IS THERE A COMBINED DOSE-RESPONSE EFFECT OF CIGARETTE SMOKING AND ALCOHOL USE DURING PREGNANCY ON BIRTH WEIGHT IN A DIVERSE WESTERN CAPE COMMUNITY OF SOUTH AFRICA?

by

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Thesis presented in partial fulfilment of the requirements for the degree of Master of Science in the Faculty of Medicine and Health Sciences at Stellenbosch University.

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APRIL 2022

DECLARATION

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Date: April 2022

ABSTRACT

Introduction: Prenatal cigarette exposure (PCE) and prenatal alcohol exposure (PAE) are associated with obstetric complications such as intrauterine growth restriction. This could lead to small for gestational age (SGA) fetuses (who are either constitutionally or pathologically small), potentially resulting in low birth weight (LBW), preterm delivery, perinatal mortality, and infant mortality.

Despite public health warnings and awareness campaigns, a high prevalence of PCE (47 %) and PAE (34 – 51 %) is still reported in South Africa (SA), an upper-middle-income country. This may contribute to the high prevalence (14.2 %) of preterm birth and LBW found in SA, making PCE and PAE two of the largest preventable causes of fetal/infant morbidity and mortality.

Many studies have assessed the effect of PCE and PAE separately, focusing on adverse pregnancy outcomes. However, the combined dose-response relationship between PCE and PAE on birth weight remains unclear.

This study aimed to determine whether there is a combined dose-response effect of cigarette smoking and alcohol during pregnancy on birth weight in a diverse cohort of a well-defined geographical area of low socioeconomic status in the Western Cape community of SA.

Method: Data from the Safe Passage Study, a large, prospective, multidisciplinary study who enlisted 11 892 pregnant women of diverse ancestry residing in well-defined residential areas between August 2007 and January 2015 from two clinical sites were used.

Exposure data was collected at 30-day intervals preceding the last recorded exposure. PCE was captured by asking about the participant's smoking habits (i.e. quantity and frequency of smoking a tobacco cigarette on a typical day or chewing tobacco during a typical week) using grouped frequency options (detailed under methodology). PAE was captured using quantity questions such as sharing of drinks, duration for each drinking occasion, type/brand of beverages consumed, number, container size, and iced or frozen. All drinking was converted to number of standard drinks per day. Brink *et al.* formulated a nine-level alcohol-smoking exposure grouping to examine the prenatal dose-relationship on birth weight.

Data from the South African cohort was used for this study. Only patients with singleton pregnancies that resulted in a live birth with birth weight, infant sex, and gestational age (GA) recorded at birth were included. Birth weight data were converted to birth weight z-scores and centiles according to the reference ranges of the Intergrowth-21st Project and Gardosi. Distributions of z-scores and proportions of SGA (< p10, < p5 and < p3) fetuses were compared across the nine-level alcohol-smoking exposure groups, as well as the collapsed four-level alcohol-smoking exposure groups.

Results: The percentage of newborns identified in our study as SGA was significantly higher than expected. Compared against the nine-level alcohol-smoking exposure grouping, the highest percentage was seen in the dual exposure groups (either or both heavy exposure). The same was seen in the smoking and drinking (SD) category when compared against the four-level alcohol-smoking exposure grouping.

Conclusion: Alcohol and smoking exposure has a combined dose-response effect on birth weight and the proportion of SGA infants, especially when one or both exposures are high.

OPSOMMING

Inleiding: Prenatale sigaretblootstelling (PSB) en prenatale alkoholblootstelling (PAB) word geassosieer met verloskunde komplikasies soos intrauterine groeibeperking. Dit kan lei tot klein vir gestasie (KVG) fetusse (wat normaal of patologies klein is), wat moontlik lei tot lae geboortegewig (LGG), premature kraam, perinatale mortaliteit en babasterftes.

Ten spyte van Openbare Gesondheid-waarskuwings en bewusmakingsveldtogte, word ‘n hoë voorkoms vir PSB (47 %) en PAB (34 – 51 %) steeds in Suid-Afrika (SA), ‘n hoër-middel-inkomste land, aangemeld. Dit kan bydra tot die verhoogde voorkoms (14.2 %) van premature kraam en LGG wat in SA gevind word, wat PSB en PAB twee van die grootste voorkombare oorsake van fetale/baba-morbiditeit en -mortaliteit maak.

