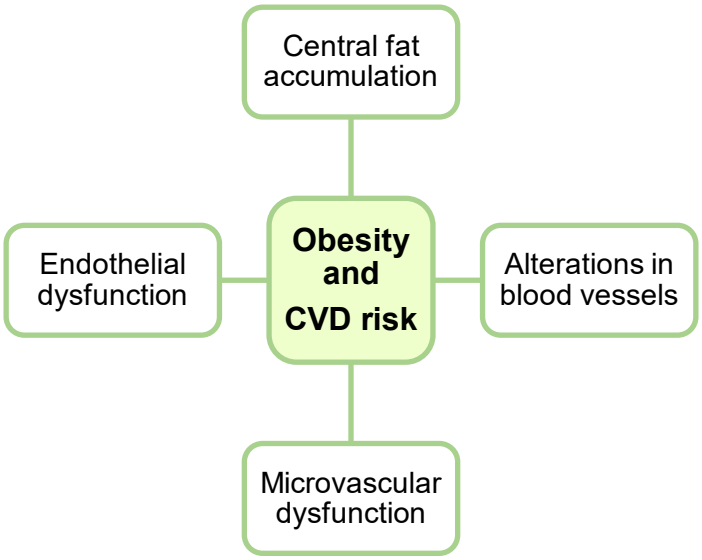

Figure 11. Obesity-related influences on CVD risk.

Structural alterations in the vascular system in obese individuals occur as a likely response to high blood pressure. Vessels exposed to high blood pressure show increased basement membrane thickness and vessel stiffness. As obesity progresses, the microvascular system atrophies, the vessel diameter decreases and local tissue ischemia might occur (45).

The microvascular bed changes, a process called “microvascular rarefaction”, which is characterized by decreased number of vessels, branching patterns and altered microvessel morphology. As a result, proper perfusion is disturbed. Such microvascular changes might be present even before macrovascular disease clinically manifests (44).

Due to chronic activation of endothelial cells, obesity is associated with endothelial dysfunction which is a pathological sign of early development of atherosclerosis [Figure 12]. Endothelial dysfunction is characterized by altered

uptake and metabolism of the vasodilator adenosine, followed by changes in L-arginine uptake and metabolism. L-arginine is a substrate for NO synthesis. Thus, NO production is compromised and vasodilatation cannot be performed properly. The vasoconstrictor ET-1 is increased in obese individuals presumably involved in endothelial dysfunction as well (45).

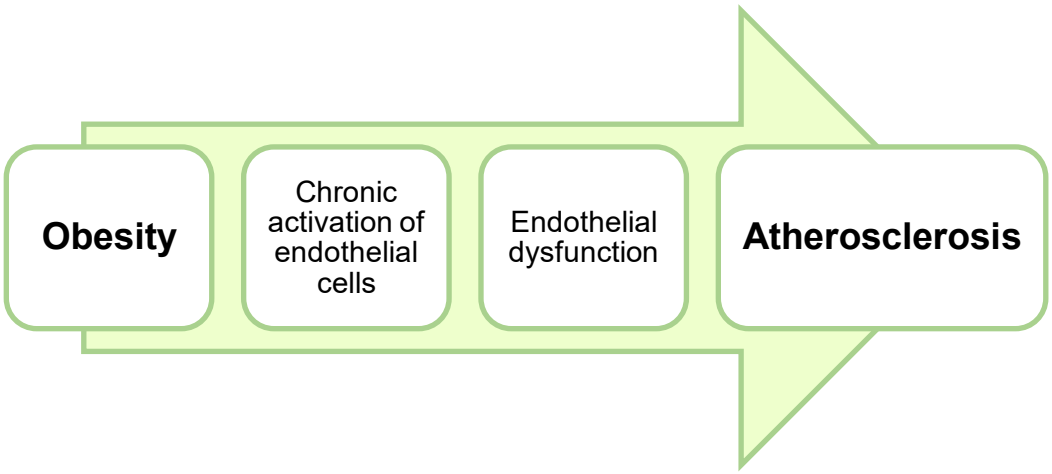

Figure 12. Obesity and the development of atherosclerosis.

3.3.1.2 Maternal cardiovascular system in pregnancy

The maternal cardiovascular system is altered during an obese mother's pregnancy (46). Adaptations of the cardiovascular system in pregnancy are necessary because of physiological requirements. The mechanisms, which regulate these adjustments, are controlled by sex steroids. Animal models have indicated that even environmental factors such as maternal nutrition might influence these mechanisms. Oxygen and nutritional needs of the developing fetus are demanding and require adjustment of the maternal cardiovascular system. For example, during pregnancy, there is a 40% increase in blood volume and heart enlargement. Especially, an increase in blood volume is necessary to supply the uterus with sufficient blood. Furthermore, vasodilatation occurs. Due to the fact that obese women already experience chronic preexisting endothelial activation, these pregnancy adaptions lead to further endothelial dysfunction (45).

Maternal obesity might influence placental function, and thus, affect fetal cardiovascular development (45). Fetal (organ) growth and development are dependent on the placenta. The establishment of a functioning placenta includes an

adaptation of maternal spiral arteries to become low-resistance blood vessels. To form the maternal decidua, endovascular trophoblast cells infiltrate the low-resistance vessels, transform and enlarge them. In this process, the endothelial and muscular lining of uterine arterioles is replaced by cytotrophoblast cells (45). Maternal endothelial dysfunction may induce aberrant trophoblast invasion which may cause vascular insufficiency (45).

3.3.1.3 Fetal cardiovascular system/development

An adverse maternal fat distribution and metabolic profile might have long lasting effects on the cardio-metabolic development of the fetus (42). There are two periods during development (embryo, fetal/early neonatal life), when the heart is vulnerable to certain stressors. During embryogenesis the heart walls are more vulnerable to hemodynamic forces which can alter gene expression. During the fetal/early neonatal period binucleated and terminally cardiomyocytes arise (47).

Cardiomyocyte development is crucial for the offspring's cardiovascular health because the number of myocytes is determined *in utero*. Replicating cardiomyocytes form the expanding myocardium. The proliferation is mediated by factors such as IGF, angiotensin II, cortisol and arterial pressure load. However, certain factors suppress the proliferation, for example tri-iodo-L-thyronine (T_3), atrial natriuretic peptide (ANP), reduced cardiac systolic load and ventricular wall stress. Latter one might result in limited cardiac expansion and regeneration of myocytes, which are, however, important for a normal functioning heart though. A reduction in number of cardiomyocytes causes mechanical stress and a greater contractile force generation. As a consequence, cardiomyocytes enlarge and the chambers of the heart hypertrophy to compensate wall stress (45) [Figure 13].

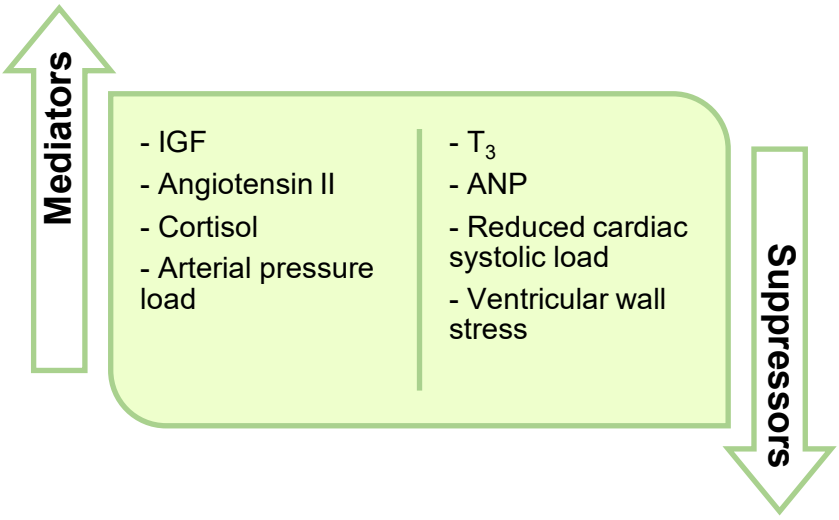

Figure 13. Mediators and suppressors of cardiomyocyte development.

As a consequence of maternal obesity cardio-metabolic disorders in the offspring can arise, for instance hypertension (43). One reason for development of hypertension is microvasculature dysfunction, which results from an adverse intrauterine environment (44). The exact mechanism, how the hypertension pathway is programmed, is still unclear. Autonomic control regulates blood pressure, but in the case of maternal obesity, the offspring's cardiac autonomic balance might be shifted to an elevated sympathetic nervous system. This was assessed by using a fetal electrocardiography (ECG) (43). Because of mechanical stimulation, the myocardium can be affected directly as well (45).

As already mentioned above endothelial dysfunction influences placenta function. Due to placenta insufficiency a lot of problems can arise, for example an elevated fetal ANP secretion while having a normal umbilical vein blood flow. However, an altered umbilical vein blood flow pattern is linked to causing fetal myocardial cell damage. The cell damage is linked to an elevation in systemic venous pressure, a redistribution of cardiac output in favor of the left ventricle and an increase in the right ventricular afterload. The fetal heart, especially the cardiomyocytes, are susceptible to long lasting loading conditions and placental insufficiency can cause myocyte hypertrophy consecutively. A rise in systolic load to the fetal heart has been postulated as underlying reason (45).

3.3.2 Changes in offspring's cardiovascular system

An association between maternal obesity and the offspring's health has been identified, but the exact mechanisms need to be more investigated. More research has to be done on the fetal cardiovascular programming (45).

