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„Interacting effects of maternal pre-pregnancy weight status and smoking during pregnancy on foetal development and the moderating effect of the new-born's sex"

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Abstract

Maternal pre-pregnancy weight status, smoking during pregnancy and male sex of the foetus are independent risk factors for adverse birth outcomes.

With obesity levels globally on the rise and the consistently high prevalence of smoking during pregnancy, this study aims to examine interacting effects of an unhealthy maternal weight status and smoking during pregnancy on foetal growth and the moderating effect of the new-born's sex.

This medical record-based retrospective study investigated a sample of 4141 singleton term-births from the years 1990 to 1995 which took place in Vienna, Austria. Independent and interacting effects were assessed by univariate and multivariate statistical methods.

Maternal underweight and smoking were associated with reduced foetal growth whereas maternal overweight/obesity associated with increased foetal growth. Male new-borns were heavier and bigger than females. Adjusted mean differences between smoking and non-smoking mothers declined for birthweight from 153.3g (p<0.001) in underweight mothers to 67.0g (p=0.622) in the obese group, for head circumference from 0.51 cm (p = 0.001) to 0.02 cm (p = 0.921) and for birth length from 1.04 cm (p<0.001) to 0.14 cm (p=0.622).

In males the negative effect of smoking was getting stronger with increasing maternal BMI for birth weight and birth length. However, for head circumference the trend was opposite. The higher vulnerability of males to the interacting effects of maternal smoking and unhealthy weight status can be interpreted according to the male disadvantage hypothesis.

Public health programs should target the identified risk groups of underweight and overweight/obese smoking mothers of male new-borns.

Introduction

An important window in human ontogeny is the intrauterine phase, in which foetal growth and development is influenced by a multitude of factors. Genetics is not only driving this development but also the environment plays an important role in shaping human intrauterine growth. Many lifestyle-related factors of the mother act on the development of the child during pregnancy. Factors such as, an unhealthy pre-pregnancy weight status, namely underweight or overweight/obesity, and cigarette smoking. However, overweight and obesity gained pandemic dimensions, and underweight still remains a threat in some regions of the world like sub-Sahara Africa and south Asia (NCD risk factor collaboration, 2016). Furthermore, despite the decline in smoking prevalence in the last decades, cigarette smoking during pregnancy remains as one of the most important preventable behaviours that depicts a high risk for the developing child (Reitsma et al., 2017). These factors are of great importance not only for the health of the mother, but above all, for the health of the child. Besides these environmental factors, intrinsic factors also influence the intrauterine development including the sex of the foetus. Therefore, it is important to investigate the relationships between these factors to not only gain more insight in the complex interactions of factors shaping human growth but also to identify high risk groups which than can be targeted by prevention measures in the periconceptional and perinatal phase. Thus, this thesis will deal with the question if and how maternal pre-pregnancy weight status, smoking during pregnancy and the sex of the foetus are interacting with each other and how it influences foetal growth. The following sections will give background information on prevalence and importance for foetal growth and birth outcomes regarding these three investigated factors.

Maternal pre-pregnancy weight status

Overweight and obesity prevalence worldwide

Overweight and especially obesity is a major global health problem and has reached pandemic proportions. Obesity is defined as the excessive accumulation of adipose tissue, which can compromise the individual's health. Overweight and obesity is classified according to body mass index (BMI) cut-off points. A BMI of 25.00-29.99 kg/m²is defined as overweight and a BMI >30 kg/m² as obese (WHO, 2000). According to the WHO over 1.9 billon adults are considered to be overweight and of these 1.9 billion, 650 million were obese in the year 2016. This accounts for 39% and 13% respectively of the global adult population (WHO, 2021). For the WHO European Region, the estimated prevalence of overweight and obese adults is 59%, with males being more affected (63%) than females (54%). For

obesity, the prevalence is 23% in adults. However, more females (24%) are living with obesity than men (22%) (WHO Regional Office for Europe, 2022). Over the last decades obesity levels have been globally on the rise. Since 1975, the prevalence of obesity rose by 138% and for overweight including obesity by 51% in the WHO Europe Region (WHO Europa, 2022). On the global level it is estimated that by 2030, 1 in 7 men and 1 in 5 women will be affected by obesity which accounts for over 1 billion people (World Obesity Federation, 2022).

In 2019, the prevalence for overweight persons in Austria was 34.3% and 16.5% were obese. Men had higher prevalence of overweight (41.4%) and obesity (17.9%) than women with 27.4% and 15% respectively. Compared to other European countries the overweight and obesity prevalence in Austria is in the lower third (Statistik Austria, 2020). The highest numbers of people being affected by overweight and obesity in Europe can be found in Turkey and Malta with approximately 66% (WHO Regional Office for Europe, 2022). However, obesity is no longer just a major problem in high-income countries. Over the last decades the obesity numbers in middle and low-income countries are on the rise. Especially in Africa there is a significant increase in obesity prevalence. It is estimated that there will be a threefold increase in obesity from the year 2010 to 2030 (World Obesity Federation, 2022).

Factors contributing to the globally increasing prevalence of overweight and obesity

There are several reasons that drive the obesity pandemic. One major cause is the so-called obesogenic environment, which describes structural and lifestyle changes. On the one hand the changes contribute to a high caloric intake through high processed foods which contains lots of sugar. On the other hand, there are changes that lead to a reduction in physical activity and therefore a reduction in calories metabolised, like less physical labour, increase in motorized mobility, infrastructure like elevators or escalators and so on (Meldrum et al., 2017). In addition, the obesogenic environment is strongly connected to urban areas and the continuing increased trend towards urbanisation worldwide contributes to the obesity problem (Kirchengast & Hagmann, 2021). Furthermore, in recent years more and more evidence showed that the gut microbiome plays a major role in metabolic and inflammatory processes. A reduction in the microbiome diversity, caused through factors linked to our modern lifestyle, like our diet of high processed food or the use of antibiotics, contributes to metabolic diseases and obesity (Boulangé et al., 2016).

Another explanation of the problematic increase in obesity prevalence in our modern societies comes from evolutionary medicine and the concept of an evolutionary mismatch, meaning that the environment humans are adapted to does not match with our modern environment which leads to the increase of lifestyle related non communicable diseases including obesity. In that context a famous

hypothesis is the “thrifty genes hypothesis” by Neel (1962). He proposed that there has been a positive selection of so-called “thrifty genes” that favour the accumulation of fat storages in times with sufficient food supply. This leads to an advantage in times of food shortages and famine. However, in our modern industrialized world, where high caloric food is more or less always available, these “thrifty genes” prepare the organism for times of food shortage and famines that never come and therefore contributes to the risk of developing obesity. Nevertheless, this hypothesis is still under debate and has been criticized for example by Speakman (2008).

Influence of overweight and obesity on foetal growth and birth outcomes

The rise in overweight and obesity prevalence is a global health problem which also affects women in reproductive age and has therefore negative implications for female reproduction. The weight status of the mother has an influence on the foetal development and pregnancy outcome. Pregnancies of obese mothers are often considered as high-risk pregnancies. Sebire et al. (2001) showed that maternal obesity is not only associated with several complications during pregnancy for the mother like increased risk for gestational diabetes or preeclampsia but also for the child with higher rates of intrauterine death. The higher risk in obese mothers for perinatal mortality, stillbirth and miscarriage is also supported by Vasudevan et al. (2011) and Ghimire et al. (2020).

Furthermore, maternal pre-pregnancy overweight and obesity has consequences for foetal growth. Studies of ultrasonographic measures of foetal growth demonstrated that foetuses of obese mothers have different growth patterns form the first trimester onwards (Pölzlberger et al., 2017). The study of Zhang et al. (2018) showed that for foetuses of obese women, the femur and humerus length were longer at 21 and 38 weeks’ of gestation. In addition, foetal head circumference and estimated foetal weight was significantly larger in the obese group. Pölzlberger et al. (2017) also found a positive association of a higher BMI with larger foetal dimensions in the third trimester. This accelerated growth of the foetus also has consequences on the new-born parameters. Neonates of overweight and obese mothers have higher birth weight, birth length and bigger head circumference (Kirchengast & Hartmann, 1998; Pölzlberger et al., 2017; Zhang et al., 2018). In addition, the risk for macrosomia, a birth weight > 4000g, is elevated in new-borns of overweight and obese mothers (Dai et al., 2018). In contrast, a high maternal pre-pregnancy BMI is also associated with a higher risk for low birth weight (LBW) or foetal growth restriction (Lewandowska, 2021).

Influence of maternal underweight on foetal growth and birth outcomes

Despite the fact that worldwide there are more people affected by obesity than underweight, underweight remains still a problem in sub-Saharan Africa and South Asia. Parallel to the global trend of increasing overweight and obesity levels it can be observed that the prevalence of those who are underweight has steadily decreased over the last decades. The prevalence of underweight, defined as a BMI <18.5 kg/m², decreased globally in men from 13.8% in 1975 to 8.8% in 2014 and in women from 14.6% to 9.7%. The highest prevalence of underweight is found in South Asia with 23.4% in men and 24% in women in 2014 followed by central and east Africa with approximately 15% in men and 12% in women (NCD risk factor collaboration, 2016).

Not only is obesity a risk factor for foetal development, also underweight of the mother displays a higher risk for the development of the foetus. The study of Ehrenberg et al. (2003) reported higher risks of intrauterine growth restriction and LBW. Furthermore, Kirchengast and Hartmann (1998) could show that in underweight mothers the incidence of LBW neonates is significantly higher in comparison to normal and overweight/obese women.

This section demonstrated the worldwide problem of an unhealthy weight status and its consequences for female reproduction, foetal growth, and birth outcomes. In the next section, the problem of cigarette smoking during pregnancy, its prevalence, and the negative effects on the development of the foetus are examined in more detail.

Maternal smoking during pregnancy

Global trends in smoking prevalence and smoking during pregnancy

Another stress factor on foetal development and growth is nicotine consumption during pregnancy. Global prevalence of smoking has decreased over the past decades due to the implementation of strict tobacco control measures and public health prevention programs in many countries. From 1990 to 2015 the global prevalence of smoking decreased for men by 28.4% and for women by 34.4% leading to a smoking prevalence of 25% for men and 5.4% for women in the year 2015 (Reitsma et al., 2017). Nevertheless, smoking still depicts a major public health issue which is estimated to be responsible for 7.1 million deaths in the year 2017 (Stanaway et al., 2018). Despite the widespread knowledge of the harmful effects of smoking, especially the risk of tobacco consumption for the developing child, smoking during pregnancy still remains a major health concern.

The study of Smedberg et al. (2014) compared the prevalence of smoking during pregnancy of women in 15 European countries. They reported that the highest prevalence of smoking before pregnancy was found in Croatia (50%) and the lowest in Sweden (25%). The prevalence of women who continued smoking during pregnancy was highest in Croatia (18.9%) and lowest in Iceland (4.2%). The prevalence of nicotine consumption before pregnancy in Austria was 31.7% and during pregnancy 4.9%, which was the second lowest in this study. They further showed that women with less resources and a lower socioeconomic status were more likely to continue smoking during pregnancy. In the United States the prevalence of cigarette smoking before pregnancy in the year 2016 was 9.4% and 7.1% during pregnancy. The highest prevalence was found for Non-Hispanic White women, and women with less than a high school education, which also indicated the strong connection of socioeconomic status of the mothers with smoking habits (Kondracki, 2019). It has been reported that in low- and middle-income countries the prevalence of tobacco use is lower than in high income countries. Shukla et al. (2021) conducted a survey on tobacco use in 42 low- and middle-income countries. They reported a prevalence of cigarette smoking before pregnancy of 1.09% and during pregnancy of 0.69%. They found no significant difference in the prevalence of smoking before and during pregnancy and concluded that the awareness of the harmful effects of smoking on foetal development and the risks for the infants' health might not be that widespread in low and middle-income countries compared to high income countries.

The negative effects of smoking on intrauterine development and birth outcomes

The negative effects of tobacco consumption during pregnancy on foetal development and birth outcomes are well documented. Maternal smoking during pregnancy increases the risk of the neonate to have a low birth weight, which is below 2500g (Huang et al., 2017; Phung et al., 2003). Furthermore, the effects on the new-born parameters of birth weight, birth length and head circumference are evident and are documented by many studies. New-borns of mothers who smoke during pregnancy have significantly lower mean birth weight (Kirchengast & Hartmann, 2003; Koger et al., 2021; Pietersma et al., 2022; Suzuki et al., 2016), shorter birth length and smaller head circumference (Kirchengast & Hartmann, 2003; Koger et al., 2021; Shiohama et al., 2021). Moreover, the birth mode is affected by maternal smoking. Kirchengast & Hartmann (2003) found a higher risk for caesarean sections for mothers who smoked during pregnancy.

Cigarette smoking during pregnancy affects even the embryonic morphology and the foetal development from the first trimester onwards (Pietersma et al., 2022). Mook-Kanamori et al. (2010) reported also a shorter crown to rump length in the first trimester in foetuses of smoking mothers compared to non-smoking mothers. Jaddoe et al. (2007) compared foetal growth patterns between smoking and non-smoking mothers. They found cigarette smoking during pregnancy was associated

with an impaired growth of abdominal circumference, femur length and head circumference. From 18-24 weeks of gestation onwards the foetuses of smoking mothers had smaller femur length and from 25 weeks of gestation onwards smaller abdominal and head circumference. The strongest effect was found for femur length indicating that peripheral tissues are more affected by smoking. In line with these findings is the meta-analysis by Abraham et al. (2017). They assessed the effects of maternal nicotine consumption during pregnancy on foetal growth and could show reduced head size and femur length in the second trimester and reduced head size, femur length and estimated foetal weight in the third trimester in foetuses of smoking mothers.