Baie studies het die effek van PSB en PAB afsonderlik nagevors met die fokus op nadelige swangerskapuitkomste. Die gekombineerde dosis-respons-verwantskap tussen PSB en PAB op geboortegewig is egter nog onduidelik.

Hierdie studie se doel was om vas te stel of daar 'n gekombineerde dosis-respons-effek van sigaretrook en alkohol gebruik tydens swangerskap op geboortegewig is in 'n diverse kohort van 'n goed gedefinieerde geografiese gebied met lae sosio-ekonomiese status in die Wes-Kaapse gemeenskap van SA.

Metode: Data is gebruik van die Safe Passage-studie, 'n groot, voornemende, multidissiplinêre studie wat 11 892 swanger vroue van uiteenlopende afkoms in goed gedefinieerde woongebiede tussen Augustus 2007 en Januarie 2015 vanaf twee kliniese terreine betrek het.

Blootstellingsdata was ingesamel met intervalle van 30 dae voor die laaste aangetekende blootstelling. PSB was vasgelê deur te vra oor die deelnemer se rookgewoontes deur gebruik te maak van gegroepeerde frekwensie-opsies (gedetailleerd onder metodologie) (d.w.s. hoeveelheid en gereeldheid van ‘n tabak sigaret rook op ‘n tipiese dag of tabak kou gedurende ‘n tipiese week). PAB was bepaal deur vrae soos die deel van drankies, duur van elke drinkgeleentheid, tipe/handelsmerk van verbruikte drank, aantal, houergrootte en ys of bevrore hoeveelheid. Alle gebruik van alkohol is omgesit na aantal standaard drankies per dag. Brink *et al.* het 'n nege-vlak alkohol-rookblootstelling groepering geformuleer om die prenatale dosis-verhouding op geboortegewig te ondersoek.

Data van die Suid-Afrikaanse-kohort is vir hierdie studie gebruik. Slegs pasiënte met enkel-swangerskappe wat gelei het tot 'n lewende geboorte met geboortegewig, geslag van baba en swangerskapsduurte wat by geboorte aangeteken is, is ingesluit. Geboortegewigdata is omgeskakel na geboortegewig z-tellings en sentiele volgens die pasgebore populasie-gebaseerde verwysingsreekse van die Intergrowth-21st Projek en dié van Gardosi (aangepas by individuele pasiëntkenmerke). Verspreidings van z-tellings en proporsies van KVD (< p10) fetusse en ernstige KVD (< p5 of p3) is vergelyk oor die nege-vlak alkohol-rookblootstelling groepe sowel as die ineengestorte vier-vlak alkohol-rookblootstelling groepe.

Uitslae: Die persentasie pasgeborenes wat geïdentifiseer is as KVG, is aansienlik hoër as wat volgens literatuur verwag word. In vergelyking met die nege-vlak alkohol-rookblootstelling groepering, is die hoogste persentasie hiervan gesien in die dubbele blootstelling groepe (een of albei hoë blootstelling). Dieselfde is gesien in die rook en drink

(SD) kategorie wanneer dit vergelyk word met die vier-vlak alkohol-rookblootstelling groepering.

Gevolgtrekking: Alkohol en rookblootstelling het 'n gekombineerde dosis-respons-effek op geboortegewig en die proporsie van KVD-babas het, veral wanneer een of albei blootstellings hoog is.

ACKNOWLEDGEMENTS

I would like to thank Prof Lut TGM Geerts, Prof Hein J Odendaal, and Dr Shantal Windvogel for their guidance and support throughout this study as well as Prof D Nel for the statistical analysis.

A big thank you to the Safe Passage Study, conducted by the Prenatal Alcohol in Sudden Infant Death Syndrome and Stillbirth (PASS) network, for allowing me to use the data collected. Special thanks to the study participants, the midwives who collected the data, and the data capturers who electronically documented and validated the data during the main study.