The *in utero* environment influences the offspring's risk for CVD. Specific levels of biomarkers such as E-selectin and vascular adhesion molecule-1, which function as stimulating factors for monocytes and lymphocytes in the atherosclerotic process, are also altered in offspring born to obese women. These initiate atherosclerosis by allowing monocytes and lymphocytes to attach to endothelial cells (45).

3.3.2.1 Blood pressure, heart rate and other parameters

The Amsterdam Born Children and their Development-Study (ABCD-Study) found a connection between high mpp BMI and high blood pressure in 5-6 year old children (43,45). Linear associations and similar results for male and female offspring were found between mpp BMI and the offspring's systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP) (43).

Gademan et al. revealed that an increase per unit of mpp BMI is associated with an increase in SBP (+ 0.14 mmHg) and DBP (+ 0.11 mmHg) in 5-6 year old offspring when adjusted for offspring traits, such as sex. After adjustment for maternal confounders the association was reduced (43). This association was found by other researchers as well (48,49). For instance, an increase of one SD of mpp BMI is associated with a 1.1 mmHg rise in SBP and DBP in 32 year old offspring (50).

No link, however, was revealed between high mpp BMI, HR and resting PEP. The RSA at rest was only associated to mpp BMI before adjustment. They consider PEP a valid measure for the sympathetic drive, which has a role in the regulation pathway of blood pressure (43).

Birthweight was inversely related to the offspring's blood pressure. At high risk for high blood pressure are children with low birthweight born to obese mothers. The offspring's BMI is a mediator between mpp BMI and blood pressure at age 5-6.

The children's BMI showed a positive association with PEP and a negative association with HR (43).

3.3.2.2 Cardiovascular events, morbidity and mortality

Cardiovascular events describe a number of disorders, such as angina, myocardial infarction, stroke, other cerebrovascular diseases, peripheral artery disease and other CVD (51). In non-diabetic populations the HbA_{1c} is a risk marker for CVD and predicts the individual's mortality (37). Reynolds et al. suggest that the intrauterine environment plays a role in influencing the offspring's risk for premature mortality (51).

Maternal BMI determines the offspring's risk for cardiovascular morbidity and mortality (13). Even after adjusting for partner's social class, gestational age, offspring's sex and birthweight, gestation weight, mother's age at delivery, Reynolds et al. identified a connection between maternal obesity and increased cardiovascular events (hazard ratio 1.27), increased all-cause mortality (hazard ratio 1.35) and the risk for premature death (< 55 years) (hazard ratio 1.40) in offspring aged 34-61 years. These offspring also showed a higher hospital admission rate for cardiovascular events (hazard ratio 1.29) (51). A Finnish study revealed higher numbers of death from coronary heart disease in men, who were thin at birth and were born to a mother with an increased pregnancy BMI. However, women of short stature were excluded from this study (11).

3.3.2.3 Cardiovascular anomalies and congenital heart defects

Maternal obesity puts the offspring at high risk for cardiac malformations (18). Congenital heart defects are the most common malformations and because of increasing prevalence of maternal obesity they are not uncommon anymore, especially in the United States. These defects include, for example, all right and left outflow tract obstruction defects, atrial septal defects, hypoplastic left heart syndrome, aortic stenosis, pulmonic stenosis and tetralogy of Fallot (52). Interestingly the risk for overweight women to conceive a child with congenital heart defect is not higher (OR 1.00). The risk increases at an approximate BMI of 30 kg/m^2 (52).

Also a meta-analysis highlighted that offspring born to obese mothers were predisposed to a congenital heart defect (moderate obese OR 1.15; extremely obese OR 1.29) (1). Mills et al. revealed that maternal obesity is a risk factor for all congenital heart defects (45) (obese women OR 1.11; extremely obese women 1.33 (52)).

Myocardial hypertrophy is also associated with a high maternal BMI, which might be caused by placental insufficiency (45).

3.3.2.4 Offspring's adverse biomarkers

Children born to women with a higher mpp BMI reveal an increase in certain biomarkers for endothelial dysfunction. For instance, E-selectin and vascular adhesion molecule-1, which are circulating cellular and vascular adhesion molecules, are increased (45).

3.4 Pancreatic changes

3.4.1 General information

Due to their influence on adult morbidity and mortality, T2DM and obesity are major public health problems (42). By 2025 about 380 million people will suffer from T2DM (53). Diabetes is an important comorbidity of obesity and mpp obesity is independently associated with an increased risk of IR in the offspring (54), which promotes the development of T2DM (9).

3.4.1.1 Insulin's physiology

Insulin is an endocrine (54) and anabolic (2) hormone produced and secreted by pancreatic β-cells (2,54). Insulin controls the body's glucose levels, lipid and protein homeostasis as well as cell growth/proliferation/survival and differentiation (54).

Insulin is composed of two peptide chains, which are linked by two disulfide-bonds. It is synthesized in the rough endoplasmic reticulum (RER). Firstly, a single polypeptide chain, the preproinsulin, is being synthesized, transported into the lumen of the RER and folded. During this process the signal peptide is cleaved

resulting in proinsulin. Then, proinsulin is transported to the Golgi apparatus where a part of the peptide, called C-peptide, is cleaved and the mature insulin is formed. The mature insulin and the cleaved C-peptide are stored in granules, which are released upon adequate stimulation of the β-cells. Stimuli promoting secretion are glucose, certain amino acids, FFAs, hormones (e.g. glucagon-like peptide), adrenalin and an increase in parasympathetic tone. Equal amounts of C-peptide and insulin are released, however, the half-life of C-peptide is longer (> 30min), for which reason it is used for diagnosis. Insulin secretion is inhibited by an increase in sympathetic tone and somatostatin (2) [Figure 14].

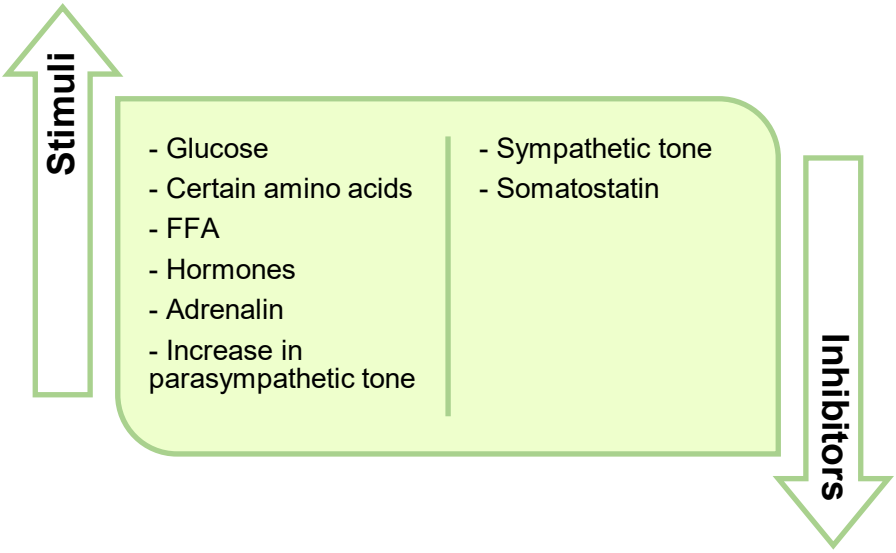

Figure 14. Stimuli and inhibitors of insulin secretion.

Classical insulin target tissues are the liver, skeletal muscle and adipose tissue (2), but almost all cells and tissues express insulin receptors and are thus, influenced by insulin (54).

The insulin receptor is composed of two α- and two β-subunits. The α-subunits bind insulin, whereas the β-subunits possess tyrosine kinase activity. Insulin binding to the receptor induces an activation of tyrosine kinase domains resulting in autophosphorylation of the receptor. This enables binding of members of the insulin receptor substrate family (IRS) which are then also phosphorylated. After the IRS is phosphorylated, it can bind to phosphatidylinositol-3-kinase (PI_3K), which leads to a translocation and phosphorylation of protein kinase B (PKB). PKB is the central effector molecule for the metabolic effects of insulin (2).

3.4.1.2 Pathophysiology

An excess of adipose tissue causes a low-grade chronic inflammation and an impaired insulin metabolism (55) and is associated with increased IR (11). IR is a pathophysiological condition with an impaired response to normal insulin levels in target tissues, e.g. adipose tissue. IR arises when receptor expression or cellular response function reduce. Defects in cellular response after insulin binding to the receptors are most likely the cause (54). IR leads to overproduction of FFA and increasing secretion of triglyceride rich lipoproteins (1) and is a precursor of T2DM (11).

Obesity is linked to a chronic inflammatory state and cellular stress signaling network accompanied by tissue damage. Metabolic factors, such as leptin and adiponectin, inflammatory markers, such as IL-6 and TNFα, and also nutrients, such as glucose, amino acids and FFA are associated to obesity-induced IR because of activation of stress-responsive proteins (e.g. c-Jun-NH2 terminal kinase (JNK)) (54) [Figure 15].

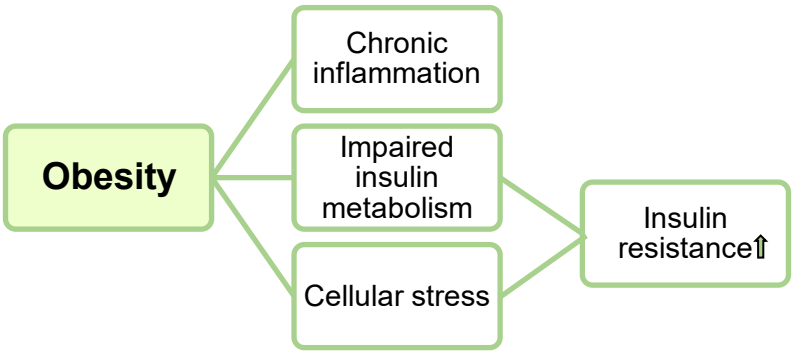

Figure 15. The link between obesity and insulin resistance.