However, smoking during pregnancy not only affects intrauterine growth and development but also has negative consequences for the further health and development of the child mediated by epigenetics and foetal programming (Knopik et al., 2012). There are several studies reporting that smoking during pregnancy increases the risk of overweight and obesity in childhood (Oken et al., 2008; Suzuki et al., 2011). The study of Brannigan et al. (2021) showed that when the mother smoked more than five cigarettes per day the odds that the child develops a personality disorder is 2.5 higher in comparison to non-smoking mothers. Moreover, nicotine consumption during pregnancy increased the risk for adverse neurodevelopmental outcomes (Kiechl-Kohlendorfer et al., 2010). This whole body of evidence demonstrates the strong negative effects of maternal cigarette smoking during pregnancy on foetal growth and development and further health of the child.

Interacting effects of several stress factors on foetal growth

In the sections above the individual risks of an unhealthy maternal weight status and nicotine consumption during pregnancy were discussed. However, foetal growth is a multidimensional process which is influenced by different factors during pregnancy. Therefore, the question arises whether these stress factors interact with each other and have additive negative effects on the developing child when both occur together. Studies have already shown some interacting effects of risk factors during pregnancy like the additive effect of advanced maternal age and nicotine consumption (Koger et al., 2021; Zheng et al., 2016). Thus, one aspect of this thesis will be to investigate possible interacting effects of maternal pre-pregnancy weight status and smoking during pregnancy. Another aspect this thesis will focus on, is the possible moderating effect of the new-borns sex on the interaction of maternal pre-pregnancy weight and smoking.

Effects of the sex of the child on foetal growth and birth outcomes

An often-neglected aspect in studies of risk factors on foetal development is the influence of the sex of the child. Sex differences in growth and development are well documented and studied especially from puberty onwards, whereas during childhood there are not much sex differences. However, the

effect of sex through genetic, hormonal, and physiological differences between male and female individuals, could have consequences as early as during foetal development.

Several studies have reported higher mortality and morbidity rates and higher risk for adverse birth outcomes in male neonates compared to females. The study of Vatten & Skjærven (2004) demonstrated a higher mortality of males early in pregnancy indicated by a higher male/female sex ratio. At week 16 of gestion the ratio was 2.48 which declined to a sex ratio of 1.17 at weeks 37-39 and at weeks 40-42 the ratio was almost 1.0. Perinatal mortality was 21% higher in males. Moreover, males had higher rates of preterm birth. They concluded that there are stronger selection forces acting on males in utero leading to the observed higher mortality during pregnancy. In addition, Di Renzo et al. (2007) reported similar observations that at the beginning of the pregnancy the male/female ratio is extremely high and declines at week 20 until it is stabilized at term. Furthermore, mothers of male foetuses are at higher risks for several pregnancy complications like higher rates of gestational diabetes or caesarean sections. Stevenson et al. (2000) investigated short term outcomes in very low birth weight neonates (<1500g) and compared them between boys and girls. They found a higher mortality rate for male infants (22%) in contrast to females (15%). Furthermore, male neonates had higher risks for adverse birth outcomes like a lower APGAR 1 and 5 score, higher risk for being intubated or receiving resuscitation medication. Kirchengast and Hartmann (2009) could show that several maternal stress factors during pregnancy have a stronger impact on male foetal development and new-born parameters than on females. However, the recent study of Christians & Chow,(2022) could find no evidence for a significant difference in mortality between males and female neonates or differences in adverse birth outcomes.

The “male disadvantage hypothesis” established by Naeye et al. (1971) tried to explain the higher mortality and morbidity of male in comparison to female new-borns. The hypothesis states that males are more sensitive to stress factors acting on them during intrauterine development than females and therefore they have a higher rate of morbidity, mortality, and adverse birth outcomes. Therefore, the sex of the new-born should also be considered as a moderating effect when looking into interactions between stress factors on foetal development.

Research question and relevance of the topic

As described in the sections above maternal pre-pregnancy weight status, smoking during pregnancy and the new-born`s sex are important independent factors influencing foetal growth and birth outcomes. Human intrauterine development and foetal growth is a complex interaction of various factors, which have been getting more and more attention in recent years. According to the Developmental Origin of Health and Disease (DOHaD) hypothesis the intrauterine development is a

key time window in human ontogeny and can have severe consequences for the further health of the individual (Gluckman et al., 2008). Therefore, the study of these complex interactions of factors on human intrauterine development should be of high interest – not only to gain further knowledge in the field of human development, but also for politicians and public health experts to take the right measures to ensure the health and wellbeing of the next generation. Especially with the background of obesity levels globally on the rise, and despite a decline over the past decades, with a still too high proportion of smoking mothers during pregnancy. Therefore, the aim of this thesis is to investigate the effects of maternal pre-pregnancy weight status, smoking during pregnancy and the sex of the foetus on the new-born parameters and testing if there are interacting effects of maternal weight status and tobacco consumption during pregnancy and whether the new-born`s sex is moderating these effects.

Hypotheses

Following hypotheses will be tested in this thesis:

1) There is an additive negative effect of the maternal pre-pregnancy weight status underweight and smoking during pregnancy on the new-born parameters bright weight, bright length, head circumference and one- and five-minute APGAR scores.

2) There is an additive negative effect of the maternal weight status overweight/obesity and smoking during pregnancy on the new-born parameters bright weight, bright length, head circumference and one- and five-minute APGAR scores

3) The additive negative effect of maternal weight status and smoking during pregnancy is stronger in male than in female new-borns.

Material and Methods

This thesis is a retrospective medical record-based study, which investigates a sample of 4141 mother-child pairs from the University Clinic for Gynecology and Obstetrics in Vienna. The births took place between the years 1990 to 1995. Only singleton term births, which are defined as delivery between the 39th and 40th gestational week, are included. The gestational age was obtained by two ultrasound examinations before the 12th gestational week and by counting the number of weeks from the last menstrual bleeding to the day of birth. The exclusively nulliparous women are of Austrian or Central European origin. An inclusion criterion is that the women had to complete all prenatal check-ups of the Austrian mother-child passport.

Furthermore, all women had to be healthy with no registered diseases before and during their pregnancy. This means that they had no protein or glucose in the urine, no hypertension, no HIV infection nor preeclampsia or gestational diabetes. Further strict exclusion criteria were alcohol abuse, congenital malformation of the foetus and assisted reproduction or IVF. All new-borns with an APGAR 1 and 5 score of < 2 were excluded.

Maternal parameters

Maternal parameters, which were obtained at the first prenatal check-up are maternal age, body height and pre-pregnancy weight status. The maternal stature was measured with a standard anthropometer to the nearest 0.5 centimetre. Pre-pregnancy body weight was obtained by measuring the body weight at the first prenatal check up to the nearest 0.1 kilogram. Additionally, the woman was asked for her body weight before conception and the mean of the measured and reported value gives the pre-pregnancy body weight. Maternal pre-pregnancy BMI is calculated the following way: pre pregnancy body weight (kg) / maternal stature $(m)^2$. Weight status groups are defined according to the cut-off points from the World Health Organization (WHO, 2000):

- <18.5 kg/m^2 = underweight
- 18.5 - 24.99 kg/m^2 = normal weight
- 25.00 - 29.99 kg/m^2 = overweight
- >30 kg/m^2 = obese

Smoking status is assessed by interviewing the women at the perinatal check-ups about their smoked cigarettes per day before and during pregnancy. The limitations of assessing nicotine consumption with the self-reporting method is further discussed in the limitations section.

The number of smoked cigarettes per day are categorized as following:

- 0 cigarettes/day
- 1-5 cigarettes/day
- 6-10 cigarettes/day
- 11-20 cigarettes/day
- >20 cigarettes/day

New-born parameters

The new-born parameters were measured immediately after birth. The birth weight was measured in gram (g) with a new-born scale, birth length in centimetres (cm) with an infantometer from head to heel and the head circumference was measured in cm with a measuring tape. The APGAR score after 1 minute and 5 minutes are a measure for the vital functions of the new-born which include skin colour, the pulse rate, reflex irritability, muscle tone and breathing (Casey et al., 2001).

Statistical analysis

To test for normal distribution of the investigated variables a Kolmogorow-Smirnow test was used. Most variables were not normally distributed, therefore nonparametric tests were used in group comparisons. First, basic descriptive statistic of the samples main variables was conducted. For the further statistical analysis, the smoking categories were summarised in non-smoking during pregnancy (0 cigarettes/day) and smoking during pregnancy (1-5; 6-10; 11-20; >20 cigarettes/day). Differences in smoking prevalence between the maternal pre-pregnancy weight status groups were tested with a Chi^2-test. In the next step differences between the weight status groups and new-born parameters were tested with a Kruskal-Wallis *H*-test and Dunn-Bonferroni post-hoc test and differences between male and female new-borns were tested with a Mann-Whitney *U*-test. Multivariate linear regression models were used to test for independent effects of maternal BMI, smoking during pregnancy (no/yes) and new-born's sex (male/female) on the new-born parameters. Maternal stature, weight gain during pregnancy and maternal age were included in the models as confounding factors.

To test for interacting effects of maternal pre-pregnancy weight status and smoking during pregnancy univariate group comparisons between non-smoking and smoking mothers in each weight status group for maternal and new-born parameters were calculated with a Mann-Whitney *U*-test. Next, adjusted mean differences with 95% confidence intervals of new-born parameters between the smoking and non-smoking group for each weight status group were calculated. The mean differences were adjusted for maternal age, stature, and weight gain during pregnancy.

The moderating effect of the new-born's sex on the interaction of weight status and smoking was assessed by calculating adjusted mean differences between males and females for the smoking and non-smoking groups within every maternal weight status group. Mean differences were adjusted for maternal age, stature, and weight gain during pregnancy.

Results

Descriptive statistics of the sample

The sample consists of 4141 mother – child pairs. For descriptive statistics see table 1. The mothers have a mean age of 25.2 years (SD = 5.6 years). The youngest mother is 13 years old and the oldest 46 years. On average the women are 163.7 cm (SD = 6.4 cm) tall and have a mean pre-pregnancy weight of 60.46 kg (SD = 10.96 kg) and an average pregnancy weight gain of 12.6 kg (SD = 5.5 kg). The proportion of women with the weight status underweight is 7.3%, with the status normal weight 72.9%a, 15.4% are overweight and 4.4% are obese. Smoking prevalence before pregnancy is 36.1% and 28.8% during pregnancy.

On average the new-borns weigh 3386g, the lightest new-born weighing 1800g and the heaviest 5150g. Only 1.7% of the new-borns have a low birth weight and 8.6% are macrosomic. The mean birth length of the neonates is 49.9 cm (SD = 1.9cm) and the mean head circumference is 34.4 cm (SD = 1.4 cm). The sex ratio of the new-borns is 50.5% male and 49.5% female.

Table 1: descriptive statistics of the sample

maternal parameters	mean (SD)	range	*N* (%)
age (years)	25.2 (5.6)	13 - 46	4141
stature (cm)	163. 7 (6.4)	120 - 188	4104
gestational weight gain (kg)	12.96 (5.5)	-6 - 38	4141
pre-pregnancy weight (kg)	60.46 (10.96)	43 - 130	4141
end of pregnancy weight (kg)	73.41 (11.98)	44 - 143	4141
pre-pregnancy BMI (kg/m²)	22.55 (3.79)	14.15 – 52.78	4104
< 18.50 kg/m²			300 (7.3%)
18.50 – 24.99 kg/m²			2988 (72.9%)
25.00-29.99 kg/m²			633 (15.4%)
>30.00 kg/m²			180 (4.4%)
nicotine consumption before pregnancy			
smoker			1496 (36.1%)
non-smoker			2645 (63.9%)
nicotine consumption during pregnancy			
smoker			1186 (28.8%)
non-smoker			2955 (71.4%)
new-born parameters	mean (SD)	range	*N* (%)
sex			
male			2093 (50.5%)
female			2048 (49.5%)
birth weight (g)	3386.4 (429.5)	1800 - 5150	4141
birth length (cm)	49.9 (1.9)	31 - 58	4136
head circumference (cm)	34.4 (1.4)	30 - 40	3815
APGAR 1	8.6 (1.1)	2 - 10	4106
APGAR 5	9.8 (0.6)	4 - 10	3877
birth weight categories			
low birth weight (<2500g)			69 (1.7%)
normal birth weight (2500-4000 g)			3717 (89.8%)
macrosomia (>4000g)			355 (8.6%)

Comparison of smoking prevalence between the weight status groups

Looking at the smoking prevalence before pregnancy in the different weight status groups the overweight and normal weight group have the highest numbers of non-smokers with approximately 65%, the lowest amount of non-smokers is in the underweight group with 56%. In **figure 1** the number of smoked cigarettes per day can be seen. Before pregnancy, the underweight and obese group show the highest prevalence of mothers smoking 11-20 cigarettes/day or >20 cigarettes/day. In the underweight group 21% of the mothers are smoking 11-20 cigarettes/day and 8.7% over 20 cigarettes and in the obese group 20% and 11.7% respectively.

During pregnancy, a reduction in the total amount of smoking mothers and the number of smoked cigarettes/days can be observed in every weight status group. As before pregnancy the normal weight and overweight group are having the highest number of non-smokers with 72.1% and 71,1% respectively. The number of heavy smokers with 11-20 or >20 smoked cigarettes per day are still the highest in the underweight and obese group, however the prevalence reduced to 8.3% and 2% respectively for the underweight group and 10.6% and 0.6% respectively for the obese mothers.