The Safe Passage Study was funded from the following NIH grants:

U01 HD055154 (NICHD, NIAAA)

U01 HD045935 (NICHD)

U01 HD055155 (NICHD)

U01 HD045991 (NICHD)

U01 AA016501 (NIAAA, NIDCD)

To my husband and daughters, thank you for your continuous support and selfless love. I am forever indebted to you as you sacrificed so much during my research and writing. Without your support, this journey would not be possible.

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LIST OF ABBREVIATIONS

AC:	Abdominal circumference
AGA:	Appropriate for gestational age
ANOVA:	Analysis of variance
BMI:	Body mass index
BPD:	Bi-parietal diameter
D:	Drinking only
EFW:	Estimated fetal weight
FARD:	Fetal alcohol related disorders
FGR:	Fetal growth restriction
FL:	Femur length
g:	Grams
G:	Gravidity
GA:	Gestational age
Ha:	Alternative hypothesis
HC:	Head circumference

Ho: Null hypothesis

HSND: Heavy smoking, no drinking

HSLD: Heavy smoking, low drinking

HSHD: Heavy smoking, heavy drinking

IG: Intergrowth-21st

ISUOG: International Society of Ultrasound in Obstetrics and Gynecology

IUGR: Intrauterine growth restriction

LBW: Low birth weight

LSD: Least significant difference

LSND: Low smoking, no drinking

LSLD: Low smoking, low drinking

LSHD: Low smoking, high drinking

NIAAA: National Institute on Alcohol Abuse and Alcoholism

n: Number of available data

NP: Northern Planes

NSND: No smoking or drinking

NSLD: No smoking, low drinking

NSHD: No smoking, heavy drinking

P: Parity

P: P-value

p10: 10th centile

p5: 5th centile

p3: 3rd centile

PAE: Prenatal alcohol exposure

PASS: Prenatal Alcohol in Sudden Infant Death Syndrome and Stillbirth Network

PatID: Patient identification

PCE: Prenatal cigarette exposure

RR: Relative risk

S: Smoking only

SA: South Africa

SD: Smoking and drinking

Std. Dev.: Standard deviation

SGA: Small for gestational age

SIDS: Sudden infant death syndrome

SPS: Safe Passage Study

USA: United States of America

UK: United Kingdom

WHO: World Health Organization

LIST OF DEFINITIONS

Dose-response = Describes the relationship between an exposure (e.g. PCE and PAE) and the risk of the outcome (e.g. growth restriction).

Dose-response relationship = Describes the association between increasing levels of exposure with either an increase or decrease in risk outcome.

Small for gestational age (SGA) = An infant who is smaller in size than the norm, with a birth weight below the 10th percentile for the sex-specific reference population, this includes a constitutionally small healthy infant and those who are pathologically small.

Fetal or intrauterine growth restriction (FGR or IUGR) = A pathologic failure of an infant to meet its growth potential with a birth weight or fetal weight below the 10th percentile for a given gestational age at birth AND subsequently at risk of adverse outcomes.

Low birth weight (LBW) = Birth weight less than 2500g, regardless of gestational age at the time of birth.

Preterm birth = Birth prior to 37 weeks of gestation.

Anthropometry = The scientific study of measurements and proportions of the human body.

Low smoking = Smoking more than 0 to less than 6.5 cigarettes per day during pregnancy.

Heavy smoking = Smoking more or equal to 6.5 cigarettes per day during pregnancy.

Standard drink = Defined as 14g of pure alcohol per day.

Low total standard drinks = Less than 32 standard drinks during pregnancy.

Heavy total standard drinks = 32 or more but less than 80 standard drinks during pregnancy.

Very heavy total standard drinks = More than 80 standard drinks during pregnancy.

Binging = Four or more drinks per occasion.

Low binging = Less than 4 total binge episodes during pregnancy.

Heavy binging = Four or more but less than 8 binge episodes during pregnancy.

Very heavy binging = Eight or more binge episodes during pregnancy.

Chapter 1

INTRODUCTION

This chapter will briefly discuss the prevalence and adverse effects associated with prenatal alcohol and smoking exposure, give an overview of the research question, problem statement, hypothesis, aims, and objectives.