Cellular stress implies a role in a process called endoplasmic reticulum (ER) stress response. The ER is an intracellular membranous network important for synthesizing and processing secretory and membrane proteins and controls folded proteins. Correct folded proteins transit to the Golgi apparatus. Misfolded or unfolded proteins are not transported and stay within the ER. The ER is highly sensitive to changes in the cellular environment (e.g. overnutrition or a rise in synthesized secretory proteins). These so-called “stressor signals” disrupt ER homeostasis and gather unfolded proteins in the ER lumen, a situation called ER

stress. As a consequence the “unfolded protein response” (UPR) or “ER stress response” signaling pathway adapts ER functions. These adaptions include a decrease in translocations of new proteins into the lumen and an increase in retrotranslocations and degradations of misfolded proteins. Additionally a transcriptional activation of UPR-responsive genes occurs. These adjustments are necessary to avoid irreversible cell damage and apoptosis (54).

In obesity, ER stress is harmful especially in combination with preexisting inflammation and induction of IR. This is also referred to as the obesity-inflammation-ER stress cycle [Figure 16]. Some pro-inflammatory cytokines, such as TNFα, can directly and deleteriously influence the function and viability of β-cells. However, anti-inflammatory cytokines, such as IL-4 and resistin can prevent ER stress development. Treatment of β-cells with these preventative cytokines stops the negative influence (54).

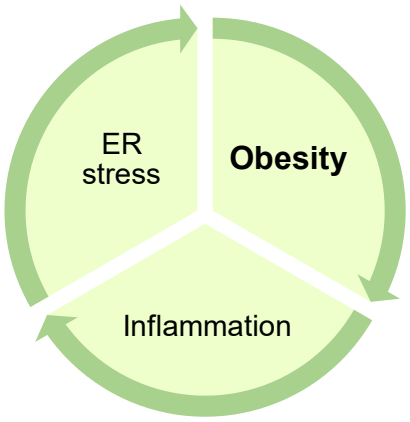

Figure 16. Obesity-inflammation-ER stress cycle.

Cellular stress links maternal obesity and the elevation of circulating and subcellular markers of IR and implies a role in ER stress response. Evidence has shown that an increase of ER stress markers in adipose tissue is associated with insulin, which leads to the idea that ER stress might also exist after the development of IR (54).

The pathogenesis of T2DM includes the UPR. Pancreatic β-cells possess high concentrations of immature insulin in their ER lumen during times of chronic stress environment, which occurs in overnutrition and maternal hyperglycemia. This

process is followed by cell death, which leads to pancreatic β-cell loss and peripheral IR (54).

In general, the maternal glucose metabolism changes in pregnancy, for instance maternal hepatic glucose production increases by 30% (55). Moreover, insulin secretion and sensitivity change (11), for example insulin sensitivity reduces by 50-60% (17). Additionally, as the pregnancy progresses, the maternal IR increases by 60% (55) and circulating glucose levels rise and certain hormones, such as cortisol and progesterone, intensify IR (11) [Figure 17].

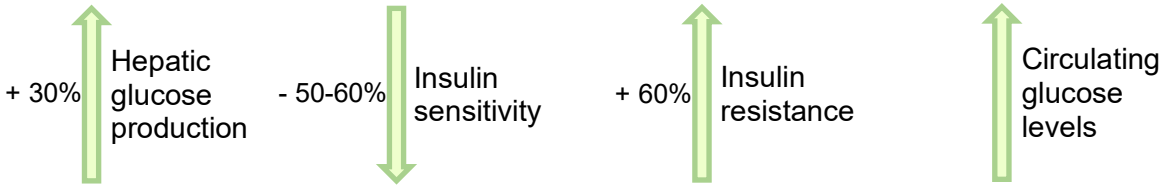

Figure 17. Changes in maternal glucose metabolism during normal pregnancy.

Obesity during pregnancy negatively influences IR even more (11). This affects preexisting inflammation (55) and thus, impairs fetal development (11). Mothers with a high BMI are already at a higher risk for developing metabolic abnormalities, such as glucose intolerance, (37) and maternal hyperglycemia. Other factors such as genetics, age and ethnicity affect the susceptibility as well (56).

However, their oral glucose tolerance test (OGTT) is often negative for GDM despite higher fasting glucose concentrations (10). HbA_{1c} is a marker for chronic hyperglycemia. If HbA_{1c} levels are ≥ 5.7% (= 39 mmol/mol), a prediabetic condition is present. The prospective PEACHES Mother-Child Cohort revealed that one third of nondiabetic obese mothers had an HbA_{1c} of ≥ 5.7% at delivery representing a state of maternal dysglycemia during pregnancy (37).

The metabolism in obese pregnant women is also influenced by cytokines. These promote IR and a pro-inflammatory state. Pro-inflammatory cytokines induce ER stress in the placenta. For instance, maternal obesity increases inflammatory cytokines and macrophage infiltration in the placenta. Additionally, leptin was increased in maternal serum (54). The inflammatory state, which is found in obese

pregnant women, is often transferred to the fetus. IL-6, which is a pro-inflammatory cytokine, plays a role in this process and higher levels were found in the umbilical cord blood of offspring born to obese mothers (54). As maternal cytokines do not cross the placenta maternal inflammation cannot be directly compared to fetal inflammation (55).

3.4.1.3 Insulin during obese pregnancy

Insulin cannot cross the placenta (9,15,54). However, maternal glucose is transported through the placenta (15,54). Depending on maternal glucose levels, fetal glucose levels rise as well and may stimulate the fetal pancreas to secrete the required amount of insulin (15). Maternal obesity and overnutrition create a hyperglycemic environment (15,54) resulting in fetal hyperglycemia (57). This promotes fetal insulin secretion (15) leading to fetal hyperinsulinemia (9). Hyperinsulinemia stimulates fat accretion and cell proliferation and thus, promotes fetal growth (57). In fact, maternal obesity is an independent risk factor for fetal hyperinsulinemia (31).

Due to the obesity related IR and the resulting higher amounts of circulating glucose in pregnancy, the offspring is adequately provided with more glucose (11). Even if obese mothers do not develop diabetes, they create an environment, which increases the offspring's susceptibility to IR (31). Even before the OGTT fetal β-cells might be programmed to secrete more insulin (58) and high fetal insulin levels are an important anabolic factor especially during *in utero* development. This might result in fetal overgrowth (55), for example offspring born to obese, GDM-negative mothers, who had a higher HbA_{1c} at delivery, were more likely to be born LGA (OR 3.48) and had a higher birthweight in general (increased by a mean of 186 g) (37). Macrosomic children have more adipose tissue, which increases their susceptibility to develop obesity and diabetes mellitus (DM) later in life (36).

3.4.2 Changes in the offspring

3.4.2.1 Changes in C-peptide, insulin and glucose levels

The Hyperglycemia and Adverse Pregnancy Outcomes-Study (HAPO-Study) revealed a strong association between high maternal BMI and neonatal

hyperinsulinemia (46). The association was present even after adjusting for maternal glycaemia. They created two logistic models: model 1 adjusted ethnicity, center, age, height, smoking, alcohol use, family history of diabetes, gestational age at OGTT, baby's sex and parity (OR for different BMIs: 28.5-32.9 kg/m^2: 2.18; 33.0-37.4 kg/m^2: 3.11; 37.5-41.9 kg/m^2: 3.04; ≥ 42 kg/m^2: 4.30). Model 2 additionally adjusted for fasting glucose and mean arterial pressure (OR for different BMIs: 28.5-32.9 kg/m^2: 1.66; 33.0-37.4 kg/m^2: 2.13; OR for 37.5-41.9 kg/m^2: 1.90; ≥ 42 kg/m^2: 2.33) (58).

The prospective PEACHES Mother-Child Cohort also revealed that offspring, who were born to obese mothers had higher cord blood serum C-peptide levels (increased by 0.09 ng/ml). Particularly high C-peptide concentrations (≥ 90th percentile) were furthermore linked to a 3.27-fold increase in the risk of being born LGA (37).

Catalano et al found that neonates born to obese mothers had higher fasting umbilical cord insulin (9.2 ± 4.7 µU/ml) and glucose (66 ± 14 mg/dl) levels when comparing them to lean mothers (umbilical cord insulin (7.0 ± 3.8 µU/ml) and glucose (60 ± 13 mg/dl) levels) (55). Cord blood insulin levels independently predict the offspring's week one PPA and SCA, were positively associated with neonatal SFT and fat mass and are inversely related to the weight gain at the age of two (31). McIntyre et al. demonstrated that the presence of fetal hypoglycemia rises with higher maternal BMI. However, the results were not significant (OR≈1) (58). Moreover, offspring of obese mothers also had higher insulin levels as newborns (31) and higher non-fasting glucose levels as young adults (10).

3.4.2.2 Insulin sensitivity, insulin resistance and diabetes mellitus

Maternal obesity has been linked to a reduction of insulin sensitivity in the offspring (54) and the offspring's insulin sensitivity is inversely related to visceral fat (31).

Fetal IR is also strongly associated with maternal obesity and even after adjusting for maternal confounders the link was still present, suggesting an involvement of genetic or epigenetic factors (55). Offspring born to obese mothers are more likely to develop IR in later life (54,59). For example, insulin might lead to perinatal programming of obesity and thus, cause IR and the development of T2DM (9). Usually a peripheral IR rather than hepatic IR can be found in neonates (55).