Before pregnancy, the Chi^2- test shows a significant difference in the smoking prevalence between the weight status groups ($Chi^2 = 12.182$; $df = 3$; $p = 0.007$). In **table 2** the frequencies for smoking and non-smoking mothers can be seen. In the underweight and obese group there are more smoking mothers than expected with 44% and 42% respectively. The normal weight and overweight group having approximately the same prevalence of smokers with 35.5% and 34.4% respectively.

Comparing the prevalence of non-smokers with smokers before pregnancy a Chi^2 -test also shows a significant difference between the weight status groups ($Chi^2=8.258$; $df=3$; $p = 0.041$). The underweight and obese group have more smoking mothers than the normal or overweight group. The underweight group having the highest number of smokers with 35%, the normal weight and overweight group having approximately the same prevalence of smoking mothers with 28% and 29% respectively (see **table 3**).

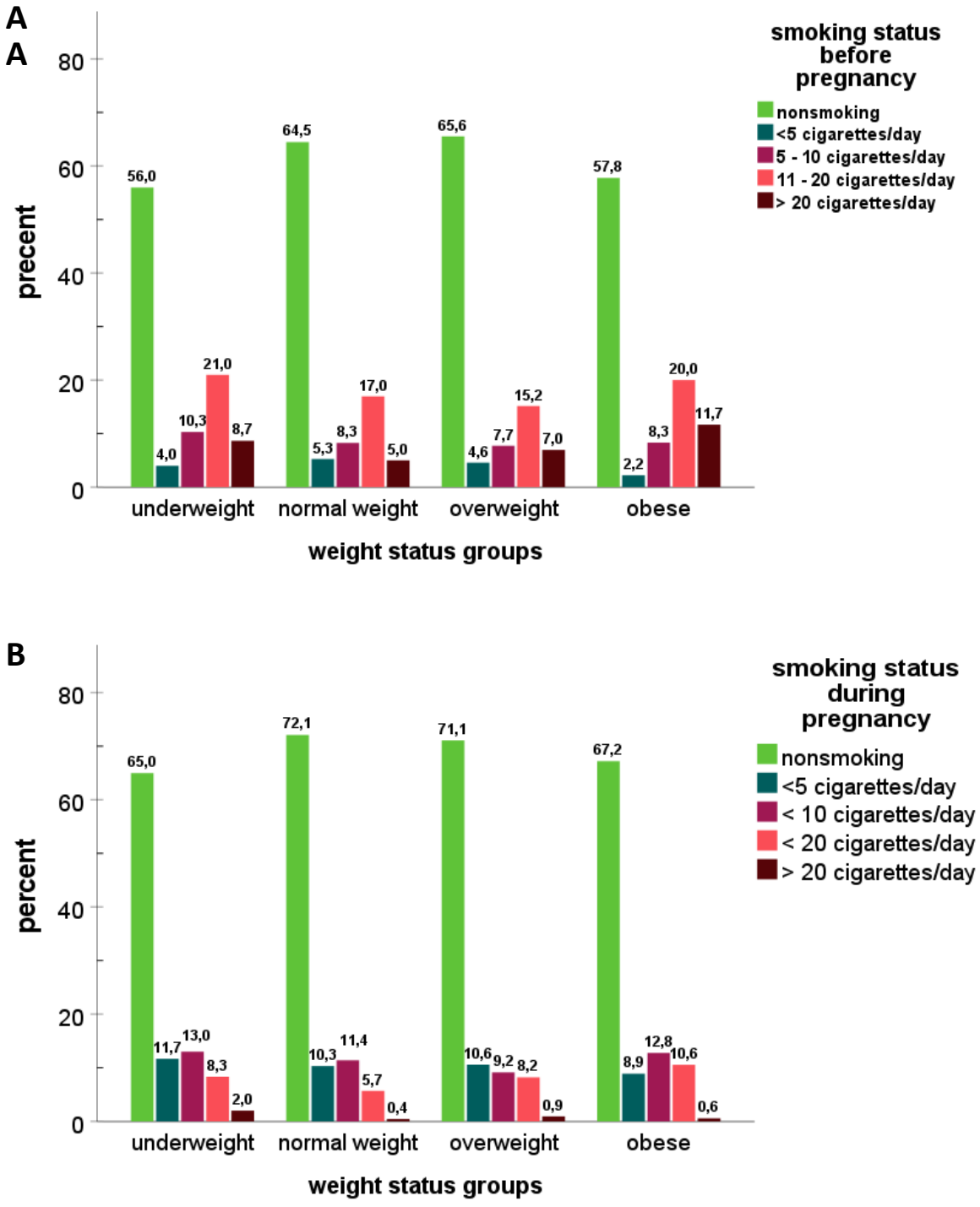

Figure 1: prevalence of smoking mothers and smoked cigarettes/day for **A)** before pregnancy and **B)** during pregnancy

Table 2: Comparison of smoking prevalence before pregnancy between the weight status groups

		smoking status before pregnancy	
weight status		non-smoking	smoking
underweight	%	56.0	44.0
	N	168	132
	expected *N*	191.2	108.8
	standardised residuals	-1.7	2.2
normal weight	%	64.5	35.5
	N	1927	1061
	expected *N*	1904.6	1083.4
	standardised residuals	0.5	-0.7
overweight	%	65.6	34.4
	N	415	218
	expected *N*	403.5	229.5
	standardised residuals	0.6	-0.8
obese	%	57.8	42.2
	N	104	76
	expected *N*	114.7	65.3
	standardised residuals	-1.0	1.3
Chi²-test: value = 12.182; *df* = 3; *p*-value = 0.007			

Table 3: Comparison of smoking prevalence during pregnancy between the weight status groups

		smoking status during pregnancy	
weight status		non-smoking	smoking
underweight	%	65.0	35.0
	N	195	105
	expected *N*	213.7	86.3
	standardised residuals	-1.3	2.0
normal weight	%	72.1	27.9
	N	2155	833
	expected *N*	2128.2	859.8
	standardised residuals	0.6	-0.9
overweight	%	71.1	28.9
	N	450	183
	expected *N*	450.9	182.1
	standardised residuals	0.0	0.1
obese	%	67.2	32.8
	N	121	59
	expected *N*	128.2	51.8
	standardised residuals	-0.6	1.0
Chi²-test: value = 8.258; *df* = 3; *p*-value = 0.041			

Comparison of new-born parameters between weight status groups

In **table 4** the comparison of the new-born parameters between the maternal weight status groups can be seen. A Kruskal-Wallis *H*-test shows a significant difference between the groups for birthweight ($p<0.001$). A Dunn-Bonferroni post hoc test shows significant differences between all weight status groups except between the overweight and obese mothers. The obese mothers having the heaviest neonates with a mean birth weight of 3573g and the underweight women having the lightest with a mean birth weight of 3261g.

For birth length all groups except the overweight and obese mothers differ significantly from each other (see **Table 4**). The obese women having the largest neonates with a mean birth length of 50.51cm and the smallest new-borns are in the underweight group with on average 49.35cm birth length.

Comparing of the head circumference of the new-borns between the weights status groups showed significant differences between all groups except between the obese and overweight mothers (see **table 4**). The smallest mean head circumference can be found in the underweight group with 34.04cm and the largest in the obese group with a mean of 34.82cm.

The Kruskal Wallis *H*-test for the new-born parameters APGAR 1 and APGAR 5 score showed no significant difference between the four maternal weight status group. Comparing the frequencies of LBW in the different weight status groups the highest amount of LBW can be found in the normal weight group with 1.8% followed by the underweight mothers with 1.7%. The lowest amount of LBW is in the obese group (0.6%).

Table 4: comparison of new-born parameters between maternal weight status groups with Kruskal-Wallis *H*-test

		Weight status groups (BMI)			
		<18.5	18.5-24.99	25.00-29.99	>30
Birth weight (g)	*N*	300	2988	633	180
	Mean	3261.3	3366.9	3483.1	3573.2
	SD	394.2	418.4	462.7	431
	Median	3200	3350	3450	3600
	Q1/Q3	3000/3542	3100/3650	3200/3800	3250/3893
Kruskal-Wallis *H*-test	*H*	96.058***[a,b,c,d,e]			
Birth length (cm)	*N*	300	2985	631	180
	Mean	49.35	49.86	50.16	50.51
	SD	1.82	1.84	2.07	1.67
	Median	49	50	50	51
	Q1/Q3	48/51	49/51	49/51	49/51
Kruskal-Wallis *H*-test	*H*	60.034***[a,b,c,d,e]			
Head circumference (cm)	*N*	278	2758	578	168
	Mean	34.03	34.35	34.66	34.82
	SD	1.23	1.39	1.41	1.40
	Median	34	34	35	35
	Q1/Q3	33/35	33/35	34/36	34/36
Kruskal-Wallis *H*-test	*H*	64.424***[a,b,c,d,e]			
APGAR 1	*N*	297	2966	627	178
	Mean	8.64	8.67	8.57	8.57
	SD	1.12	1.07	1.28	1.34
	Median	9	9	9	9
	Q1/Q3	8/9	8/9	8/9	8/9
Kruskal-Wallis *H*-test	*H*	0.593			
APGAR 5	*N*	283	2810	585	167
	Mean	9.79	9.76	9.71	9.77
	SD	0.56	0.60	0.69	0.69
	Median	10	10	10	10
	Q1/Q3	10/10	10/10	10/10	10/10
Kruskal-Wallis *H*-test	*H*	3.911			
Low birth weight (LBW)	*N*(%)	5 (1.7%)	54 (1.8%)	9 (1.4%)	1 (0.6%)

Significance Levels: * p<0.05, ** p< 0.01, *** p<0.001,

Dunn-Bonferroni post-hoc test: [a] = sign. difference between underweight and normal weight, [b] = sign. difference between underweight and overweight, [c] = sign. difference between underweight and obese, [d] = sign. difference between normal weight and overweight, [e] = sign. difference between normal weight and obese, [f] = sign. difference between overweight and obese

Comparison of new-born parameters between male and female new-borns

In the next step the new-born parameters between male and female neonates are compared. Male new-borns have significant higher birthweight, birth length and head circumference than females (see **table 5**). There is no significant difference between the males and females in the APGAR 1 and APGAR 5 scores. Female neonates have higher LBW prevalence with 2.2% than males with 1.1% (Chi^2=6.973; *df*=1; *p* = 0.008).

Table 5: comparison of new-born parameters between males and females with Mann-Whitney *U*-test

		N	Mean	SD	Median	Q1/Q3	*p* -value
Birth weight (g)	Males	2093	3454.6	425.3	3450	3150/3750	<0.001
	Females	2048	3316.7	422.5	3300	3050/3600	
Birth length (cm)	Males	2091	50.37	1.80	50	49/52	<0.001
	Females	2045	49.41	1.84	49	48/51	
Head circumference (cm)	Males	1918	34.64	1.40	35	34/36	<0.001
	Females	1897	34.14	1.34	34	33/35	
APGAR 1	Males	2078	8.62	1.16	9	8/9	0.179
	Females	2028	8.67	1.09	9	8/9	
APGAR 5	Males	1967	9.74	0.63	10	10/10	0.167
	Females	1910	9.77	0.61	10	10/10	
Low birth weight (LBW)	Males	24 (1.1%)					
	Females	45 (2.2%)					

Independent effects of weight status, sex of new-born and smoking status during pregnancy of the mother on the new-born parameters

To see the independent effect of the three variables maternal weight status, smoking during pregnancy and new-born sex on the new-born parameters multivariate linear regression analyses were performed. Maternal stature, weight gain during pregnancy and maternal age were included as confounding factors.

Table 6 shows the results of the regression models. The results show an independent positive effect of BMI on birth weight, birth length and head circumference, however a significant negative effect on APGAR 1 and 5 score. For smoking during pregnancy, the models show a significant negative effect on birth weight, birth length and head circumference. For APGAR 1 and 5 there is no significant independent effect. The regression models also show a significant

independent effect of the new-borns sex on birth weight, birth length and head circumference. If the new-born is female, they have lower values for these three parameters. There is no significant effect of the sex on the APGRA 1 and 5 scores.

Table 6: Independent effect of BMI, smoking during pregnancy and new-born's sex on new-born parameters birth weight, birth length, head circumference, APGAR 1 and APGAR 5 corrected for confounding factors maternal age, maternal stature, and weight gain during pregnancy

	birth weight (R^2 = 0.170)			
Independent variables	*B*	SE of *B*	*Beta*	*p*-value
Maternal age	4.211	1.120	0.055	<0.001
Maternal stature	11.864	0.970	0.176	<0.001
Weight gain	17.499	1.144	0.223	<0.001
BMI	24.218	1.653	0.214	<0.001
Smoking during pregnancy [a]	-147.734	13.603	-0.156	<0.001
Sex [b]	-127.471	12.234	-0.148	<0.001
	birth length (R^2 = 0.172)			
	B	SE of *B*	*Beta*	*p*-value
Maternal age	0.015	0.005	0.043	0.003
Maternal stature	0.054	0.004	0.184	<0.001
Weight gain	0.057	0.005	0.165	<0.001
BMI	0.075	0.007	0.152	<0.001
Smoking during pregnancy [a]	-0.662	0.060	-0.159	<0.001
Sex [b]	-0.923	0.054	-0.245	<0.001
	head circumference (R^2 = 0.105)			
	B	SE of *B*	*Beta*	*p*-value
Maternal age	0.016	0.004	0.065	<0.001
Maternal stature	0.032	0.003	0.148	<0.001
Weight gain	0.030	0.004	0.117	<0.001
BMI	0.058	0.006	0.158	<0.001
Smoking during pregnancy [a]	-0.317	0.048	-0.103	<0.001
Sex [b]	-0.471	0.043	-0.169	<0.001
	APGAR 1 (R^2 = 0.010)			
	B	SE of *B*	*Beta*	*p*-value
Maternal age	0.005	0.003	0.026	0.099
Maternal stature	0.011	0.003	0.063	<0.001
Weight gain	-0.015	0.003	-0.073	<0.001
BMI	-0.013	0.005	-0.043	0.007
Smoking during pregnancy [a]	-0.007	0.039	-0.003	0.865
Sex [b]	0.050	0.035	0.023	0.150
	APGAR 5 (R^2 = 0.007)			
	B	SE of *B*	*Beta*	*p*-value
Maternal age	0.005	0.002	0.041	0.013
Maternal stature	0.003	0.002	0.033	0.045
Weight gain	-0.007	0.002	-0.064	<0.001
BMI	-0.005	0.003	-0.033	0.045
Smoking during pregnancy [a]	-0.001	0.022	-0.001	0.967
Sex [b]	0.022	0.020	0.018	0.269

a = smoking during pregnancy coded as 0 for non-smoking and 1 for smoking; b = sex is coded as 0 for male and 1 for female

Interacting effects of weight status and smoking during pregnancy on new-born parameters

To investigate the interacting effects of maternal weight status and smoking during pregnancy the smoking and non-smoking mothers within every weight status group were compared. In **table 7** a comparison of the maternal parameter's stature, weight gain during pregnancy and age can be seen and in **table 8** the comparison of the five new-born parameters.