It is well recognised, in scientific literature, that maternal cigarette smoking and alcohol consumption during pregnancy can influence fetal growth [1–3], mental development, and behaviour of the unborn child [2–5]. Maternal cigarette smoking (referred to as 'prenatal cigarette exposure' (PCE)) is associated with fetal growth restriction (FGR) [6–8], low birth weight (LBW) [1,3,5,6,8–11], a smaller head circumference [10], spontaneous miscarriage [5], preterm delivery [3,5,6,9], placenta praevia, abruptio placentae, vaginal bleeding during pregnancy [3,6,9], and perinatal and infant mortality [3,6]. It is also associated with adverse neonatal and long-term outcomes such as attention and behaviour problems, along with mildly reduced intellectual abilities [3,5,10,12] and childhood obesity [7]. Maternal alcohol use (referred to as 'prenatal alcohol exposure' (PAE)) on the other hand is associated with fetal alcohol related disorders (FARD) (craniofacial dysmorphologies, neurodevelopmental delay, behavioural and psychosocial problems in childhood and beyond, fetal growth restriction (FGR)) [10,12–17], small for gestation age (SGA) at birth [16,18], LBW, preterm delivery [15,16,18,19], spontaneous miscarriage, stillbirth [11,12,15,18] and sudden infant death syndrome (SIDS) [11,17,19].

Larkby and Day [20] stated that alcoholic women in general experience numerous problems during pregnancy, often due to depression or stress-related social problems e.g. unstable

marriages, violent alcoholic partners, poor finances, and child-care concerns [12,20]. These problems could contribute to the severity of the adverse effects of alcohol as the fetus is not just exposed to the teratogenic effect of alcohol, but to the adverse effects related to the external factors that exist in the alcoholic women's life.

Despite awareness campaigns and public health warnings displayed in clinics, public places, on cigarette packets and alcohol containers, a large number of pregnant women continue to expose their unborn children to these unhealthy habits [6,12,21,22] as most find it difficult to quit [6] or relapse later in pregnancy [23]. South Africa (SA), an upper-middle-income country, has a 47 % [24,25] prevalence of PCE compared to high-income countries such as the United States of America (USA), France, and Germany, where it ranges between 13 and 24 % [6,12]. The prevalence of PAE in SA ranges from 34 – 51 % [13,26,27] compared to Russia (36.5 %), the United Kingdom (UK) (41.3 %), and Ireland (60.4 %) [15]. The global prevalence of prenatal alcohol consumption in the population overall is approximately 9.8 % [15]. These exposures may contribute to the high prevalence (14.2 %) of preterm birth, LBW, and SGA seen in SA compared to the 7 % seen in high-income countries [28], making PCE and PAE two of the largest preventable causes of fetal and infant morbidity and mortality [1] in SA.

There is a tendency for pregnant women to indulge in both behaviours making it difficult to distinguish between the effect of a single exposure on fetal growth. It therefore remains unclear what the influence of these two risk factors is on fetal growth, especially those that trigger the restriction thereof [3]. Various results have been published, some studies found a significant relationship between PCE and PAE [29–31], whereas others did not [32,33].

Many studies have assessed the effect of PCE and PAE separately with the focus on adverse pregnancy outcomes. While there is no doubt that heavy usage during pregnancy poses a risk for the fetus, it is uncertain if there is a combined dose-response relationship between PCE and PAE [8,12], especially on birth weight. Previous studies indicate that the adverse effects of fetal exposure are duration dependant. Thus, to assess the risk of exposure to the fetus [21] one should identify the quantity, frequency, and pattern of combined alcohol and cigarette smoking exposure [10,21,34] throughout pregnancy.

This study aimed to determine whether there is a combined dose-response relationship between cigarette smoking and alcohol use during pregnancy on birth weight in a diverse, predominantly low socioeconomic status, community in a well-defined geographical area in the Western Cape of SA. The reason why we selected this cohort was that the birth weight distributions of the two clinical sites of SPS differed significantly, hence each site was encouraged to analyse their data separately. A recent article by Odendaal *et al.* [11] from the main SPS study reported a prevalence of 54.6 – 63.8 % for PAE and 68.4 % - 73.3 % for PCE in the SA cohort. This is slightly higher than the prevalence previously reported by several authors [13,26,27].

NULL HYPOTHESIS (Ho)

There is no combined dose-response effect of cigarette smoking and alcohol use during pregnancy on birth weight.