Catalano et al. identified a positive correlation between maternal and neonatal IR. In their study mpp BMI was positively correlated with the offspring's IR. With increasing mpp BMI, the offspring's IR rose as well (55). Offspring born to obese mothers were more insulin resistant than those born to lean mothers and even had a higher IR at birth (11,46,55). This supports the suggestion that the fetus might secrete more insulin in early development (55). The offspring's susceptibility to develop IR was also higher in their 20s when born to obese mothers (11).

Fetal circulating cytokines, e.g. umbilical cord IL-6/leptin/TNF-α, were not associated with IR (55).

IR leads to the development of T2DM (11), which is a non-communicable disease. Because of rapid increase of obese individuals with a fatty phenotype, not only genetics but also environmental and epigenetic factors are thought to influence its development (54). HbA_{1c} is a marker for chronic hyperglycemia and is especially important for diagnosing and managing T2DM (37). This association is reflected by the relation between birthweight and the prevalence of T2DM identified in two meta-analyses that revealed inverse (53) as well as U-shaped (10,53) relationships (53).

3.5 Respiratory, atopic outcomes and autoimmune diseases

3.5.1 General information

The prevalence of early-onset inflammatory non-communicable/allergic/respiratory diseases such as asthma and allergy is rising (13,60-62), especially since the 1970s (63). For example, asthma is one of most common chronic diseases in children. In 2004, asthma caused costs of more than 3000 million € for the European Union (63). Maternal obesity affects the offspring's respiratory system (61) and risk at asthma, allergic and immune diseases (13) and is not only found in children but also in adults (64). Thus, offspring of obese mothers are hospitalized more often, have more doctor visits, school absences, child disabilities (62) and activity limitations (63).

3.5.1.1 Causes

The mechanisms underlying the association between maternal obesity and respiratory diseases are still unknown (65). Finding these mechanisms is difficult because maternal social and behavioral characteristics, such as age, income and smoking, may be linked to maternal obesity and adverse respiratory outcomes in the offspring (61). Evidence has shown that genetics (63), environmental factors (63), modes and time of delivery (61), low birthweight (61), gestational hypertensive disorders (62,65), maternal history of asthma (62) and maternal smoking (62) are involved. For example, C-sections in obese women are associated with a higher risk of wheezing in their offspring (61) and a familial history of atopy influences the development of asthma (64). Even the child's growth and infectious and atopic mechanisms might play a role. However, even after adjusting for these variables, there remains an effect of maternal obesity (65).

3.5.1.2 Inflammation

Early-onset inflammatory non-communicable diseases might be a consequence of obesity-related inflammation. The pathways leading to adverse outcomes are multifactorial (13). In obese individuals a low-grade chronic inflammation and an increase in leptin and adiponectin can be found. Leptin is pro-inflammatory, has been linked to current/atopic/non-atopic asthma, might elevate the individual's airway responsiveness causing an exacerbation of asthma. Adiponectin is anti-inflammatory, reduces allergic airway inflammation and hyperresponsiveness (60) and modulates the immune process (61).

In obese, pregnant women inflammatory mediators (61), high levels of estrogen and insulin (62) and even non-atopic mechanisms (64) affect the intrauterine environment and fetal development (61). These intrauterine and fetal alterations might occur due to these inflammatory factors or impaired placental function (61), but none of the mentioned mechanisms have been identified for sure (62).

3.5.1.3 Microbiome

One of the risk factors for developing asthma and allergies might be a decrease in microbial diversity, especially intestinal dysbiosis. In recent years, the important role of the microbiological ecosystems in obese individuals has been identified (13). The microbiome, which is composed of different bacterial populations, might be involved in modulation of weight gain and altered metabolism and thus, might promote obesity (14).

An aberrant gut microbiome is also related to maternal obesity and especially mpp weight and GWG affect the microbial composition (13). During pregnancy the mother's bacterial load increases and microbial diversity changes. For instance, in the course of pregnancy *Proteobacteria* and *Actinobacteria* increase. This intestinal dysbiosis is most pronounced during the third trimester. At the same time, a rise in pro-inflammatory cytokines in the stool occurs (14).

Additionally, maternal intestinal permeability changes in pregnancy because of alterations in the intestinal barrier functions. Studies have shown that microbiome is present in the intrauterine environment and within intrauterine tissues, e.g. umbilical cord blood and meconium. It is not fully understood how bacteria are translocated into the fetal compartment, but maternal immune cells, such as dendritic cells, and an alteration in maternal intestinal permeability might be involved (14).

If pregnant mothers take probiotics, the fetal gut also becomes colonized by these bacteria (14). Evidence in human studies has shown that in pregnancy, a diet including probiotic fiber has beneficial effects for the maternal microbiome. In different animal studies, it was shown that dietary fiber was metabolized by microbial fermentation into short-chain fatty acid (SCFA) metabolites, which prevent allergic asthma development. Offspring of women, who were given high concentrations of SCFA during pregnancy, had fewer doctor visits for coughs and wheezing (13).

The decrease in the offspring's microbial diversity begins *in utero* (13). An altered maternal microbiome leads to developmental changes in the fetal intestinal tract, especially the gastrointestinal tract, increasing the offspring's susceptibility to life-long disease and altered gut function (14). Therefore the offspring's immune and metabolic system might be altered as well (13).

3.5.1.4 Lung development in offspring of obese mothers

The fetal immune and respiratory system are susceptible to a compromised intrauterine milieu, which is created by maternal obesity (61). The pulmonary development, which occurs *in utero* and during childhood (60), might be affected by mpp obesity leading to smaller airways, impaired lung function and childhood asthma (65). Leptin receptors are expressed in lung tissue (60,65) and are involved in regulating lung growth (61) and fetal lung development (65). Thus, leptin might be associated with respiratory diseases (60,65) [Figure 18].

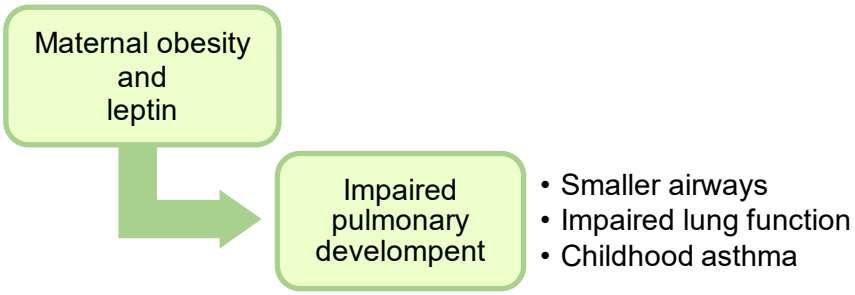

Figure 18. Effect of maternal obesity on fetal pulmonary development.

The immune system develops *in utero* and in early childhood (60). High levels of leptin and pro-inflammatory cytokines may affect immune system development. The rise in pro-inflammatory cytokines might also increase the offspring's susceptibility to an adverse development of the fetal immune system and risk of infectious and atopic diseases after birth (65). Leptin and adiponectin might lead to reduced immunologic tolerance to antigens (60), which leads to asthma in the offspring (64). If systemic immune dysregulation and tissue-specific effects occur during susceptible periods in development, these may cause allergic diseases (13).

Offspring born LGA (64) and especially child obesity influence the offspring's susceptibility to asthma, wheezing (60), atopic sensitization, elevated serum immunoglobulin E (IgE) and atopic dermatitis (64).

3.5.2 Adverse outcomes in the offspring

3.5.2.1 Asthma and wheezing

Maternal obesity is independently linked to asthma (60,64,65), wheezing (60,65), airway reactivity in the offspring (64) and LGA born offspring (64). Wheezing during childhood can lead to persistent wheezing and may even cause asthma (61) [Table 3].

Table 3. List of studies demonstrating the influence of maternal obesity on offspring's risk at asthma and wheezing.

Influence of maternal obesity on offspring's risk at asthma			
Kind of asthma	**Offspring's age**	**Maternal BMI (kg/m^2)**	**Details**
ever asthma	meta-analysis		• OR 1.31 (1,13)
	three years	≥ 30	• OR 1.52 • adjusted: OR 1.34 (62)
	first 7 years of life	30 ≤ BMI < 35	• OR 1.54 (60)
		≥ 35	• OR 1.52 (60)
	8-10 years	high maternal BMI	• higher risk (11)
	15-16 years		• 3.0% per kg/m^2 (63)
current asthma	meta-analysis		• OR 1.21 (1,13)
	15-16 years		• 2.9% per kg/m^2 (63)
Influence of maternal obesity on offspring's risk at wheezing			
Kind of wheezing	**Offspring's age**	**Maternal BMI (kg/m^2)**	**Details**
ever wheeze	meta-analysis		• OR 1.31 (1,13)
	6-18 months	≥ 30	• increased risk of 3.3 percentage points (61)
	15-16 years	≥ 30	• OR 1.07 • prevalence of asthma: 2.7% per kg/m^2 (63)

		high mpp weight	• OR 1.22 (63)
preschool	one year	≥ 30	• OR ≈ 0.85 (65)
	two years	≥ 30	• OR ≈ 1.25 (65)
	three years	≥ 30	• OR ≈ 1.4 (65)
	4 years	≥ 30	• OR ≈ 1.45 (65)
current	meta-analysis		• OR 1.21 (1,13)
	15-16 years	≥ 30	• OR 1.52 • prevalence of asthma: 3.5% per kg/m^2 (63)
		high mpp weight	• OR 1.52 (63)
recurrent (> 4 episodes)	6 months to 6 years	≥ 30	• OR 3.51 (64)
	over two years	≥ 30	• OR 3.44 (64)
early transient	first 7 years of life	30 ≤ BMI < 35	• OR 1.29 (60)
		≥ 35	• OR 1.33 (60)
persistent	first 7 years of life	30 ≤ BMI < 35	• OR 1.62 (60)
		≥ 35	• OR 1.44 (60)
late-onset	first 7 years of life	30 ≤ BMI < 35	• OR 1.48 (60)
		≥ 35	• OR 1.87 (60)

In a study within the Danish National Birth Cohort, Harpsøe et al. revealed that maternal obesity associates with asthma and wheezing. The link was strongest for current asthma in 7 year old offspring. After stratifying them in two groups (offspring with/without atopic eczema or hay fever), the odds given above were always higher in groups without atopic eczema of hay fever (offspring with a combination of early transient wheezing and atopic eczema/hay fever: OR 1.15; offspring without the combination of early transient wheezing and atopic eczema/hay fever: OR 1.41) (60). This study also found a stronger link between obese, non-atopic children and doctor-diagnosed current asthma than between obese, atopic children (60). In general, obesity increases the risk of airway hyperresponsiveness (61). Kumar et al. showed that the significance of associations did not change after adding two more markers in the offspring (cord-blood IgE levels

and eczema). However, when the child's BMI was also added, the effect of maternal obesity on recurrent wheezing was reduced (64).