Maternal parameters

For maternal age there is a significant difference between smoking and non-smoking mothers in all weight status groups except in the underweight group. In the normal weight, overweight and obese group the non-smokers are significantly older than the smokers. In the obese and overweight group, the smoking mothers are significantly taller than the non-smoking. In the normal weight and underweight group there is no significant difference. Regarding the parameter weight gain during pregnancy there is a significant difference between smokers and non-smokers in the normal weight, overweight and obese group. Smoking women having a higher mean weight gain during pregnancy (see **table 7**).

New-born parameters

The univariate comparisons with a Mann-Whitney *U*-test of non-smokers and smokers within every weight status group for the new-born parameters showed for birthweight a significant difference in the underweight and normal weight group (see **table 8**). In the underweight group the non-smoking mothers have significantly heavier new-borns with a mean birthweight of 3311g in comparison to the smokers with 3168g. In the normal weight group, the neonates of non-smokers have a higher mean birthweight with 3409g in comparison to the smokers with 3256g. In the overweight and obese group there is no significant difference in mean birth weight between the smoking groups.

For the new-born parameter birth length there is a significant difference between the smoking groups in the underweight and normal weight group. In both these groups the new-borns of the non-smokers are significantly taller (see table 8). The neonates in the overweight and obese group do not differ significantly in birth length between smoking and non-smoking mothers.

Head circumference is significantly larger for new-borns of non-smoking women in the underweight and normal weight group. For the overweight and obese group there cannot be found any significant difference in the new-borns head circumference.

Regarding the APGAR 1 and 5 score the comparison of the neonates of smoking and non-smoking women in the weight status groups does not show any significant difference.

Table 7: comparison of maternal somatic parameters between smoking and non-smoking during pregnancy for each weight status group

		weight status groups (BMI)							
		underweight		normal weight		overweight		obese	
		non smoking	smoking	non smoking	smoking	non smoking	smoking	non smoking	smoking
age (years)	*N*	195	105	2155	833	450	183	121	59
	mean	23.39	23.2	25.16	24.31	26.76	25.4	28.5	25.69
	SD	4.65	5.0	5.43	5.48	5.76	5.88	5.86	5.68
	median	23	22	25	23	26	24	28	24
	Q1/Q3	20/26	19/26	21/28	20/27	22/31	21/30	24/33	21/30
Mann-Whitney-*U*-test	*U*	9723		806884***		35449.5**		2576**	
stature (cm)	*N*	195	105	2155	833	450	183	121	59
	mean	166.04	165.6	163.62	163.52	162.62	164.87	162.39	164.97
	SD	5.51	4.82	6.25	6.18	6.94	6.77	7.18	8.39
	median	165	165	164	164	162	164	163	165
	Q1/Q3	162/170	162/169	160/168	160/168	158/167	160/170	158/167	161/170
Mann-Whitney-*U*-test	*U*	9776.5		888068.5		48740.5***		4526**	
weight gain during pregnancy (kg)	*N*	195	105	2155	833	450	183	121	59
	mean	13.51	14.12	12.97	13.9	11.41	14.02	9.5	11.85
	SD	5.09	4.69	5.12	5.47	6.04	6.25	5.77	7.58
	median	13	15	13	14	11	14	9	13
	Q1/Q3	10/17	11/17.5	10/16	10/17	7/15	10/18	5/13	6/18
Mann-Whitney-*U*-test	*U*	11307.5		976406***		51247.5***		4311.5*	

significance level: * p<0.05, **p<0.01, ***p>0.001

Table 8: comparison of new-born parameters between smoking and non-smoking during pregnancy for each weight status group

		weight status groups							
		underweight		normal weight		overweight		obese	
		non smoking	smoking	non smoking	smoking	non smoking	smoking	non smoking	smoking
birthweight (g)	*N*	195	105	2155	833	450	183	121	59
	mean	3311.49	3168	3409.73	3256.01	3499.07	3443.66	3590.25	3538.31
	SD	355.8	443.9	412.24	414.17	464.02	458.48	426.4	441.94
	median	3300	3100	3400	3250	3475	3450	3640	3600
	Q1/Q3	3050/3550	2850/3450	3150/3700	3000/3520	3200/3800	3150/3700	3250/3900	3200/3860
Mann-Whitney-*U*-test	*U*	7881.5***		715289.5***		38611		3378.5	
birth length (cm)	*N*	195	105	2152	833	448	183	121	59
	mean	49.7	48.7	50.04	49.39	50.27	49.87	50.54	50.44
	SD	1.65	1.94	1.8	1.85	1.89	2.43	1.66	1.71
	median	50	49	50	50	50	50	51	51
	Q1/Q3	49/51	48/50	49/51	48/51	49/51	49/51	50/51	49/51
Mann-Whitney-*U*-test	*U*	7167.5***		715971.5***		37549.5		3461	
head circumference (cm)	*N*	182	96	2007	751	409	169	109	59
	mean	34.21	33.69	34.44	34.11	34.72	34.51	34.79	34.86
	SD	1.24	1.13	1.39	1.37	1.43	1.35	1.44	1.35
	median	34	34	34	34	35	34	35	35
	Q1/Q3	33/35	33/34	34/35	33/35	34/36	34/35	34/36	34/36
Mann-Whitney-*U*-test	*U*	6653***		659707***		31458		3343.5	
APGAR 1	*N*	192	105	2140	826	447	180	120	58
	mean	8.6	8.72	8.67	8.65	8.57	8.58	8.68	8.36
	SD	1.16	1.04	1.07	1.09	1.29	1.26	1.12	1.69
	median	9	9	9	9	9	9	9	9
	Q1/Q3	8/9	8/9	8/9	8/9	8/9	8/9	8/9	8/9
Mann-Whitney-*U*-test	*U*	10662		875985.5		40450.5		3228.5	
APGAR 5	*N*	183	100	2010	800	411	174	110	57
	mean	9.79	9.79	9.76	9.75	9.71	9.7	9.77	9.75
	SD	0.496	0.7	0.56	0.597	0.71	0.64	0.553	0.91
	median	10	10	10	10	10	10	10	10
	Q1/Q3	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Mann-Whitney-*U*-test	*U*	9430		794264		34673		3285.5	

significance level: * p<0.05, **p<0.01, ***p>0.001

Adjusted mean differences for interacting effects of weight status and smoking during pregnancy for new-born parameters

After univariate comparisons of the new-born parameters between non-smoking and smoking mothers in the different weight status groups, multivariate models were performed to control for confounding factors which also influence foetal growth. Therefore, adjusted mean differences were calculated which are controlled for maternal stature, weight gain during pregnancy and maternal age. **Table 9** shows the adjusted mean differences and 95% confidence intervals for each new-born parameter between smoking and non-smoking women within every weight status group. A visualisation of the trend of the interacting effects of smoking status during pregnancy and maternal weight status represented by the adjusted mean differences can be seen in **figure 2**.

For birthweight there are significant adjusted mean differences in the underweight group with 152.34g, in the normal weight group with the highest difference of 166.15g and in the overweight group with 119.04g. The smallest adjusted mean difference shows the obese group with only 66.98g, which is not significant.

The highest significant adjusted mean difference regarding birth length can be found in the underweight group with 1.04cm, the normal weight and overweight group have similar differences with 0.69cm and 0.63cm, respectively. The lowest difference is in the obese group with only 0.14cm adjusted mean difference, however this is not significant.

A similar pattern can be found for the new-born parameter head circumference. The underweight group having the highest significant adjusted mean difference between smoking and non-smoking mothers with 0.51cm, followed by the normal weight and overweight group with 0.33cm and 0.32cm, respectively. There is no significant adjusted mean difference in the obese group with 0.02cm.

The multivariate models for APGAR 1 and 5 scores showed no significant adjusted mean differences between the smoking groups for any weight status group (see **table 9**).

Table 9: comparison of adjusted mean differences of new-born parameters between smokers and non-smokers for each weight status group

	birth weight (g)					
	non smokers		smokers			
weight status	mean (SD)	*N*	Mean (SD)	*N*	adjusted mean difference (95% CI)[a]	*p*-value
underweight	3311.5 (355.8)	195	3168 (443.9)	105	153.34 (240.0 – 65.7)	0.001[b,c]
normal weight	3409.7 (412.2)	2155	3256.0 (414.2)	833	166.15 (197.8 – 134.6)	<0.001[b,c,d]
overweight	3499.1 (464)	450	3443.7 (458.5)	183	119.04 (195.9 – 42.2)	0.002[b,c,d]
obese	3590.3 (426.4)	121	3538.3 (441.9)	59	66.98 (207.4 - -73.4)	0.348

	birth length (cm)					
	non smokers		smokers			
	mean (SD)	*N*	Mean (SD)	*N*	adjusted mean difference (95% CI)[a]	p-value
underweight	49.7 (1.65)	195	48.7 (1.94)	105	1.04 (0.64 - 1.44)	<0.001[c]
normal weight	50.04 (1.8)	2152	49.39 (1.85)	833	0.69 (0.55 - 0.83)	<0.001[b,c,d]
overweight	50.27 (1.89)	448	49.87 (2.43)	183	0.63 (0.27 – 0.98)	0.001[c,d]
obese	50.54 (1.66)	121	50.44 (1.71)	59	0.14 (-0.41 – 0.68)	0.622[d]

	head circumference (cm)					
	non smokers		smokers			
	mean (SD)	*N*	Mean (SD)	*N*	adjusted mean difference (95% CI)[a]	p-value
underweight	34.21 (1.24)	182	33.69 (1.13)	96	0.51 (0.22 – 0.80)	0.001[c,d]
normal weight	34.44 (1.39)	2007	34.11 (1.37)	751	0.33 (0.22 – 0.45)	<0.001[b,c,d]
overweight	34.72 (1.43)	409	34.51 (1.35)	169	0.32 (0.07 – 0.57)	0.012[b,c,d]
obese	34.79 (1.44)	109	34.86 (1.35)	59	0.02 (-0.49 – 0.45)	0.921

	APGAR 1					
	non smokers		smokers			
	mean (SD)	*N*	Mean (SD)	*N*	adjusted mean difference (95% CI)[a]	p-value
underweight	8.6 (1.16)	192	8.72 (1.04)	105	0.13 (-0.14 – 0.4)	0.340
normal weight	8.67 (1.07)	2140	8.65 (1.09)	826	0.01 (-0.8 – 0.09)	0.879 [c,d]
overweight	8.57 (1.29)	447	8.58 (1.26)	180	0.05 (-0.18 – 0.28)	0.662[c]
obese	8.68 (1.12)	120	8.36 (1.69)	58	0.27 (-0.17 – 0.71)	0.226

	APGAR 5					
	non smokers		smokers			
	mean (SD)	*N*	Mean (SD)	*N*	adjusted mean difference (95% CI)[a]	p-value
underweight	9.79 (0.50)	183	9.79 (0.7)	100	0.01 (-0.13 – 0.15)	0.905
normal weight	9.76 (0.56)	2010	9.75 (0.60)	800	0.002 (-0.05 – 0.05)	0.947
overweight	9.71 (0.71)	411	9.7 (0.64)	174	0.01 (-0.12 – 0.14)	0.876
obese	9.77 (0.55)	110	9.75 (0.91)	57	0.02 (-0.21 – 0.26)	0.864

a = adjusted for age of the mother, maternal stature and weight gain during pregnancy; b = significant for parameter age mother($p<0.05$); c = significant for parameter weight gain during pregnancy; d = significant for maternal stature