ALTERNATIVE HYPOTHESIS (Ha)

There is a combined dose-response effect of cigarette smoking and alcohol use during pregnancy on birth weight.

RESEARCH AIM AND OBJECTIVES

The main aim of the study was to determine if there is a combined dose-response effect of PCE and PAE on birth weight when compared to non-smokers and non-drinkers in a diverse, predominantly low socioeconomic status, community in a well-defined geographical area in the Western Cape of SA. All birth weights were transformed into centiles and z-scores according to published estimated fetal growth and newborn standards of INTERGROWTH 21st Project [35] and that of Gardosi [36].

To achieve the main aim of the study and address the research question, the following objectives were identified:

- Determine and compare the proportion (%) of infants who were defined as SGA (< p10) or severely SGA (< p5 or p3), according to the population-based GA and sex-specific newborn birth weight reference ranges of the INTERGROWTH-21st Project [35] across the nine-level and four-level alcohol-smoking exposure groups (discussed in more detail under Study design and Methodology). The same was done for the proportion (%) of infants who were defined SGA (< p10) or severely SGA (< p5 or p3), according to the GA sex-specific birth weight reference ranges, customised to individual patient characteristics of Gardosi [36].

- Compare the distribution of birth weight centiles and z-scores according to the INTERGROWTH-21st Project [35] population-based GA and sex-specific standards for newborn birth weight between the nine-level and four-level alcohol-smoking exposure groups. The same was done according to Gardosi's [36] customised individual patient characteristics and GA sex-specific birth weight reference ranges.

Chapter 2

LITERATURE REVIEW

This chapter reviews the literature on the effects of prenatal alcohol and smoking exposure during pregnancy on birth weight.

Poor *in utero* fetal growth not only poses a threat to the health of the fetus in the antenatal period but also to the neonate in the postnatal period [37]. It influences fetal programming leading to long-term diseases [5,37], such as the increased risk of intellectual disability, memory and attention deficits, reduced gross motor skills in school-aged children [38], and increased risk of diabetes, metabolic syndromes, hypertension, coronary heart disease, and dyslipidemia in adulthood [39,40].

The biological mechanisms by which PAE and PCE affect fetal growth remain unclear [41]. Bakker and Jaddoe [41] acknowledged that several elements which are related to maternal smoking could contribute to decreased perfusion of the placenta and fetus. Nicotine and carbon monoxide are the main teratogenic elements found in cigarette smoke which is known to harm the fetus. Nicotine causes vasoconstriction leading to reduced placental perfusion and fetal oxygenation [42]. It also subsequently influences the hemodynamic impulses that are responsible for the development of the placental and fetal vascular system [43,44]. Carbon monoxide on the other hand is a product of smoking, which is rapidly absorbed in the bloodstream where it attaches to hemoglobin and forms carboxyhemoglobin, which may cause fetal hypoxia [45].

1. Low birth weight and SGA

The two distinct, but independent processes by which birth weight is regulated are the duration of gestation and the rate of intra-uterine fetal growth. LBW is thus caused by either a short gestation period or reduced growth (also referred to as SGA) or a combination of the two [46]. The World Health Organization (WHO) defined LBW as a newborn with a birth weight of less than 2500g [46–48]. Preterm on the other hand refers to an infant who is born 'too early' at a GA of less than < 37 weeks [46,49]. Infants can also be LBW if they are born SGA, meaning that they are smaller in size than the birth norm for age, with a birth weight below the 10th percentile [6,46,50] for the sex-specific reference range or birth weight that is more than 2 standard deviations below the mean value for gestation [6,51]. Some SGA fetuses are healthy infants that are constitutionally small whereas others are pathologically small and are termed growth restricted [39,52,53]. Growth restricted infants have not reached their genetic growth potential as a result of fetal, placental, or maternal factors [6,54–58] and are subsequently at risk of severe neonatal morbidity and mortality and poor postnatal outcomes due to prematurity and deprivation (e.g. respiratory distress syndrome, necrotizing enterocolitis [6,59], and cerebral palsy [46,60,61]). Several authors conclude that multiple factors such as maternal disease (e.g. anemia, chronic hypertension [62,63]), maternal malnutrition [62–64], maternal infection [62,63] (e.g. rubella, cytomegalovirus [65,66], sexually transmitted diseases [62,63,65,66]), fetal malformation, genetic and chromosomal disorders/syndromes [62,63,67], harmful substances (e.g. smoking, alcohol, cocaine [62,63,68–70]) and uteroplacental dysfunction [71] (e.g. pre-eclampsia [62,63] and abruptio placentae) can increase the risk of FGR. It is therefore important for antenatal and postnatal healthcare services to identify those infants at risk as about 10 % of infants are SGA at birth [72]. Gardosi suggests that one needs to adjust for physiological variation