3.5.2.2 Further outcomes

Maternal BMI was not associated with an offspring's higher risk for current/previous/early transient/persistent/late-onset atopic eczema and atopic eczema ever (OR 0.98 (64)) (13,64), sensitization (mainly to aeroallergens) (13), hay fever (13,60) and food allergies (OR 0.93) (64).

Håberg et al. revealed that the number of offspring with lower respiratory tract infections (LRTI) increases with a higher maternal BMI. After adjusting for background variables and obstetric problems, the association was no longer present. Episodes of LRTIs during childhood can lead to wheezing and asthma in the offspring's later life (61).

Kumar et al. showed that maternal obesity was negatively linked to the log of cord blood IgE (64).

3.6 Neurological disorders and changes

3.6.1 General information

Concomitantly to obesity the prevalence of neurological disorders also increased in the last years. Maternal obesity is considered to be involved in the development of these diseases, as it is a risk factor for neurodevelopmental disorders, such as autism spectrum disorders (ASD) (66).

3.6.1.1 Causes and mechanisms

A correct brain development is required to allow unrestricted and life-long performances of functions, such as cognitive, language and motor functions. Especially as a fetus and during early life, influencing factors determine these performances. The last trimester is the most important period for brain development because during this time neuronal determination, synaptogenesis and dendritic arborization occur (67).

Besides maternal obesity, other factors such as maternal stress (68), an improvement of diagnostic tools (66), increasing awareness (66), maternal behavior (68), genetics (69), lifestyle (69), environmental factors (69), maternal intelligence (13), maternal mental health (13), socioeconomic factors (13,67) and postnatal influences (13) contribute to determine neurodevelopmental performance (66). For instance, it is postulated that maternal stress might influence the placental environment, the offspring's epigenetics and thus, behavior (68).

Maternal obesity is accompanied by changes such as inflammation, hyperlipidemia, lipotoxicity, hyperglycemia and IR (68). Due to these changes, the offspring's brain development (70) and programming of neural circuits (68) is negatively affected [Figure 19]. The offspring's behavior is altered and the overall susceptibility to disorders, such as attention deficit hyperactivity disorder (ADHD) and anxiety, is increased (68).

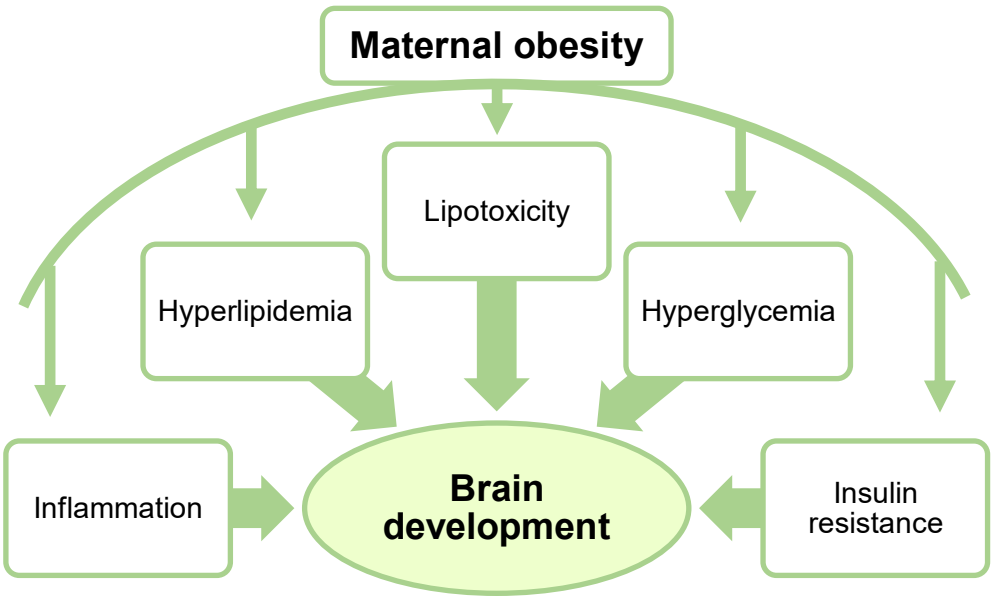

Figure 19. Influence of changes related to maternal obesity on offspring's brain development.

Maternal obesity can affect the offspring's behavior directly, by altered intrauterine programming and indirectly, by an altered maternal behavior (68). The inflammatory milieu found in obese women was postulated to influence fetal neurodevelopmental processes by under- or overactivating them. Such affected

processes may include neuron proliferation/differentiation, myelination and synapse formation (70) [Figure 20]. Due to the inflammatory state in obese individuals, certain mediators (CRP, IL-6, TNFα) and (pro-) inflammatory cytokines are increased. A link between increased inflammatory markers and neurodevelopmental disorders, such as ASD, ADHD, and neuropsychiatric disorders, such as depression, was shown (66). Factors, such as nutrients (FFA, glucose) (66,70) and hormones (leptin, insulin) (66,68,70), are also increased and involved in the development of adverse neuropsychiatric disorders (66).

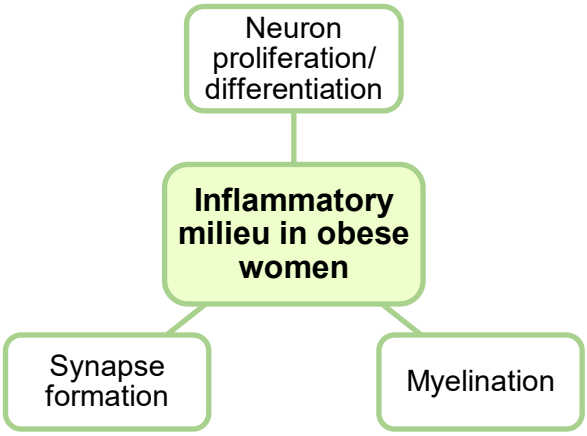

Figure 20. Influence of maternal inflammatory milieu on fetal neuronal development.

Leptin secretion is regulated by body fat (68). Leptin receptors are expressed in the entire brain, especially in regions involved in the regulation of behavior, e.g. cortex, hippocampus and amygdala (66) and in wiring of brain regions, such as the hypothalamus (68). Throughout pregnancy, circulating leptin levels do not rise until almost all neural circuits in the hypothalamus are built. In obese women, leptin levels are elevated and thus, may influence brain circuitry involved in behavior regulation and physiology. For instance, hyperleptinemia is present in children with ASD (68).

Obese women display an increase in inflammatory cytokines and maternal obesity causes a placental inflammatory response. Placental dysfunction in maternal obesity is associated with high leptin and inflammatory cytokine levels and is relevant for ASD development (68).

The developing fetal brain experiences inflammation, which leads to an impaired development of neural circuits, e.g. the serotoninergic (5-HT), dopaminergic (DA) and melanocortinergic system (66). Neurotransmitters such as serotonin and dopamine might also be affected by maternal high-fat consumption. The development of these signaling pathways is directly influenced by high levels of cytokines, hormones and nutrients. Especially, the serotoninergic, dopaminergic and melanocortinergic systems, which are important for behavioral regulation, are affected and all three are sensitive to cytokine levels (68). In general, serotonin is important for neural development, e.g. synapse formation, neurogenesis and neural migration. Moreover, it plays a role in emotional regulation (66). If the 5-HT system is affected and dysregulated, the offspring's risk at mental health disorders increases (66,70). Thus, it is hypothesized that increased inflammatory cytokines suppress the development of the 5-HT system leading to impaired serotoninergic function. If serotonin is reduced, certain disorders, such as ADHD and anxiety, can arise (66). The rewarding signaling pathway is altered as well. Due to an elevation of inflammatory cytokines, the development of the DA neural circuit is suppressed, leading to a higher risk for offspring for show reward-related behaviors (66).

Glucocorticoids are involved in fetal growth, brain development and organ maturation. By binding to their receptors, which are expressed in fetal and placental tissues, they act as transcription factors and increase expression of their target genes. Glucocorticoids are involved in the development of the hypothalamic-pituitary-adrenal axis and affective behavior (18).

Also maternal age plays a role in the neurodevelopment. Higher maternal age is linked to increased maternal weight and higher susceptibility for offspring to be diagnosed with neurodevelopmental disorders, such as ASD (66).