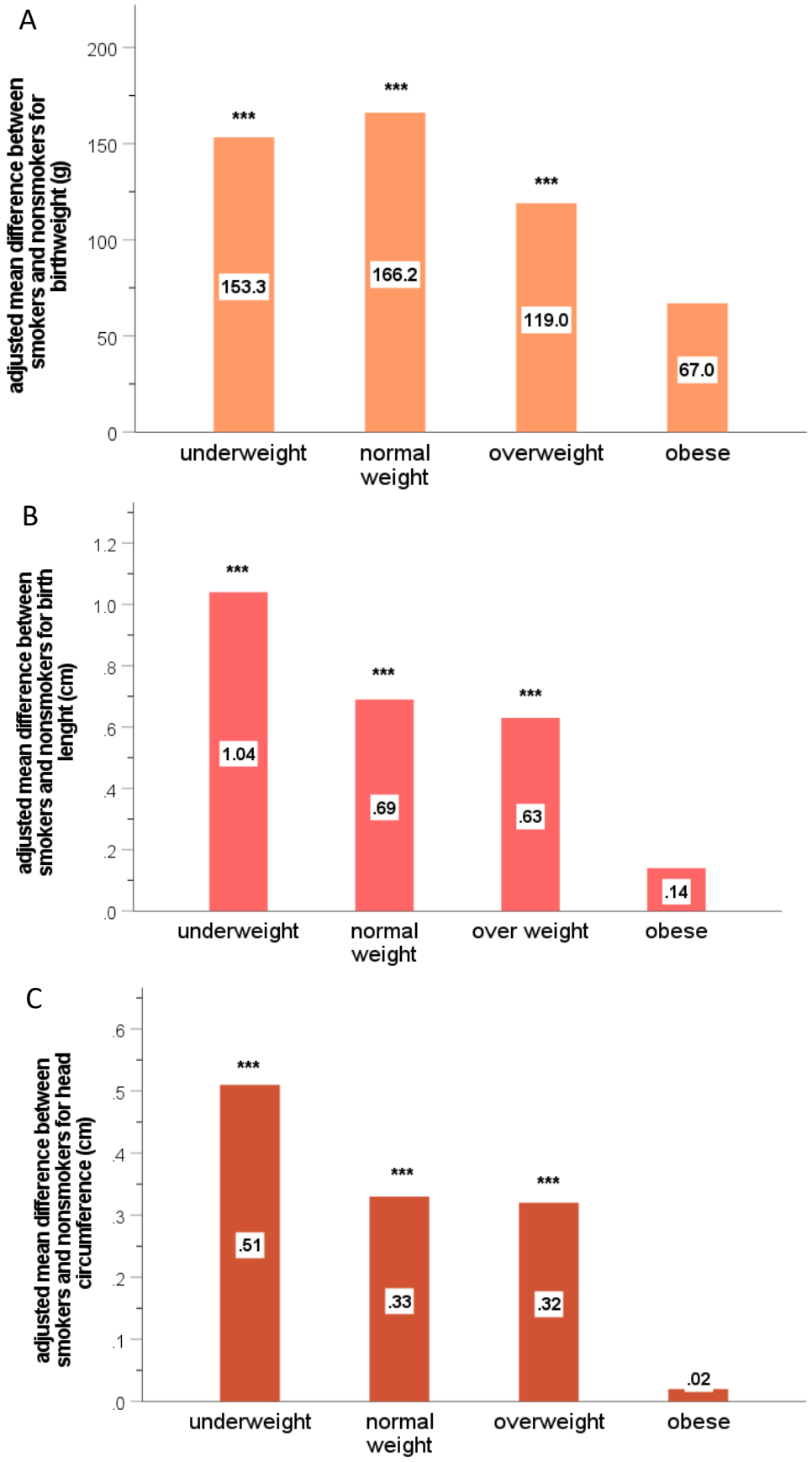

Figure 2*:* Comparison of the adjusted mean differences for the new-born parameters between smoking and non-smoking mothers between the maternal weight status groups. *** = significant difference ($p > 0.05$). **A)** shows the adjusted mean difference for birth weight **B)** shows the adjusted mean difference for birth length **C)** shows the adjusted mean difference for head circumference

New-born sex as moderating effect on interaction of maternal weight status and smoking during pregnancy

As a last step the effect of the new-born's sex on the interacting effects of maternal weight status and smoking during pregnancy on the new-born parameters is investigated. Therefore, the smoking groups within every weight status group are divided into male and female neonate subgroups. **Table 10** shows the descriptive statistics of the different subgroups.

In the next step multivariate linear regression models were calculated to get the adjusted mean differences between the sexes for the non-smoking and smoking mothers within every weight status group. The models are adjusted for the confounding factors maternal stature, weight gain during pregnancy and maternal age. **Table 11** shows the mean and SD for the male and female neonates within every subgroup and the adjusted mean difference with the 95% confidence interval.

Birth weight

Looking at the parameter birth weight in the smoking mothers there is only a significant adjusted mean difference between males and females in the underweight and normal weight group. A trend can be observed that the sex difference is getting smaller from underweight to the obese group (see **figure 3**). The underweight group has the highest sex difference with females being 202.6 g lighter than males (p = 0.019) and in the obese group there is the smallest difference with 54.5g, which is not significant.

In comparison to the smoking mothers the trend in the non-smoking mothers is opposite. The overweight and obese group are having higher adjusted mean differences between male and female new-borns. The highest sex difference for neonates of non-smoking mothers can be found in the obese group with males being 259.3 g heavier than females and the lowest in the normal weight group with 115.4g. For all weight status groups of non-smoking women, the adjusted mean sex differences are significant.

Birth length

In the smoking mothers' groups, the adjusted mean sex difference is highest in the underweight group with males being 0.96cm taller than females (p = 0.008) and smallest in the obese group with 0.77cm difference, which is not significant. The sex difference for birth length in the normal and overweight group is rather similar with males being 0.87cm (p < 0.001) and 0.86cm (p = 0.014) taller, respectively.

The trend in the non-smoking mothers is going in the opposite direction with the overweight and obese groups having the higher adjusted mean sex differences and the underweight group having the smallest (see figure 3). The highest difference can be found for the overweight mothers with male new-borns being 1.35cm taller. The male neonates of underweight mothers in comparison are only 0.75 cm taller than the female. All adjusted mean differences being significant.

Head circumference

For the new-born parameter head circumference, the trend for the adjusted mean sex differences between the weight status groups is rather similar for the smoking and non-smoking women (see **figure 3**). The smallest sex difference in the smoking mothers regarding head circumference can be found in the underweight group with males having a 0.28cm larger head circumference, this difference is not significant (see **table 11**). The highest adjusted mean difference has the obese group. In this group the males are having a 1.07 cm larger head circumference ($p = 0.001$).

The weight status group with the smallest adjusted mean sex difference in head circumference for the non-smoking mothers can be found in the normal weight group with males having a 0.41cm larger head circumference than female new-borns ($p < 0.001$). The underweight group is having a slight bigger difference with 0.5cm ($p = 0.007$) and the biggest difference is found in the obese group. Male new-borns of obese non-smoking mothers are having a 0.75cm larger head circumference than the female ones ($p = 0.008$).

APGAR 1 and 5 score

For APGAR 1 there are no significant adjusted mean differences between male and female new-borns in any smoking and weight status subgroup (see **table 11**). The only significant adjusted mean difference for the parameter APGAR 5 can be found in the obese non-smoking group. Females having a 0.26 higher adjusted mean APGAR 5 score than male new-borns ($p = 0.014$).

Table 10: comparison of sex differences of new-born parameters between smoking and non-smoking mothers during pregnancy for each weight status group

		weight status groups															
		underweight				normal weight				overweight				obese			
		non-smoking		smoking		non-smoking		smoking		non-smoking		smoking		non-smoking		smoking	
		m	f	m	f	m	f	m	f	m	f	m	f	m	f	m	f
birthweight (g)	*N*	105	90	43	62	1098	1057	402	431	230	220	102	81	58	63	29	30
	mean	3386	3224	3331	3055	3472	3345	3311	3205	3599	3394	3478	3401	3719	3472	3559	3519
	SD	331.3	365.1	462.4	396.4	414.0	400.6	414.2	408.1	441.8	464.5	433.6	487.4	384.5	431.6	433.0	456.9
	median	3350	3200	3350	3025	3450	3350	3300	3250	3600	3400	3500	3350	3665	3500	3600	3575
	Q1/Q3	3150/ 3600	2950/ 3450	2950/ 3650	2800/ 3300	3200/ 3750	3090/ 3600	3050/ 3550	2950/ 3450	3300/ 3900	3100/ 3673	3195/ 3713	3050/ 3700	3448/ 3975	3200/ 3750	3250/ 3875	3175/ 3870
birth length (cm)	*N*	105	90	43	62	1096	1056	402	431	230	218	102	81	58	63	29	30
	mean	50.11	49.22	49.51	48.15	50.48	49.58	49.84	48.97	50.91	49.60	50.25	49.40	51.16	49.97	50.79	50.10
	SD	1.58	1.61	2.04	1.67	1.75	1.76	1.83	1.78	1.79	1.76	1.92	2.90	1.57	1.55	1.15	2.07
	median	50	49	49	48	51	50	50	49	51	50	50	50	51	50	51	50
	Q1/Q3	49/51	48/50	48/51	47/49	49/52	48/51	49/51	48/50	50/52	49/51	49/51.25	48/51	50/52	49/51	50/51.5	48/51.25
head circumference (cm)	*N*	95	87	38	58	1019	988	360	391	209	200	93	76	52	57	29	30
	mean	34.49	33.91	33.97	33.5	34.65	34.22	34.34	33.91	35.01	34.41	34.84	34.12	35.19	34.4	35.38	34.37
	SD	1.22	1.20	1.10	1.11	1.41	1.33	1.36	1.35	1.40	1.40	1.37	1.22	1.44	1.35	1.21	1.30
	median	34	34	34	33.5	35	34	34	34	35	35	35	34	35	34	35	34
	Q1/Q3	34/35	33/35	33/34	33/34	34/36	33/35	33/35	33/35	34/36	34/35	34/36	33/35	34/36	34/35	34.5/36	34/35
APGAR 1	*N*	104	88	43	62	1092	1048	398	428	229	218	100	80	58	62	29	29
	mean	8.56	8.65	8.63	8.79	8.65	8.70	8.66	8.64	8.57	8.57	8.48	8.70	8.43	8.9	8.31	8.41
	SD	1.3	0.97	1.16	0.96	1.09	1.04	0.96	1.18	1.21	1.36	1.51	0.86	1.33	0.84	2.04	1.30
	median	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
	Q1/Q3	8/9	8/9	8/9	8.75/9	8/9	8/9	8/9	8/9	8/9	8/9	8/9	8/9	8/9	9/9	7.5/9	8/9
APGAR 5	*N*	97	86	42	58	1028	982	388	412	212	199	95	79	55	55	28	29
	mean	9.8	9.77	9.71	9.84	9.75	9.78	9.78	9.72	9.71	9.72	9.61	9.80	9.65	9.89	9.61	9.90
	SD	0.45	0.55	1.00	0.37	0.60	0.60	0.51	0.67	0.69	0.74	0.75	0.46	0.67	0.37	1.26	0.31
	median	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Q1/Q3	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	9/10	10/10	9/10	10/10	10/10	10/10

Table 11: comparison of adjusted mean differences of new-born parameters between males and females for each weight status and smoking group

	birth weight (g)					
	males		females			
weight status and smoking status	mean (SD)	*N*	Mean (SD)	*N*	adjusted mean difference (95% CI)[a]	*p*-value
underweight and smoking	3331 (462.4)	43	3055 (396.4)	62	-202.6 (-371.6 - -33.5)	0.019 [c]
normal weight and smoking	3311 (414.2)	402	3205 (408.1)	431	-101.2 (-154.8 - -47.7)	<0.001 [c,d]
overweight and smoking	3478 (433.6)	102	3401 (487.4)	81	-72.6 (-198.1 – 52.9)	0.255 [c,d]
obese and smoking	3559 (433)	29	3519 (456.9)	30	-54.5 (-282.9 – 173.9)	0.634
underweight and nonsmoking	3386 (331.3)	105	3224 (365.1)	90	-124.3 (-219.7 - -28.9)	0.011 [b,c]
normal weight and nonsmoking	3472 (414)	1098	3345 (400.6)	1057	-115.4 (-148.2 - -82.6)	<0.001 [b,c,d]
overweight and nonsmoking	3599 (441.8)	230	3394 (464.5)	220	-218.6 (-297.3 - -139.9)	<0.001 [b,c,d]
obese and non-smoking	3719 (384.5)	58	3472 (431.6)	63	-259.3 (-409.9 - -108.7)	0.001
	birth length (cm)					
	males		females			
	mean (SD)	*N*	Mean (SD)	*N*	adjusted mean difference (95% CI)[a]	*p*-value
underweight and smoking	49.51 (2.04)	43	48.15 (1.67)	62	-0.96 (-1.66 - -0.25)	0.008 [c]
normal weight and smoking	49.84 (1.83)	402	48.97 (1.78)	431	-0.87 (-1.10 - -0.63)	<0.001 [c,d]
overweight and smoking	50.25 (1.92)	102	49.40 (2.90)	81	-0.86 (-1.54 - -0.17)	0.014 [b,c]
obese and smoking	50.79 (1.15)	29	50.10 (2.07)	30	-0.77 (-1.65 – 0.10)	0.082
underweight and nonsmoking	50.11 (1.58)	105	49.22 (1.61)	90	-0.75 (1.20 - -0.31)	0.001 [c]
normal weight and nonsmoking	50.48 (1.75)	1096	49.58 (1.76)	1056	-0.85 (-1.00 - -0.71)	<0.001 [b,c,d]
overweight and nonsmoking	50.91 (1.79)	230	49.60 (1.76)	218	-1.35 (-1.66 - -1.03)	<0.001 [c,d]
obese and non-smoking	51.16 (1.57)	58	49.97 (1.55)	63	-1.29 (-1.86 - -0.73)	<0.001 [d]
	head circumference (cm)					
	Males		Females			
	mean (SD)	*N*	Mean (SD)	*N*	adjusted mean difference (95% CI)[a]	*p*-value
underweight and smoking	33.97 (1.10)	38	33.50 (1.11)	58	-0.28 (-0.73 – 0.18)	0.228 [c,d]
normal weight and smoking	34.34 (1.36)	360	33.91 (1.35)	391	-0.42 (-0.61 - -0.23)	<0.001 [c,d]
overweight and smoking	34.84 (1.37)	93	34.12 (1.22)	76	-0.70 (-1.10 - -0.31)	0.001 [d]
obese and smoking	35.38 (1.21)	29	34.37 (1.30)	30	-1.07 (-1.69 - -0.44)	0.001

	head circumference (cm)					
	males		females			
	mean (SD)	*N*	mean (SD)	*N*	adjusted mean difference (95% CI)[a]	*p*-value
underweight and nonsmoking	34.49 (1.22)	95	33.91 (1.20)	87	-0.50 (-0.86 – -0.14)	0.007 [c]
normal weight and nonsmoking	34.65 (1.41)	1019	34.22 (1.33)	988	-0.41 (-0.52 - -0.29)	<0.001 [b,c,d]
overweight and nonsmoking	35.01 (1.40)	209	34.41 (1.40)	200	-0.66 (-0.92 - -0.40)	<0.001 [b,c,d]
obese and non-smoking	35.19 (1.44)	52	34.40 (1.35)	57	-0.75 (-1.30 - -0.20)	0.008