(e.g. ethnicity, maternal height, maternal weight, parity, sex [51,73–77], GA at birth, birth weight, and outcome [77]) to improve detection of truly growth restricted infants.

When studying international birth weight distributions in public health care circles the question often arises whether the prevalence of SGA should be based on a single birth weight cut-off, a single birth weight-according-to-GA reference, or whether there should be different cut-off references for different regions or countries. Sex-specific references for birth weight-according-to-GA are in demand across different regions of the world as there is a sex-difference in birth weight, as newborn boys tend to weigh more at birth than newborn girls. The stillbirth and infant mortality rates are however lower in girls compared to boys and we, therefore, assume that the 'smallness' of girls relative to boys is physiologically 'normal' and not pathologic [78]. Other commonly known differences in birth weight-according-to-GA such as an increase in birth weight and a decrease in LBW rates in wealthy high-income countries compared to low-to middle-income countries [79] or differences according to maternal characteristics and anthropometry (ethnicity, parity, maternal height, pre-pregnancy maternal BMI), and singletons versus multiple pregnancies [46] are not so clearly categorised as physiologically 'normal' or pathologic [78].

The etiology of SGA varies significantly globally. Cigarette smoking is undoubtedly responsible for the majority of SGA births in areas where a huge portion of women expose themselves and their unborn children to PCE. Other causes include primiparity, short stature, a low body mass index (BMI) prior to pregnancy, hypertensive disorders of pregnancy which could lead to pre-eclampsia, alcohol and drug use, low gestational weight gain, congenital anomalies, and other genetic factors. In low-income countries, nutritional factors such as short stature, a low BMI prior to pregnancy, and low gestational

weight gain contribute to the much larger fraction of SGA births where smoking during pregnancy is scarce or non-existent [78].

Furthermore, there are diverse outcomes for the development, survival, and morbidity of preterm and SGA neonates. Preterm births account for the largest fraction of infant mortality, whereas SGA neonates are known to have an increased risk of infant mortality and stillbirth [78,79]. According to Kramer [78], the international SGA birth prevalence, based on birth weight below the 10th centile according to the birth weight references of Williams *et al.* [80], was last estimated by the WHO in 1998 and it showed 30 million newborns per year are SGA, being 20.8 % of total births. In total, 75 % of SGA infants were found to be from Asia, 20 % from Africa, and 5 % from Latin America [78].

The most important cause of perinatal mortality remains LBW. Factors that might be associated with LBW and its subsequent risk are psychological and social stress, social disadvantage like income, housing, education, smoking, caffeine, and alcohol consumption during pregnancy. No common understanding is found to date about the effect on birth weight of any of these factors, with exception of maternal smoking during pregnancy which demonstrated that smokers tend to have smaller babies compared to non-smokers. The effects of passive paternal or environmental smoking are still unclear. There are also inconsistent results and opinions about the effects these factors might have on fetal growth as well as the mechanism by which they could disturb growth. An effort should be made to become knowledgeable about these factors as well as their influence on fetal growth as this could reduce associated risks [81]. The study of Brooke *et al.* [81], found a significant association between birth weight and PAE. Birth weight decreased as the consumption of alcohol during pregnancy increased. Women who consumed 100g or more of alcohol in a week had a mean birth weight of 137g less than

non-drinkers at term. When observing increased consumption of caffeine (e.g. coffee, tea, cola, and cocoa) similar and more significant findings were found. A significant effect was noted between total caffeine intake and birth weight with no significant dose-response tendency.