If the mother's eating habits are additionally adverse, the offspring's relationship with eating and food is altered, leading to eating disorders, such as anorexia nervosa (66).

An accumulation of environmental insults to the CNS might therefore be another mechanism associating maternal obesity to disorders (69).

3.6.2 Disorders and changes

3.6.2.1 Cognitive Impairments

Cognitive impairments may result from various other disorders, but cognitive impairments themselves are associated with maternal obesity (13,66). In these regards, not only intelligence but also executive function might be affected by maternal obesity. Executive function is required for planning, organization, adjustment and self-regulation to achieve goal-directed action/behavior. It is the human's coordinating system, but its definition and measurement are difficult. A model has been conducted using three parameters: inhibition (suppressing responses), shifting (flexibly moving between tasks) and updating (monitoring of mental content). Using this mode, an interrelation between intelligence and executive function has been identified. However, genetics might still have a higher impact on intelligence and executive function than maternal obesity (70).

Offspring born to obese mothers experience decreased cognitive, language, mathematical and reading scores. They were also affected by mild intellectual disabilities (66). One study found a decrease in language scores in 8 year old offspring (66) and delayed language skills in general (1,66).

Torres-Espinola et al. revealed that 6 month old offspring born to obese women had higher language, cognition and expressive language scores (13,67). However, at the 18 month follow-up no significant differences were present when analyzing continuous variables, except lower gross motor scores. Since this is the first study showing higher scores at 6 months, these changes need to be validated. These scores are probably just temporary representing a short-term effect. The results postulate that offspring might have poorer neurodevelopmental abilities if the increase at 6 months arises. This theory is supported by results of this study because a high composite language score at 6 months shows a correlation with the low gross motor score at 18 months (67).

Maternal obesity was also associated with a lower cognitive performance during infancy (70), a lower general intelligence in 3-4 year old offspring (70) and a reduction in intelligence quotient (IQ) in a low socioeconomic African American population (66,67). In fact, there is an U-shaped association between mpp BMI and the offspring's IQ in childhood (67). Pugh et al. identified a relationship between mpp

BMI and the 10 year old offspring's IQ or executive function only after adjustment for different confounders (e.g. maternal race, fetal gender and income). The intelligence decreased with a maternal BMI higher than 22 kg/m^2. A nonlinear relationship was found between mpp BMI and the IQ at the age of 10. The offspring's IQ decreased by a few points with an increasing mother's BMI (maternal BMI 24 kg/m^2: -0.5 points; 30 kg/m^2: -2.1 points; 32 kg/m^2: -2.5 points; 34 kg/m^2: -3.2 points). A reduction by 2-3 points is still modest, but it is postulated that offspring of severely obese women might have a more drastic decrease. An increase in executive function perseverative errors indicating a lower executive function was not found. However, the offspring's executive function time-to-complete was longer in offspring born to obese mothers (maternal BMI 24 kg/m^2: +2.0 seconds (s); 30 kg/m^2: +8.1s; 32 kg/m^2: +10.1s; 34 kg/m^2: +12.7s). The executive function results suggest an association between a higher mpp BMI and the updating dimension (monitoring of mental content). Another study found offspring born to obese mothers had lower inhibition performance (suppressing responses) (70).

However, another study revealed no association between maternal obesity and impaired cognition, but a decrease in language scores. These different associations might occur due to demographic factors, obesity prevalence in study populations and different measures and scales (66).

3.6.2.2 Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is a neurodevelopmental disorder and its prevalence is increasing. Individuals with ADHD are also more susceptible to other behavioral disorders and male individuals are more likely to be affected. The diagnosis is usually given in childhood or adolescence. The affected persons are very active, cognitively impaired, impulsive and have memory and focus problems. All these problems ultimately affect the everyday life. They have troubles with peers, experience academic difficulties, complications with substance abuse, unintentional injuries and criminality (66).

It was shown that obese mothers have a two-fold increased risk (46,66), a hazard ratio of 1.64 (1) and a higher risk in general (1,66) of having an offspring with ADHD. Additionally, offspring born to obese mothers were affected more severely when considering teacher-rated ADHD symptoms (1,66), which are, for example,

inattention (11) and having difficulties dealing with emotions (11,46). However, results were often inconsistent and even disappeared after adjusting in full-sibling comparisons (13).

3.6.2.3 Autism Spectrum Disorders (ASD)

ASD are neurodevelopmental disorders, which include a range of conditions. The prevalence has risen about 30% over the last few years and males are 5-times more likely to be affected than females. ASD conditions are characterized by dysfunctional social skills and restricted/repetitive interests and activities. Cognitive impairment is often a typical trait. However, not all of them are affected negatively. Some are cognitively gifted whilst others are challenged. These disorders are often emotionally and economically challenging for families. It is important to diagnose the affected early to provide an ideal treatment, allow an early intervention and reduce the overall lifetime costs (66).

Offspring born to obese mothers are 67% more likely to be diagnosed with ASD (11), have a higher risk to be diagnosed with ASD at two years old (1), as toddlers (1,66) and as children (13,66).

3.6.2.4 Anxiety and Depression

Maternal obesity makes offspring more susceptible to neuropsychiatric disorders, such as anxiety and depression. The prevalence is also rising and it was shown that these disorders are more likely to appear in women. Anxiety can be described as persistent worry and fear, which interrupt their daily lives. On the other hand, depression is associated with dysphoria. These mood disorders come with daily complications, which impair the individual's life. Social interactions of affected persons are of poor quality, relationships are strained and their self-worth is low (66).

High mpp BMI has been associated with an increased risk of disrupted emotions, for example fear and sadness (66,68), anger (68), depression and withdrawal (66). Obese women are more susceptible to give birth to high/low birthweight offspring, who are at a higher risk to be diagnosed with depression and anxiety as adolescents (66).

3.6.2.5 Schizophrenia

Schizophrenia is a disabling condition with hallucinations, delusions, disorganized speech, flat affect and impaired cognition. Its prevalence is rising. Studies have already shown a link between schizophrenia and maternal obesity (66).

The offspring's risk to develop schizophrenia increases about 24% for every maternal BMI unit during early pregnancy. Studies have shown a two-fold and a three-fold increased risk of obese mothers having offspring with schizophrenia. However, after adjusting for social class, gender and age of the mother the latter links were no longer given (66).

3.6.2.6 Anorexia and Bulimia Nervosa

Eating disorders are very common in children and adolescents, but females are more affected. Shockingly these disorders have the highest mortality amongst all neuropsychiatric disorders. Anorexia and bulimia nervosa are two of them. When individuals suffer from anorexia, they restrict themselves from food intake, have low body weight and an overall fear of gaining weight. Bulimia nervosa is characterized by recurring episodes of binge eating followed by behaviors to reduce the weight gain (66).

One study has shown that postnatal maternal obesity predicts the offspring's start of secretive/inhibited eating during the first 5 years. Offspring of mothers who suffered from binge eating had a seven-fold increased risk of becoming a binge or night eater (66).

3.6.2.7 Neural anomalies

Maternal obesity is associated with neural anomalies (18), such as neural tube defects (14,17,42,69), spina bifida (13) and hydrocephaly (42). A meta-analysis further highlighted that the OR for offspring with neural tube defects who were born to obese mothers is higher than in normal weight mothers (obese mothers: OR 1.70; severely obese mothers: OR 3.11) (1,10). There was also an increased risk for spina bifida (OR 2.24) and anencephaly (OR 1.39). These defects were associated with lower folate levels, which can be found in obese women. However, a further study found no association between low folate levels in obesity and these defects and

another study revealed that folate supplementation reduced the increased risk in obese mothers (1).

3.6.2.8 Epilepsy

Epilepsy is a neurological disorder, which is very common in children. About 50 million individuals are affected worldwide. Certain factors are more associated with childhood epilepsy, such as preterm birth, low birthweight for gestational age, anomalies and malformations of the CNS and neonatal convulsions/hypoglycemia/jaundice. However, the causes are not well understood and in about 60% of patients, no cause can be identified. If the offspring's mother was diagnosed with epilepsy, the offspring's risk at epilepsy is increased by four-fold (69).

A study by Razaz et al. found that the adjusted rates for offspring epilepsy increased with an increasing mpp BMI (normal weight mothers: 6.30/10000 child-years; extremely obese mothers: 12.4/10000 child-years). Offspring born to obese mothers had different increased rates of being diagnosed with epilepsy depending on their mother's BMI (obese women: 20%; severely obese: 30%; extremely obese: 82%). However, these rates could not be explained by obesity-related pregnancy or neonatal complications (69).

3.7 Interventions

3.7.1 General information

The obesity prevalence is rising (71). In pregnancy, women are more likely to change their lifestyle because their child is also affected (23).

Obesity affects the reproductive health and puts the mother at risk for pregnancy complications e.g. C-sections, postpartum weight retention and preeclampsia. Insulin sensitivity changes during pregnancy and IR increases. IR further increases, which predisposes the mother to develop GDM (71). Mpp weight reduction (4.5 kg) was linked to a lower chance of being diagnosed with GDM (72).

Because GWG affects all this as well, the US Institute of Medicine suggests that obese women should only gain about 5-9 kg during pregnancy (71).

Due to the antenatal and *in utero* exposure to an adverse environment, offspring born to obese mothers are at a higher risk for being born LGA and for obesity in general. Mpp BMI independently predicts the risk for delivering a LGA offspring (71). Interventional studies in obese mothers were found to be beneficial to the offspring's outcomes in later life (73).