	APGAR 1					
	males		females			
	mean (SD)	*N*	mean (SD)	*N*	adjusted mean difference (95% CI)[a]	*p*-value
underweight and smoking	8.63 (1.16)	43	8.79 (1.09)	62	0.27 (-0.16 -0.70)	0.210
normal weight and smoking	8.66 (0.96)	398	8.64 (1.18)	428	-0.02 (-0.17 – 0.13)	0.766 [b,d]
overweight and smoking	8.48 (1.51)	100	8.70 (0.86)	80	0.24 (-0.13 – 0.61)	0.204 c
obese and smoking	8.31 (2.04)	29	8.41 (1.30)	29	0.09 (-0.82 – 1.00)	0.840
underweight and nonsmoking	8.56 (1.3)	104	8.65 (0.97)	88	0.09 (-0.24 – 0.43)	0.588
normal weight and nonsmoking	8.65 (1.09)	1092	8.70 (1.04)	1048	0.05 (-0.05 – 0.16)	0.330 [c,d]
overweight and nonsmoking	8.57 (1.21)	229	8.57 (1.36)	218	0.01 (-0.23 – 0.25)	0.952
obese and non-smoking	8.43 (1.33)	58	8.9 (0.84)	62	0.52 (1.01 – 0.92)	0.014

	APGAR 5					
	males		females			
	mean (SD)	*N*	mean (SD)	*N*	adjusted mean difference (95% CI)[a]	*p*-value
underweight and smoking	9.71 (1.00)	42	9.84 (0.37)	58	0.18 (-0.12 - 0.47)	0.235
normal weight and smoking	9.78 (0.51)	388	9.72 (0.67)	412	-0.06 (-014 – 0.03)	0.177 [d]
overweight and smoking	9.61 (0.75)	95	9.80 (0.46)	79	0.19 (-0.05 – 0.38)	0.056
obese and smoking	9.61 (1.26)	28	9.90 (0.31)	29	0.32 (-0.18 – 0.81)	0.202
underweight and smoking	9.8 (0.45)	97	9.77 (0.55)	86	-0.03 (-0.18 – 0.12)	0.709
normal weight and smoking	9.75 (0.60)	1028	9.78 (0.60)	982	0.02 (-0.03 – 0.08)	0.363 [c]
overweight and smoking	9.71 (0.69)	212	9.72 (0.74)	199	0.02 (-0.12 – 0.16)	0.802 [c]
obese and smoking	9.65 (0.67)	55	9.89 (0.37)	55	0.26 (0.6 – 0.47)	0.014

a = adjusted for age of the mother, maternal stature and weight gain during pregnancy; b = significant for parameter age mother($p<0.05$); c = significant for parameter weight gain during pregnancy; d = significant for maternal stature

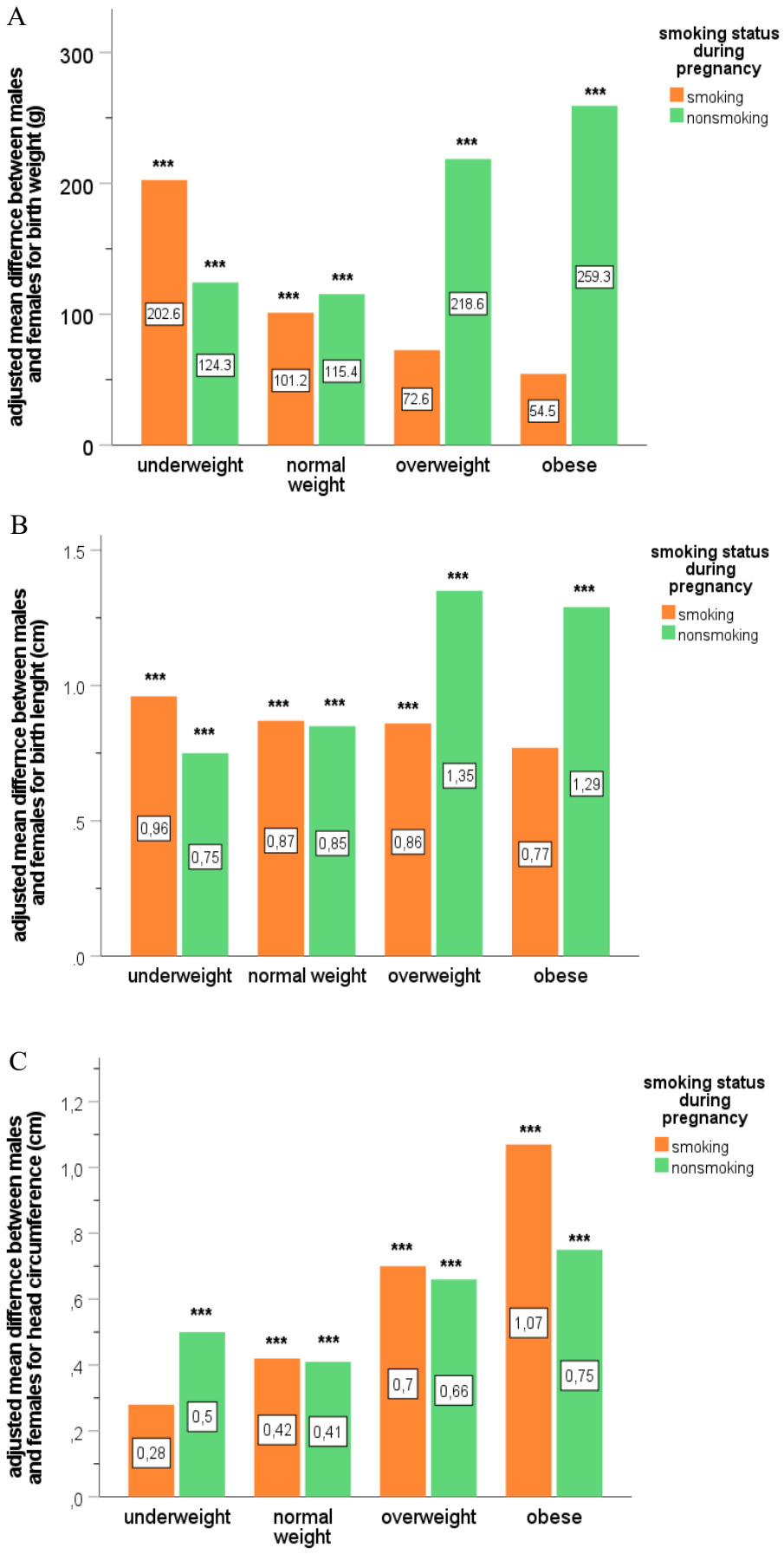

Figure 3: comparison of the adjusted mean sex difference in the new-born parameters between non-smoking and smoking mothers within every weight status group. *** = significant difference ($p > 0.05$). **A)** shows the adjusted mean differences for birth weight **B)** shows the adjusted mean differences for birth length **C)** shows the adjusted mean differences for head circumference

Discussion

The aim of this medical record based retrospective study, which assessed a sample of 4141 mother-child pairs, was to investigate possible interacting effects of maternal pre-pregnancy weight status and nicotine consumption during pregnancy on foetal growth and whether these effects are moderated by the new-born's sex.

Smoking prevalence

First the smoking prevalence of the different weight status groups was compared. The smoking prevalence in all groups was getting smaller during pregnancy. The most smoking mothers were found in the underweight and obese group. These groups had also the highest amount of smoked cigarettes per day. Similar results can be found in the study of Günther et al. (2021), which found that BMI and smoking prevalence are connected. The linkage of smoking during pregnancy and an unhealthy weight status could be influenced by the socioeconomic status (SES). It is known that smoking is related to a lower SES (Hiscock et al., 2012). An unhealthy lifestyle which also includes an unfavourable weight status is also related to lower SES like Jimenez-Mora et al. (2020) and McLaren (2007) showed.

Especially for women in high-income countries the negative association between BMI and SES is strong. In contrast, this relationship has been reversed in low-income countries until recent decades, when the trend shifted to a pattern similar to that in developed countries, where obesity is associated with low social status. McLaren (2007) points out that this shift in low-income countries is due to changes in society and nutritional behaviour which are caused by economic growth, globalization, especially of the food market, and other factors linked to modernisation.

The relationship of high smoking prevalence and smoking dose with the weight status of the mothers on the one hand and the socioeconomic status on the other hand has also to be discussed in the light of the known association of lower birthweight and low SES (Martinson & Reichman, 2016). This interrelatedness has to be considered when investigating interacting effects of tobacco consumption and weight status on foetal growth. The possible effect of SES on these interactions and the problem of not knowing the SES background of the investigated women in this study will be discussed in more detail in the limitation section of this thesis.

Independent effects of maternal weight status, smoking during pregnancy and new-born's sex on new-born parameters

The results have shown that maternal BMI, smoking during pregnancy and the new-born's sex have independent effects on the new-born parameters birth weight, birth length and head circumference. The results of each independent risk factor are discussed in the following section.

Maternal weight status

Comparison of the weight status groups showed that the obese group had children with the highest birth weight, birth length and biggest head circumference and the underweight mothers had the smallest and lightest new-borns. Several previous studies have also found this effect of maternal BMI on foetal growth (Kirchengast & Hartmann, 1998; Zhang et al., 2018). A major role in the mechanism explaining this effect are endocrine factors. Sewell et al. (2006) reported that the increase in birth weight with higher maternal BMI is primarily due to increased fat mass and not lean body mass. They argue that the over-nutritious environment of overweight and obese mothers, which hormonal milieu is characterised by increased lipid and glucose concentrations, leads to a similar hormonal milieu of the foetus like higher insulin levels. This leads to overgrowth of the foetus and especially to accelerated growth of fat mass. Like Sewell et al. (2006) the study of Kristiansen et al. (2021) supports the major role of a high maternal glucose level on regulating foetal insulin and glucose levels and therefore foetal growth. They furthermore showed that the main mediator between the association of maternal obesity and increased birth weight and fat mass percentage of the neonate was placental weight.

Nevertheless, there are not only environmental factors driving the association of birthweight and maternal weight status, but also genetic and epigenetic factors. Tyrrell et al. (2016) found in a mendelian randomization study evidence for a causal association of a genetically increased maternal BMI with a higher birth weight, which could be mediated by the effects of higher maternal fasting glucose levels.

Maternal overweight and obesity increases the risk of miscarriage (Ghimire et al., 2020) as well as macrosomia and other adverse pregnancy and health outcomes for the child (Sebire et al., 2001). Furthermore, maternal obesity leads to higher caesarean section rates (Kirchengast & Hartmann, 2018), higher risk for intrauterine growth restriction and LBW (Lewandowska, 2021).

In contrast, maternal underweight leads to reduced growth of the foetus, as the results of this study show. The underweight mothers had neonates with the lowest birth weight, shortest birth lengths and smallest head circumference. These findings are in line with Pölzlberger et al. (2017) who showed that maternal pre-pregnancy BMI is negatively correlated with new-born size. Concerning adverse birth outcomes, the effect of BMI is u-shaped, with not only overweight and obesity having a negative effect on the development and birth outcome but also underweight is increasing the risk of foetal growth restriction and LBW (Ehrenberg et al., 2003; Lewandowska, 2021).

There was no significant difference in APGAR 1 and 5 scores between the weight status groups in the univariate comparison. However, the multivariate regression model showed a significant small independent negative effect of BMI on the APGAR scores. This is further proof for the negative effect of maternal obesity on the new-born's well-being.

Smoking during pregnancy

The independent negative effects of maternal smoking on the foetal development and growth are well documented (Huang et al., 2017; Jaddoe et al., 2007; Pietersma et al., 2022; Suzuki et al., 2016). This study also has demonstrated these effects. Multivariate regression analyses showed a significant negative relation of nicotine consumption during pregnancy on birth weight, birth length and head circumference. However, no significant effect of smoking on APGAR 1 and 5 scores could be found. A more detailed analysis of maternal tobacco consumption and its effects on new-born parameters was conducted in a previous study on the same sample and can be read in Koger et al. (2021).

The variety of toxic substances contained in cigarette smoke negatively affect foetal development in various ways. Smoking induces impaired placental development, creating a hypoxic environment by reducing blood flow. It could also be shown that these effects are not only present in active but also in passive smoking mothers (Zdravkovic et al., 2005). In addition, increased levels of the heavy metal cadmium are found in the placenta of smoking women. Cadmium has toxic effects and causes structural and functional changes in the placenta (Shiverick & Salafia, 1999). Furthermore, recent studies have demonstrated that maternal tobacco consumption during pregnancy is associated with epigenetic modification of DNA methylation in the foetus that could mediate the effect of smoking on birth weight (Hannon et al., 2019; Witt et al., 2018).