Nordentoft *et al.* [82] investigated the influence of lifestyle factors such as psychosocial stressors and a social support network on prematurity, and SGA. They found that social class negatively influenced pregnancy outcomes. In their study, the evidence clearly showed a strong relationship between smoking, drinking, poor education, and stressful life events on SGA. The significance of these findings set clear guidelines when planning preventive efforts such as anti-smoking campaigns and social support networks. Anti-smoking campaigns should keep in mind that women who smoke during pregnancy are more likely to be less educated, have poor social support, and have more adverse life events. Therefore, when providing social support to these women, meticulous thought should be given to how these programs can assist women not to just stop smoking but to enhance their coping skills so that they don't default again.

2. Prenatal cigarette and alcohol exposure

According to the study of Aliyu *et al.* [3], PCE and PAE tend to be highly correlated with each other, and therefore it remains challenging to distinguish between their respective influences on fetal growth. The exact influence of these two risk factors, especially those that trigger fetal growth restriction remains unclear, as results published are conflicting. Some studies reported a significant interaction between PCE and PAE in terms of their impact on fetal growth [29–31], whereas others did not [32,33].

It is not clear how PCE affects the growth restricting effect of PAE, however similar mechanisms are seen in both exposures which could explain their counteract on fetal growth. According to Aliyu *et al.* [3], nicotine and carbon monoxide that are produced by cigarette smoke reduce blood perfusion to the placenta as it causes vasoconstriction of the arteries which in turn deprives the fetus of nutrients and oxygen [3,23]. It also elevates maternal blood pressure and heart rate, further impairing perfusion to the placenta which ultimately can lead to FGR and shortened gestation of the fetus. This leads to more premature deliveries and a risk of severe fetal/infant mortality and morbidity [1]. Prenatal exposure to nicotine and carbon monoxide is also associated with obstetric complications such as abruptio placentae, placental previa, and pre-eclampsia [83,84] and poor neonatal outcomes such as preterm birth, low birth weight, and overall perinatal mortality [1,83,84]. The exact mechanism by which PAE influences fetal growth still needs to be determined, however various common mechanisms are likely [3]. It is well documented in animal models that alcohol decreases blood perfusion to the placenta and therefore increases the risk of clotting of the intravascular system [85]. When consumed in large amounts, alcohol intake can also lead to malnutrition, secondary to insufficient dietary intake [86] as it interrupts the way the gastrointestinal system functions resulting in improper absorption of vitamins and minerals [87,88] which affects the health of the unborn fetus. Alcohol further increases maternal metabolic demands and could affect maternal energy requirements [86,88] needed for proper development and growth of the fetus *in utero*. PCE and PAE can also independently alter specific maternal micronutrient requirements, such as zinc and copper [86]. This could lead to a synergetic effect that increases the probability of FGR in newborns [3].

Shisler *et al.* [23] stated that the severity of the effect of PCE on birth weight is greatly dependent on the nicotine dose. As early as 1988, Hebel *et al.* [89] noted a dose-

response relationship of PCE on birth weight when 6 or more cigarettes per day were smoked during pregnancy. They further noted a dose-response relationship on birth weight among non-quitters when smoking was reduced to less than 5 cigarettes per day. A study by Bernstein *et al.* [90] showed that there is a strong relationship between third-trimester smoking and birth weight, with a 27g reduction in birth weight noted per cigarette consumed per day in the third trimester. Ward *et al.* [1] found a mean reduction of 86g in birth weight when women smoked 1 – 10 cigarettes per day during pregnancy, 190g when smoking 11 – 20 cigarettes per day during pregnancy, and 277g when smoking 20 or more cigarettes per day during pregnancy. The Department of Health and Human Services of the USA reported a birth weight reduction of 200 to 327g depending on the nicotine dose [23]. Backe [91] further noted a synergetic effect between PCE and maternal age. A relative risk of 3.8 for SGA was seen in mothers aged 35 and older who smoked during pregnancy, whereas no significant risk was seen in mothers aged 25 and younger. Literature [12,81] suggests that PCE might be associated with social class such as little education and poor social support or social circumstances due to poor mental health or history of partner violence. It is therefore easy to assume that PCE is more likely a class-related habit. It might also be that there is a physiological difference between smokers and non-smokers [81] or that they are more likely to report PAE and be heavy alcohol users compared to non-smokers [92,93]. Bernstein *et al.* [90] suggest that continuous efforts be made to reduce cigarette consumption throughout pregnancy as it could improve birth weight. Their findings showed improvement in birth weight even if reduction of cigarette consumption occurred only during the last half of the pregnancy.