3.7.2 Interventional options

Different interventional options are possible, e.g. diet, physical activity, behavioral modification, medications (74) and bariatric surgery (75). Bariatric surgery focuses on weight loss before conception (75) whilst other interventional studies concentrate on reducing and at least limiting GWG (71) [Figure 21].

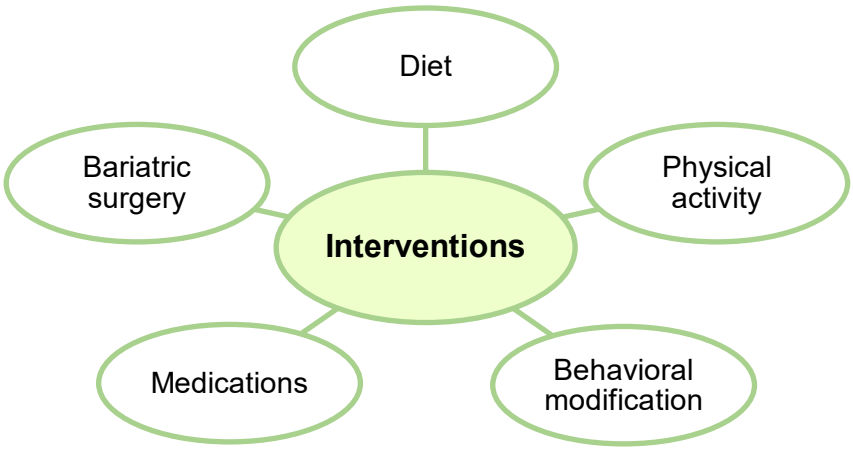

Figure 21. Interventional options to prevent adverse effects of maternal obesity on the offspring.

Due to these interventions, it could be possible to alter the offspring's programming, and thus, reduce the obesity risk. Different maternal targets have been postulated, which influence the offspring's obesity and later life disease. It is important to target behaviors, which lead to an altered maternal nutrition and reduce fetal overgrowth (76).

However, assessing the effects of antenatal interventions is difficult. The most accessible measurement is birthweight. It reflects the effects of intrauterine environment on the fetus (76).

Health professionals are advised to educate their patients, if possible before conception, about the risks of obesity and especially their importance during pregnancy (72). However, communication is often described as stressful, confusing and judgmental by women (5). There are no general guidelines, which could help health professionals guide their patients through weight loss. It is usually recommended to combine dietary modifications and physical activity (72).

The timing of interventions is important. During the periconceptional and early developmental period the fetus does not require a large amount of nutrients (16). Thus, this seems to be the best period for losing weight (1). However, it is important to find out how energy restrictions during these periods affect the offspring (72). In obese and pregnant women decreased insulin sensitivity and obesity are already present before and during early gestation. Thus, lifestyle interventions during the second trimester are less likely to show positive effects on maternal metabolism or metabolic conditions during pregnancy (74). However, due to feeling uncomfortable and a lack of energy, it is difficult for pregnant women to exercise (77). The interventional time period is short and with advancing gestation physical activity becomes more challenging. Furthermore, maternal conditions during pregnancy can be less modified because of physical adjustment during pregnancy (74).

3.7.2.1 Diet and physical activity

3.7.2.1.1 General information

Diet and physical activity changes are the first line treatment for obese women in pregnancy (78). Targets are, for example, a low glycemic index, the intake of probiotics during pregnancy and a change in nutritional habits. A change in diet seems to avoid excessive GWG, even more than physical exercise does (74). Different aspects might also be affected by diet changes, e.g. the microbiome (14), insulin response and β-cell failure (75). If high fiber and complex carbohydrate/low glycemic index diets are consumed, the successive insulin response can be reduced and therefore, β-cell failure might be decreased. However, this theory is still very

controversial (75). A so-called “Western diet” is consumed in developed countries meaning that the diet consists of higher amounts of omega-6 polyunsaturated fatty acids (ω-6 PUFA). PUFAs are immunomodulatory, alter regulation of (pro- and anti-) inflammatory cells and affect transcriptional regulation. ω-6 PUFA are more pro-inflammatory and immunoactive and ω-3 PUFAs are anti-inflammatory and associated with brain function. A low ω-3 PUFA intake is associated with obesity, inflammation, CVD and cancer (12).

Mother and offspring benefit from antenatal exercise because it limits GWG. However, the effects on the offspring are inconsistent (76). Physical exercise, such as walking and swimming, increases the non-insulin-mediated glucose use by muscles and thus, prevents GDM (75). Woman in early pregnancy should do about 30 minutes of exercise daily at moderate intensity (1).

3.7.2.1.2 Effects on offspring

A study focused on the effect of low glycemic diet on birthweight. Authors revealed a decrease in maternal GWG (12.2 kg vs. 13.7 kg), but there was no effect on birthweight, birthweight percentile, ponderal index (kg/m^3 (31)) or macrosomia (74).

It was hypothesized that supplementing ω-3 PUFA and vitamins (e.g. vitamin D) might improve adverse consequences (57). An increase in ω-3 PUFA intake might lead to a rise in anti-inflammatory effects. However, studies on humans have been difficult to conduct due to several factors, such as dosage, duration, dietary and lifestyle habits (12). Diets with high dosages of ω-3 PUFA also improve neural function and protect the brain from inflammation. This might improve the 5-HT signaling pathway and thus, reduce the risk of mental health disorders, such as ADHD and ASD because lower levels are associated with these disorders (66).

Resistance exercise during the second or third trimester affects birthweight. Continuing moderate- or vigorously-intense exercise during pregnancy also decreases birthweight and subcutaneous fat mass of neonates. The reduction of these two factors was found to be beneficial for the offspring until the age of 5 (76). The Treatment of Obese Pregnant Women-Study (TOP-Study) showed a little decrease in GWG (1.38 kg) but again no effect on birthweight or LGA status when assigning women to physical activity (74).

Combining diet and physical activity is more beneficial to mother and offspring (75). However, independent of combination of these two methods, evidence was not always consistent considering the obese women's glucose tolerance improvement. The maternal GWG and the risk to develop GDM were, in fact, reduced, but the birthweight did not change (71).

A Danish study showed that a combination of dietary guidance and a free membership in a fitness center including personal coaching reduced GWG (7.0 kg vs. 8.6 kg), but birthweight was even higher (3742 g vs. 3593 g) when compared to the control group (74).

In another study one group of obese and pregnant women participated in a dietary and lifestyle intervention. LGA born neonates occur in the intervention and the control groups (19% vs. 21%), but fewer macrosomic neonates were born in the intervention group (15% vs. 19%) (74).

The Lifestyle in Pregnancy and Offspring-Study (LiPO-Study) by Tanvig et al. compared a lifestyle intervention group of obese pregnant women to a control group of obese pregnant women and an external reference group (normal weight pregnant women). The lifestyle intervention included dietary counseling and physical activity. At the follow-up, when offspring were at a mean of 2.8 years, no statistical significant differences in median BMI z-score, AC, fasting plasma glucose/insulin/HDL/triglycerides, SBP, DBP and no higher metabolic risk factors were found in the intervention and control group. Offspring born to normal weight mothers were less likely to have an AC above the 90th percentile (3.1%; intervention group: 16.9%; control group: 6.9%). Birthweight and AC at birth (BAC) z-scores were associated with BMI z-score, AC, fasting plasma glucose/insulin/triglycerides. These links show that size at birth, in fact, predicts the offspring's metabolic risk. After adjustment for confounders, such as gender, mpp BMI and maternal age, the association was even stronger and a link between birthweight z-score and SBP was found (73).

3.7.2.2 Bariatric surgery

3.7.2.2.1 General information

Bariatric surgery is an effective way for obese women to lose weight before conception. The surgery reduces maternal and offspring's risks for certain medical, obstetric and later life problems (75). It ensures weight loss, improves fertility, obesity-related comorbidities (78), maternal insulin sensitivity and the offspring's lipid profile (72) [Figure 22]. Bariatric surgery is most successful in women with high BMIs (78). These women can only undergo this intervention after passing certain requirements, such as a BMI greater than 40 kg/m^2 or a BMI greater than 35 kg/m^2 with comorbidities (75,78).

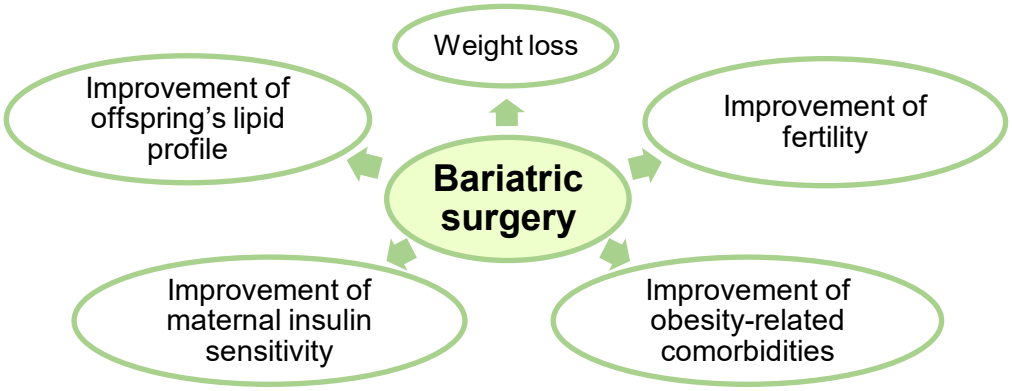

Figure 22. Positive effects of bariatric surgery.