Sex of the foetus

Also, the sex of the foetus showed an independent effect on the new-born parameters and therefore on foetal growth. The results showed that males are consistently larger and heavier than female neonates, indicating that they have different intrauterine growth patterns. Multivariate analyses, which controlled for several influencing factors, showed an independent positive effect of being male on growth. This indicates that there are intrinsic physiological mechanisms influencing growth in a sex specific manner already during pregnancy. Broere-Brown et al. (2016) conducted a study on sex specific differences on foetal growth, which also demonstrated that male new-borns had higher mean birth weight than females. Furthermore, they studied foetal growth from the first trimester onwards and could show that crown to rump length is larger in males. From the second trimester onwards head circumference and abdominal circumference was larger in males. However, femur length in the third trimester was larger in females. The difference in body weight persisted until 12 months of age, after that female infant were heavier than the males. They concluded that differences in growth patterns between the sexes can already be seen from the first trimester onwards. Another study found further evidence for different trends in foetal growth rates between males and females. de Jong et al. (1998) could show that a higher daily growth rate of males in the third trimester is leading to heavier and bigger mele neonates at birth. This all demonstrates that a sexual dimorphism in body weight, size and proportions is already present in utero.

Broere-Brown et al. (2016) argue that this sex dimorphism in in foetal growth could be explained by differences in placental function. Sex specific function of the placenta and its influence on foetal growth patterns, morbidity and mortality was also proposed by Clifton (2010). Broere-Brown et al. (2016) further discuss this sexual dimorphism in the context of foetal programming and the development and origin of health and disease theory. They state that the mechanisms behind these differences in growth and body proportions during pregnancy might also influence the sex differences in chronic diseases in adulthood.

After demonstrating the independent effects of the studied variables maternal weight status, smoking during pregnancy and the sex of the foetus on human growth and discussing the results in the context of the previous literature, the interacting effects of these factors on the new-born parameters are discussed in the next section.

Discussion of interacting effects of maternal pre-pregnancy weight status and smoking during pregnancy

Human growth and development are influenced by various maternal, environmental, social, genetic and epigenetic factors which can also influence each other. The aim of this study was not only to investigate the independent effects but also to investigate the interacting effects of maternal weight status, tobacco consumption and the new-born's sex on foetal growth. This section is dealing with the interactions of maternal pre-pregnancy weight status, underweight on the one hand and overweight/obesity on the other hand, and smoking during pregnancy.

Hypothesis 1 proposed an additive negative effect of maternal pre-pregnancy underweight and smoking during pregnancy on new-born parameters. The main findings were that for new-borns of underweight mothers the effect of smoking during pregnancy on birth weight is similar to normal-weight mothers. However, for birth length and head circumference the negative effect of tobacco consumption is getting stronger in underweight women. That indicates an additive negative effect of the two independent factors smoking and maternal pre-pregnancy underweight on these two new-born parameters. For APGAR 1 and 5 scores no significant interaction effects could be found. Hypotheses 1 can therefore be partly confirmed for the new-born parameters birth length and head circumference.

Hypothesis 2 states that maternal pre-pregnancy overweight/obesity and smoking during pregnancy have negative additive effects on the new-born parameters. For the parameters birth weight, birth length and head circumference the effects of smoking seem to be cancelled out in overweight and especially in obese mothers. Both factors which have been shown to have independent negative effects on foetal growth (Jaddoe et al., 2007; Shiohama et al., 2021) and are increasing the risk for adverse birth outcomes like LBW and foetal growth restriction (Lewandowska, 2021) do not increase the negative effects on foetal growth when occurring together. The results of this study demonstrate clearly that the proposed interaction of obesity and smoking during pregnancy goes in the opposite direction and therefore hypothesis 2 can be rejected.

Some studies have previously shown comparable results. Chattrapiban et al. (2020) found similar term birth weights when comparing new-borns of smoking overweight mothers with normal weight non-smoking mothers. In addition, the risk for SGA and LGA are also similar between those two groups. Like Chattrapiban et al. (2020) the study of La Merrill et al. (2011) showed a reduction in the harmful effects of smoking on birth weight and SGA risk in overweight and obese mothers. Furthermore, Heinz-

Partington et al. (2016) demonstrated that higher BMI reduced the effects of tobacco consumption during pregnancy on birth weight. The study of Phillips et al. (2018) investigated the associations of maternal weight status and smoking status on gestational age at delivery and risk for admission to the neonatal intensive care unit (NICU). They found for new-borns of underweight/normal weight mothers, who were smoking, a lower age at delivery and a higher risk for admission to the NCIU in comparison to non-smoking mothers. For overweight and obese mothers there was no such effect of smoking on the admission risk to the NCIU and a lower age at delivery. These studies all draw the conclusion that the negative effects of cigarette smoking during pregnancy on foetal growth is cancelled out when the mother is overweight or obese. This is in line with the results presented here, whereby this study could not only show the effect for birth weight but also for the parameters birth length and head circumference.

However, there are also studies with contrary results. A German study on 110 047 singleton births showed a significantly lower mean neonatal birth weight when comparing smoking and non-smoking mothers in the different weight status groups. Even in the obese group smoking mothers had significantly lighter new-borns than non-smokers (Günther et al., 2021). However, they did not control for confounding factors like maternal stature, gestational weight gain or maternal age. Lewandowska et al. (2020) found an additive effect of smoking and maternal obesity on the risk for foetal growth restriction (FGR) and LBW. When mothers were smoking during the first trimester and additionally were obese, the individual risk of smoking was increased. They explained the additive effect on the risk for adverse birth outcomes like LBW and FGR with higher oxidative stress and inflammation that goes along with obesity and smoking. Another evidence for the increased risk of adverse birth outcomes through a combination of maternal smoking and obesity is a study from Nepal. They showed an increased risk of miscarriage when mothers were obese and smoking in comparison to non-smoking normal-weight mothers (Ghimire et al., 2020).

This demonstrates that even when the negative effects of smoking on foetal growth seems to be cancelled out in obese mothers the risks for several adverse birth outcomes are still elevated when both risk factors co-occur. Therefore, smoking obese mothers have to be considered as a high-risk group for adverse birth outcomes. Because of that Chattrapiban et al. (2020) suggested that birth weight might not be a good predictor of the new-born's health status and potential health risks could be masked.

The analysis of the additive effects of smoking and underweight on foetal growth in previous studies showed contrary results regarding birth weight. The results of this study could not find big differences

in reduction of mean birth weight through smoking when comparing underweight and normal weight mothers. In contrast, the study of La Merrill et al. (2011) showed that the highest reduction of birth weight through smoking was present in the underweight group with 187 g (95% CI: -337g, -37g). However, in the normal weight group the reduction was quite lower with only 129g (95% CI: -170g, -87g). The results of Günther et al. (2021) also demonstrated that the underweight smoking group had the lowest mean birth weights. Furthermore, Lewandowska et al. (2020) found a higher risk for FGR in smoking underweight mothers in comparison to normal weight non-smoking women.

The results of the adjusted mean differences for birth length and head circumference presented in this study clearly indicate an additive negative effect of tobacco consumption and maternal pre-pregnancy underweight on foetal growth. Why the adjusted mean difference for birth weight did not show clear evidence for an interacting effect of smoking and underweight like the other studies could demonstrate remains unclear. The sample size for the underweight smoking and non-smoking group was relatively small and the 95% confidence interval for the adjusted mean difference was quite large ranging from 66g - 240g difference between smoking and non-smoking mothers. In addition, the underweight group had a higher upper end of the confidence interval with 240g than the normal weight group with a 95% CI of 135g to 199g. It might be possible that a bigger sample for underweight mothers would show a stronger difference between underweight and normal weight mothers for birth weight.

The biological mechanisms which cause the observed interacting effects of smoking and maternal weight status are not fully understood yet. On the one hand La Merrill et al. (2011) hypothesize that one explanation for the reduced risk of smoking through maternal obesity is caused by elevated hypertriglyceridemia which results from obesity. This could weaken the harmful effects of the toxicity of cigarette smoking on foetal growth. On the other hand, Chattrapiban et al. (2020) argue that there could be two different pathways involved which do not interfere when the foetus is exposed to the risk factors smoking and maternal obesity. Therefore, the co-occurrence of cigarette smoking and obesity do not lead to additive negative effects on foetal growth.

However, there could be underlying biological mechanisms that lead to possible long-term effects on development and health of the individual later in life. The developmental origin of health and disease hypothesis (DOHaD) states that stress factors acting on the intrauterine development can lead to an increased risk for diseases in adulthood mediated through foetal programming. It has been shown that maternal pre-pregnancy overweight/obesity as well as smoking during pregnancy increase not only the risk for obesity in childhood (Oken et al., 2008; Yu et al., 2013) but even in adulthood (Power

& Jefferis, 2002). Furthermore, a Japanese study investigated childhood growth trajectories in dependence of the combination of maternal weight status and smoking during pregnancy (Suzuki et al., 2015). Their findings indicate differences in childhood growth trajectories in different combinations of maternal pre-pregnancy weight status and smoking status. Especially boys of obese smoking mothers which were the smallest and lightest at birth showed a strong catchup growth in BMI z-scores until the age of three. At the age of 9-10 years, they had the highest BMI scores. All this evidence implicates the relevance of taking measures to prevent an unhealthy weight status and smoking during pregnancy in mothers.

Discussion of the moderating effect of the new-born's sex on the interaction of maternal pre-pregnancy weight status and smoking during pregnancy

After demonstrating the independent effects of maternal pre-pregnancy weight status and smoking during pregnancy an inverse interacting effect of both factors could be shown. With increasing maternal BMI, the negative effects of tobacco consumption on foetal growth seems to be vanishing. In the following section the moderating effect of the new-born's sex will be discussed.

The main findings were that for birth weight and for birth length with a higher maternal pre-pregnancy BMI the negative effect of smoking was getting stronger in males in relation to females. However, in underweight mothers male new-borns seem to have an advantage over females when the mothers were smoking during pregnancy. In contrast, the observed trend for the parameter head circumference was in the opposite direction. In overweight and obese mothers, the female new-borns are more affected by maternal tobacco consumption during pregnancy than males. In underweight mothers the negative effects of smoking are more pronounced in males regarding the growth of the head.

The male disadvantage hypothesis states that males are more affected by stress factors during intrauterine development and show therefore a higher morbidity and mortality (Naeye et al., 1971). Several previous studies have shown that male new-borns are at higher risk for several adverse birth outcomes (Di Renzo et al., 2007; Stevenson et al., 2000; Vatten & Skjærven, 2004). The hypothesis of this study was that the interacting effect of maternal weight status and smoking during pregnancy is stronger in male new-borns than in females. The hypothesis can only be partly confirmed for the parameters birth weight and birth length in overweight/obese mothers and for head circumference in underweight mothers.

The study of Kirchengast & Hartmann (2013) showed that maternal obesity affects male foetuses more than females. The typical increase of the new-born parameters of birth weight, birth length and head circumference caused by a higher maternal weight status was lower for males and the prevalence of macrosomia was less elevated in male than in female new-borns. They conclude that male foetal growth is more negatively affected by maternal overweight and obesity. Another study conducted by Kirchengast & Hartmann (2009) demonstrated that several maternal stress factors like nicotine consumption during pregnancy, low or high maternal age, maternal underweight or obesity is affecting foetal growth in a sex specific manner. All these maternal stress factors led to a reduction in the sex differences in new-born parameters. In addition there was no sex specific effect found regarding the APGAR scores, which is in line with the findings of this study. Kirchengast & Hartmann (2009, 2013) interpreted their findings in favour of the male disadvantage hypothesis. The results presented here add further evidence that male foetuses react more sensitive to maternal stress factors during intrauterine development.

Nevertheless, the question arises why the results for head circumference are in conflict with the expectation that male foetuses react more sensitive when both stress factors, smoking and maternal obesity, are present. An explanation could be that head circumference, birth weight and birth length could represent different dimensions of growth and the different growth patterns could be affected independently. Therefore, the interacting effect of smoking and maternal weight status differs from the trend which is visible in birth weight and birth length. It could be shown that skeletal growth, fat accumulation and head size are independent developmental paths (Kirchengast & Hartmann, 2020; Scheffler et al., 2017).

Another possibility is a different effect of the toxic substances of cigarette smoke on brain development. Head circumference is a good predictor for the growth of the brain volume and can therefore be viewed as an indicator for brain development (Lindley et al., 1999). A recent study of Shiohama et al. (2021) found that smoking during pregnancy resulted in a direct reduction of head circumference which was not mediated by placental weight ratio or placental abnormalities. Jauniaux & Burton (2007) write, that the adverse effects on foetal development are not only caused indirectly by alterations in placental function and morphology but also directly by toxic effects of smoking on the foetal cells. Additionally, cigarette smoking of the mother strongly influences different brain biological parameters of the foetus which leads to abnormalities in cell proliferation and differentiation. In the study of Lampl et al. (2003) smoking on the one hand was associated with accelerated growth of the foetal head at 20 - 22 weeks of gestation which was followed by a smaller biparietal to occipital-frontal diameter ratio and on the other hand with an altered long bone proximal/distal growth gradient

indicated through proportionally longer arms and shorter legs. Furthermore, the growth pattern for head circumference is different between males and females during intrauterine development with males having slower growth rates of head circumference during the second and third trimester (Broere-Brown et al., 2016). Due to the slower growth in head size, it might be that males can better adapt to the combined adverse effects of smoking and high maternal BMI.