Different procedures of bariatric surgery exist, such as malabsorptive (Roux-en-y gastric bypass which bypasses a part of the small intestine (78)) and restrictive procedures (adjustable gastric banding which limits the ingested amount of food (78)) (75). Both types were associated with a higher complication rate in pregnancy, for example an increase in premature rupture of membranes (OR 1.4), labor induction (OR 2.1), macrosomia (OR 2.1) and C-section (25.2% vs. 12.2%). Malabsorptive procedures are accompanied by a few complications during pregnancy, such as small bowel ischemia and nutrient deficiencies. Restrictive procedures, e.g. laparoscopic adjustable gastric banding, are becoming more common, but they are still accompanied by complications such as gastric ulcer

perforation, intragastric band migration and gastrointestinal hemorrhage. Especially latter one was found to reduce GWG and diseases like GDM (75).

Women, who underwent laparoscopic gastric banding surgery, are more likely to become pregnant unexpectedly afterwards and therefore, are advised to use appropriate contraceptive methods (75). However, oral contraceptives might not be as effective after surgery because of reduced absorption (78). They are also advised to postpone pregnancy for about 12-18 months after surgery (75,78). This time period is needed to maximize weight loss (72). Monitoring these women during pregnancy is important (78). For instance, nausea and vomiting can be reduced by adjusting the gastric bands (75).

Due to the nutrient deficiencies, which might be a consequence of bariatric surgery, folate, calcium, vitamin B12 (75), vitamin D and iron should be supplemented. After malabsorptive types of surgeries, it is important to detect even subclinical nutritional deficiencies (78).

3.7.2.2.2 Effects on offspring

Offspring of obese women, who underwent bariatric surgery, had a lower risk to develop obesity (16,28). Moreover, their birthweight (28,46), the number of macrosomic offspring, CRP and leptin was reduced. Their insulin sensitivity and lipid profile improved and their ghrelin levels increased (28). In general, more SGA than LGA babies are born which might occur due to nutritional deprivation, but these findings were not statistically significant (78). Comparing those offspring to siblings born before surgery, Smith et al. also revealed a reduced birthweight and an improved cardio-metabolic parameters (10,46). Furthermore, BMI z-score, plasma HDL/insulin/fasting blood glucose and IR were reduced (10). The prevalence of normal weight 7 year old offspring was higher (57%) than before surgery (36%) (10).

3.7.2.3 Medications

Different medications help weight management, such as anorexiants (e.g. phentermine), orlistat, metformin (74) and thiazolidinedione (75) [Figure 23]. They impact weight loss in different ways, e.g. phentermine alters the release and reuptake of appetite-impacting neurotransmitters and orlistat reduces the intestinal fat absorption (74). Metformin decreases hepatic glucose production (74), and just

as thiazolidinedione, it is an insulin sensitizer and increases insulin sensitivity. However, metformin and thiazolidinedione are able to cross the placenta (75). In general, all the mentioned medications are not indicated in pregnancies due to safety reasons and side effects (74).

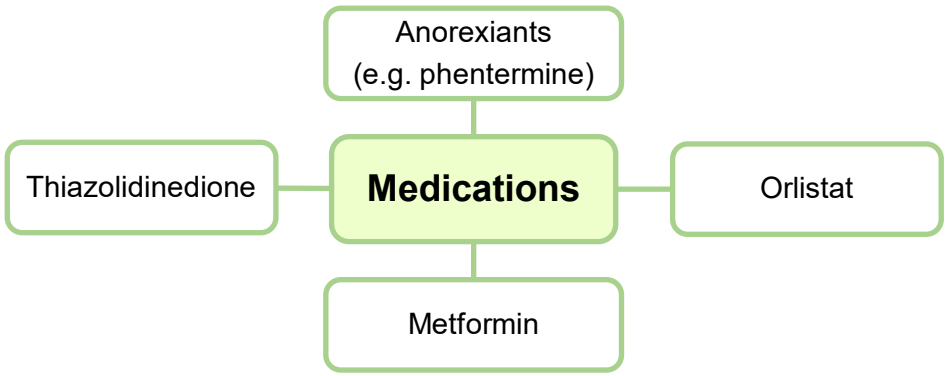

Figure 23. Available medications for weight management.

3.7.2.4 Reasons for limited success

Often, interventional studies do not show any effects on the adverse effect of maternal obesity on the offspring outcomes. The timing of the intervention is a major contributor. The pre- and periconceptional period are most important for offspring programming. Studies also suggested an association between GWG during the first trimester and the offspring's risk at obesity (73). The timing of antenatal exercise is also important and evidence has shown more effects, if exercise is performed during the second half of pregnancy (76). Other reasons are only little differences in GWG (73), the lack of evidence and poor participant compliance (71).

4 Discussion

Obesity is a major public health issue and a global epidemic and is not only present in developed but also in developing countries (5). Its prevalence is increasing in people of all ages (4) and so are the consequences of being obese (1). After reviewing current literature and investigating effects of maternal obesity on the offspring, it emerged that maternal obesity influences the offspring's later life.

Offspring born to obese mothers are more likely to be obese (7). In general, mpp BMI predicts the offspring's BMI (39) and is also the strongest predictor for a high BMI in the offspring's childhood (18).

CVD and obesity highly impact adult morbidity and mortality (42). The etiology of cardio-metabolic disease is still unclear, but genetics and lifestyle as role players are indicated (44). An adverse maternal fat distribution and metabolic profile might have long lasting effects on the cardio-metabolic development of the fetus (42). Due to the resulting adverse intrauterine development, cardio-metabolic disorders, such as hypertension, arise (43). One reason for the development of hypertension is microvasculature dysfunction (44). Additionally, the offspring's risk for cardiovascular morbidity and mortality is also to some extent determined by maternal obesity (13). The offspring is at increased risk for cardiovascular events (51) and premature death (42,45,50).

Another major public health problem is T2DM (42), which is an important comorbidity of obesity. Insulin sensitivity is reduced in offspring, who were born to obese mothers (54). Furthermore, offspring are at a higher risk for IR (54,59) and thus, promoting the development of T2DM (9).

Maternal obesity also affects the offspring's respiratory system (61) and risk at asthma, allergic and immune diseases (13) during childhood and adulthood (64). The mechanisms underlying this association are still unknown (65). However, after adjusting for different variables, e.g. genetics and environmental factors (63), maternal obesity influences later life respiratory diseases (65).

Early intra- and extrauterine development determines neurological disorders (66), such as cognitive, language and motor functions (67). Neuronal determination, synaptogenesis and dendritic arborization occur during the last trimester (67). Mainly cognitive impairments are associated with maternal obesity (13,66), such as intelligence and executive function (70). Other neurological disorders, such as

ADHD, anxiety and depression, might also be influenced by maternal obesity. Additionally neural anomalies, such as neural tube defects (14,17,42,69), spina bifida (13) and hydrocephaly (42), are linked to maternal obesity

Thus, different interventional options were discussed and investigated (76) to prevent such disorders. These include diet, physical activity, behavioral modification, medications (74) and bariatric surgery (75). The surgery focuses on weight loss before conception (75) whilst other interventional studies concentrate on reducing and at least limiting GWG (71). Assessing the interventions' success is difficult. The only intervention with definite success was bariatric surgery. Offspring born to women, who underwent bariatric surgery, had lower risk to become obese (16,28). When combining diet and physical activity, the benefit is more pronounced (75).

The purpose of this thesis was to review existing literature and summarize important studies, reviews and information. However, different limitations occurred while researching and writing this thesis. Searching PubMed with three different search terms (maternal obesity, offspring and long-term), almost no original studies but only reviews were found. Thus, additional to PubMed search, publications were further identified and picked from the reference lists of reviews and a few studies. Another interesting finding was made while writing the "Cardiovascular disease", "Pancreatic changes" and "Respiratory, atopic outcomes and autoimmune diseases" chapter. The studies found in reviews were mainly performed on animals and the whole topic lacked human data. Furthermore, many publications, which were found by PubMed research, additionally investigated the effect of maternal GDM and undernutrition, which were not topic of this thesis.

Different studies had different criteria for including or excluding subjects, investigated different time points and adjusted the results or not. The adjusting factors also differed. Moreover, many studies only used a low number of study participants.

Additionally, it is difficult to consider certain factors/habits, which occur before conception because women usually seek medical help/advice/service only after conception. For example, the given mpp BMI at the first visit might not be accurate and thus, bias the results.

Finally, pregnancy is a continuous, changing, individual process, and processes differ in each individual.

Obesity is a major health issue and a burden not only for the current but also for future generations. It is characterized by an excess of body fat, which negatively impacts the affected individual. Different lifestyles and eating habits influence the development of obesity (79), for instance the “Western diet” (80). However, the nutritional change does not only happen in the Western world. Developing countries are also part of “Westernization” (81).

The “Western diet” contains different macro- and micronutrients and is composed of saturated fats and simple carbohydrates (e.g. glucose and sucrose) (80). Low fiber and high fat intake are also two main parts. It is an obesogenic diet (81), which is characterized by a high availability and low cost of energy-dense, nutrient-poor foods and drinks. The energy intake rises immensely and causes obesity prevalence to increase (79). Additionally, nutrient-rich foods, e.g. vegetables and fruits, are less consumed (81) and energy expenditure and physical activity is decreased, e.g. due to motorized vehicles (79). In fact, it was noticed that the prevalence of certain diseases, such as asthma and allergy rises in developing countries because of “Westernization” (81).

Furthermore, obesity is linked to short sleep duration and also stress affects eating habits. Thus, stress is also a risk factor for developing obesity. Reducing stress reactivity is important to strive against the rising prevalence (79).

Obesity can only be decreased, if prevention starts early. Providing appropriate education is one part of it. Furthermore, physical activity and healthy food options should be discussed (79).

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