All this evidence indicates that maternal smoking could act on different developmental pathways affecting head size growth, long bone growth and fat accumulation independently. This could explain the difference in the sex specific reaction to the combined effects of smoking and maternal weight status between head circumference on the one side and birth weight and birth length on the other side. However, further studies are needed to investigate the different vulnerability of male foetuses in head circumference in comparison to birth weight and birth length.

The exact biological mechanisms which cause the difference in the vulnerability of males and females in foetal development which leads to higher mortality and morbidity rates in male neonates are not fully understood yet. Possible physiological causes might include sex differences in the reaction and sensitivity in foetal growth regulation like differences in the IGF-axis or the placental glucocorticoid metabolism (Murphy et al., 2006). Also sex specific differences in placenta function were discussed by Clifton (2010). Clifton proposes sex specific strategies of regulating placental gene and protein expression as well as placental function when exposed to an adverse maternal environment. The male placenta reacts only with few changes whereas the female placenta reacts with several changes. This strategy of the male foetus should guarantee continued growth even when exposed to a nonoptimal environment. However, this puts the male foetus at higher risk for impaired growth and other adverse birth outcomes. The different placental regulation in females should secure survival when exposed to another adverse event. There are also hypotheses on the ultimate causes of the sex differences in early life mortality and morbidity. Wells (2000) argues that on the basis of the Trivers -Willard hypothesis the different parental investment of the sexes drives the selection in the direction of the preference of physiological traits which lead to maximization of maternal reproductive fitness and therefore favours the ability of females to manipulate the sex ratio at birth in reaction to different environmental factors. The higher vulnerability to stress factors in early life in males could be a result of this optimization process of the maternal reproductive strategy. Wells (2000) further explains that his proposed model suggests that even under improvement of medical care, males will nevertheless always react more sensitive to early life environmental stress than females.

Limitations

The problem of self-reported smoking status

This study also has some limitations that have to be addressed. First of all, the smoking status and number of smoked cigarettes were only self-reported and not verified in any manner like by measuring cotinine levels in the blood or urine, which is a metabolite of nicotine. According to Klebanoff et al. (2001) already in the 1990s the raising awareness of the harmful effects of smoking led to pressure on pregnant women to stop or reduce smoking during pregnancy. However, when they compared the cotinine levels of the women with their self-reported smoking status, they found that the women very accurately reported whether they smoked or not. Nevertheless, the possibility of an underestimation of the smoking prevalence in this sample, which is also from the 1990s, still remains.

Influence of Socio-economic factors on mothers and child's health

Another major limitation of this study is that there is no information available of the mother's socioeconomic status (SES). It is evident that the social-economic-political-emotional environment influences human growth and development in various ways (Bogin, 2021). The socioeconomic status is a representation of different dimensions like a person's education, household income or occupation (Adler & Snibbe, 2003) but it could also be connected to marital status, ethnicity or migration background. As discussed above in the section about the association of a higher smoking prevalence and an unhealthy weight status both here in this study investigated factors, smoking and an unfavourable maternal weight status, are related to a low socioeconomic status which could be the underlying connecting factor (Hiscock et al., 2012; Jimenez-Mora et al., 2020; McLaren, 2007).

A low SES is associated with a decrease in many health measures like people living under the poverty line having a higher morbidity and mortality rate (Adler & Snibbe, 2003). The causal underlying mechanisms of the negative association of low SES and poor health are still under debate and not yet fully understood. Adler & Snibbe (2003) write that a low SES can lead to different exposure of biological, psychological and behavioural stress. Over time, the accumulation of these various stressors may damage the body's ability to regulate its stress response. This concept of allostatic load could be a possible biological pathway which explains the increased risk for diseases through a low SES.

Major et al. (2017) propose a model that explains how weight stigma and discrimination experienced by overweight and obese people negatively affect their health. A major cause for this stigmatization is

the common belief that weight is only under individual control and that it is the persons own fault that they are overweight or obese. This comes along with stereotypes like laziness, lack of discipline, weakness of will and so on. The diverse aetiology of obesity with its genetic, epigenetic and obesogenic environmental influences which cannot be altered by the individual are hereby often neglected. They further explain that this perceived social stigma either directly influences the individual's risk for disease by altering social and material life circumstances decisive to health or indirectly by stigma-avoidance behaviour or negative emotions and pathophysiological processes through increasing stress.

Neuberg & Kenrick (2018) add additional pathways through which discrimination can affect one's health. They propose a framework based on the life history theory in which discrimination and stigma experienced by people of low SES, gender, ethnicity or even obesity change the peoples "*physical and social ecologies*". These Ecologies include pollutants but also restricted and unpredictable availability of resources, unreliable social networks, biased sex-ratios or unpredictable causes of death and mortality threats. When exposed to such environments it comes to an adaptation in life history strategies to encounter these changes like social avoidance behaviour, early sexual maturity, decreased investment in parental investment, increased fat storage, frequent sex with altering partners or opportunistic risk-taking. This in turn results in a higher risk for adverse health outcomes.

All this demonstrates the complex interrelatedness of the mother's socioeconomic status with higher risk for smoking or obesity and social stigma and discrimination which affects not only the mothers but also their children's health indicated by the higher risk for LBW (Martinson & Reichman, 2016), neonatal death (As et al., 2021) or increased infant mortality rate (Zegeye et al., 2021). Therefore, it is crucial when studying foetal growth and development to take the maternal socioeconomic status into account. The environment of a low SES acts through multidimensional stressors on the development of the foetus and has therefore major implications for the health of the new-born and later adult.

Further limitations

There is no information available about the consumption of alcohol or other drugs during pregnancy that could impair foetal growth. Also, the possibility of interacting effects of those substances with the found effects cannot be ruled out. For example, it is known that there are interacting effects of smoking, alcohol and caffeine consumption (Peacock et al., 1991). Another limitation is the relatively small sample size for some groups, especially when further dividing the underweight and obese group

in subgroups of females and males for testing sex differences. Despite the clearly observable trends, confirmation of the found effects by studies with larger sample sizes is indicated. Lastly, the BMI was used to measure the maternal pre-pregnancy weight status. The body mass index, which is simply the ratio of body weight to the squared body height, does not take body composition into account. The BMI might not accurately predict body fat and lean mass values as well as distributions which limits its significance for assessing obesity in a clinical setting (Gonzalez et al., 2017). However, the BMI is a traditional and often used tool for assessing a person's weight status because it is a cheap and easy to use measure unlike other methods for determination of the weight status like bioelectric impedance analysis (BIA), dual energy X-ray absorptiometry (DEXA) or air displacement plethysmography which are expansive, invasive (exposure to X-rays using DEXA) and time consuming. Waist circumference and replacing percentiles with z-scores are two alternatives to using BMI and BMI percentiles to assess the weight status of a person (Daniels, 2009).

Relevance of findings and implications for public health measures

Smoking and obesity display two major public health problems with severe negative health outcomes not only for the mother but also for the child. Human intrauterine development and foetal growth is a multidimensional phenomenon and depends on a diverse range of genetic, environmental, and especially epigenetic influences, which have been getting more and more attention in recent years. Especially with the background of obesity levels rising globally, the investigation of the negative effects of obesity and possible interaction effects with other factors on the child's development becomes more and more important. This study could add additional evidence for the negative effects of smoking during pregnancy and an unhealthy maternal pre-pregnancy weight status and their interaction with each other on foetal growth. Furthermore, the results showed that healthcare practitioners should pay more attention during prenatal care on the child's sex and keep the different risk profiles of male and female neonates in mind.

Through foetal programming and epigenetic modifications negative environmental factors acting on the foetus during pregnancy influence not only the infant's health but also can have long term effects until adulthood. Maternal smoking and rapid infant growth, which is strongly correlated to maternal obesity, are early-life determinants of overweight and obesity (Monasta et al., 2010). In addition, intergenerational effects on foetal growth can be observed through combined effects of maternal and grandmaternal smoking (Rumrich et al., 2021). Therefore, Jacob & Hanson (2020) emphasize the importance of considering the Developmental Origin of Health and Disease concept in national policies and health care guidelines. Policy makers and stakeholders need to be aware of the major risks which

come along with the rising burden of noncommunicable diseases like obesity and the possible intergenerational effects.

The results of this thesis add more evidence to the growing body of research on the effects of maternal lifestyle factors on foetal development which has major implications not only for the infant's wellbeing but also for health in adulthood. The findings of this research call for an intensification of special prevention measures not only for pregnant women but also for women in the periconceptional period to tackle the possible negative effects of an unhealthy lifestyle on the next generation. Therefore the FIGO Pregnancy Obesity and Nutrition Initiative highlights in their position paper the need of addressing the importance of a healthy lifestyle, weight management and adequate nutritional status of both parents before pregnancy (Jacob et al., 2020).

Conclusion

In conclusion the findings of this thesis demonstrated in a first step the independent effects of the investigated factors smoking during pregnancy, maternal pre-pregnancy weight status and the sex of the foetus. Maternal underweight and smoking during pregnancy resulted in reduced foetal growth and maternal overweight/obesity in increased foetal growth. Male new-borns showed a higher birth weight, longer birth length and a bigger head circumference than females. In a next step the interaction of smoking and maternal pre-pregnancy weight status was examined. With a higher maternal BMI, the negative effects of smoking on the new-born parameters seem to be cancelled out. This is in line with several previous studies (Chattrapiban et al., 2020; Heinz-Partington et al., 2016; La Merrill et al., 2011). The over nutritious environment caused by maternal obesity and the resulting excessive growth of the foetus could overrule the negative effects of tobacco consumption. Therefore, the mean values of birth weight, bright length and head circumference do not differ anymore between smoking and non-smoking mothers in overweight and especially in obese mothers. However, this does not implicate that it is irrelevant for obese mothers whether they smoke during pregnancy or not. Nevertheless, smoking could have a diverse range of negative short and even long-term effects on the child's health and development. In a last step the moderating effect of the new-born's sex on the interaction of maternal weight status and smoking during pregnancy was investigated. For birth weight and birth length a trend was observed that with increasing maternal BMI the negative effects of smoking are getting stronger in males. For head circumference the trend was opposite with a low maternal weight status the male foetuses are reacting more vulnerable to smoking during pregnancy. These findings can be interpreted in the light of the male disadvantage hypothesis which states that males are more

vulnerable to negative effects during intrauterine development. However, the different observed trends in birth weight and length on the one hand and head circumference on the other could indicate different developmental pathway which react in a sex specific manner on the interaction of maternal nicotine consumption and maternal pre-pregnancy weight status.

Further research should focus on investigating the interacting effects of smoking and maternal weight status and the moderating effect of the new-born's sex not only on the new-born parameters but also on foetal growth patterns during pregnancy. Furthermore, research should be done to clear the underlying causal mechanisms of the found interactions like through conducting epigenome-wide association studies (EWAS) to find possible specific epigenetic modification patterns. Also important for further research is to include the maternal socioeconomic status into the investigation to disentangle the complex relation of unhealthy lifestyle factors like smoking and unhealthy weight status and the social environment the mother is living in and its effects on foetal development.

Take Home Message

The investigated factors smoking during pregnancy, an unhealthy maternal pre-pregnancy weight status and the new-born's sex play an important role in foetal growth. This study identifies underweight and overweight/obese smoking mothers of male infants as a high-risk group for impaired foetal growth. Public health programs should target these risk groups by introducing special preventative measures in the prenatal as well as in the periconceptional period.

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Zusammenfassung

Der mütterliche Gewichtsstatus vor der Schwangerschaft, Rauchen während der Schwangerschaft und männliches Geschlecht sind unabhängige Risikofaktoren für ungünstige Geburtsergebnisse.

Angesichts der weltweit zunehmenden Adipositasraten und der immer noch zu hohen Prävalenz von Rauchen während der Schwangerschaft sollen in dieser Studie mögliche Wechselwirkungen zwischen einem ungesunden Gewichtsstatus der Mutter und Rauchen während der Schwangerschaft auf das Wachstum des Fötus untersucht werden und ob diese Interaktionen durch das Geschlecht des Neugeborenen beeinflusst werden.

Diese auf Krankenakten basierende retrospektive Studie untersuchte eine Stichprobe von 4141 Einzelgeburten aus den Jahren 1990 bis 1995, die in Wien (Österreich) stattfanden. Unabhängige und interagierende Effekte wurden mit univariaten und multivariaten statistischen Methoden untersucht. Mütterliches Untergewicht und Rauchen während der Schwangerschaft waren mit einem verminderten fötalen Wachstum und mütterliches Übergewicht/Fettleibigkeit mit einem erhöhten fötalen Wachstum verbunden. Männliche Neugeborene waren schwerer und größer als weibliche. Die adjusted mean differences zwischen rauchenden und nicht rauchenden Müttern für das Geburtsgewicht reduzierten sich von 153,3g (p<0,001) in untergewichtigen Müttern zu 67,0g (p=0,622) in adipösen Müttern, für den Kopfumfang von 0,51cm (p=0,001) zu 0,02 (p=0.921) und für die Geburtslänge von 1,04cm (p<0,001) zu 0,14 cm (p=0,622). Für Geburtsgewicht und Geburtslänge wurden bei männlichen Neugeborenen die negativen Effekte des Rauchens mit steigendem mütterlichen BMI stärker. Beim Kopfumfang konnte jedoch ein gegensätzlicher Trend beobachtet werden. Die höhere Anfälligkeit männlicher Föten für die Wechselwirkungen zwischen mütterlichem Rauchen und ungesundem Gewichtsstatus kann mit der „male-disadvantage“-Hypothese erklärt werden.

Public Health Präventionsprogramme sollten auf die hier identifizierten Risikogruppen, nämlich untergewichtige und übergewichtige/adipöse rauchenden Mütter männlicher Säuglinge, abzielen.