According to Ward *et al.* [1], PCE remains a public health challenge. While there is a decrease in tobacco use seen in most high-income countries, an increase is still noted in many low- to middle-income countries [83]. In the UK it was reported that 36 % of

newborns were born to smoking mothers between 2000 and 2001 compared to 13 % who were born to mothers exposed to environmental tobacco smoke. In their study maternal smoking significantly lowered the newborn mean birth weight by 146g compared to those exposed to environmental tobacco smoke which lowered the mean birth weight by only 36g, compared to no smoking, thereby demonstrating a dose-response effect between both maternal smoking and maternal environmental tobacco smoke exposure on birth weight [1]. Odendaal *et al.* [11] found the PCE prevalence to be between 68.4 – 73.3 % in their study.

There is a consistent association between PAE and reduced birth weight [94]. The effects thereof may however be multifactorial not to forget about the possibility of the combined effects associated with smoking (i.e. maternal or environmental) and genetic factors. All of the aforementioned could increase the risk for SGA [95]. The teratogenic effect of PAE varies, ranging from subtle to severe outcomes such as FARD [96]. It is associated with reduced brain mass [96], pre- and postnatal growth restriction [97], preterm delivery, and intrauterine death [98]. Shortfalls in cognitive development have also been noted when assessing language, visuospatial function, fine and gross motor skills, ability to recall memory, pay attention and make decisions [97,99,100]. An association between mental illness, structural abnormalities of the heart, skeleton, renal, ocular, and auditory systems have also been noted [99,100]. While the harmful effects such as FARD and structural abnormalities of the fetal organ system as a result of heavy and binge drinking during pregnancy have been well documented [101–104], studies lack to show supporting evidence of the effects of low to moderate maternal consumption [4].

Several authors [105,106] reported that the first trimester is regarded as a time of unintentional exposure of alcohol to the fetus as confirmation of pregnancy is in general

only established after the first missed period. Disturbingly, a large number of women refrain from altering their drinking habits prior to pregnancy confirmation, and therefore, binge drinking might occur in this time frame, predominantly in areas where it is socially acceptable for women to consume high levels of alcohol [107,108]. For countries with a high prevalence of PAE such as SA (54.6 – 63.8 % [11]), health care providers need to be mindful of the possibility of binge drinking among their patients as it is commonly seen when women use alcohol during pregnancy [109]. One should therefore ask women of childbearing age in general whether they consume alcohol. If they answer yes, one should educate them regarding the risk of PAE and advise them to cease consumption thereof if they think about falling pregnant or might be pregnant already [109].

It is well documented, in scientific literature, that there is a dose-response relationship between heavy PAE and adverse birth outcomes [14,18,110,111]. However, inconsistent results have been found with low to moderate levels of PAE [18,46,110,112–115]. Henderson *et al.* [16], and Patra *et al.* [18] conclude from their systematic reviews that there is not enough evidence to prove an association between low PAE and adverse birth outcomes. On the contrary, the systematic review of Henderson *et al.* [16], noted that infants born to mothers with no history of PAE had poorer outcomes compared to those who reported consuming small quantities throughout pregnancy, concluding that small quantities of alcohol use during pregnancy have a slight protective effect on some of the adverse pregnancy outcomes. Similar findings were noted in the work of McDonald *et al.* [116] where a significant protective effect against SGA was noted when low to moderate quantities of alcohol were consumed during pregnancy. Further exploration is needed to test this hypothesis before one can conclude that the intake of small quantities of alcohol during pregnancy [16] is safe and all professional societies still recommend total abstinence during pregnancy.

Patra *et al.* [18] did however find a dose-response relationship between LBW and PAE once more than one standard drink per day [117,118] (defined as 14g of pure alcohol per day by the WHO and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) [119]) was consumed on average throughout the pregnancy. Ouellette *et al.* [120], found a noticeable increase in the number of SGA births with an increase in alcohol consumption, a significant increase of up to 27 % were seen among those who were heavy drinkers (45ml or more absolute alcohol on average daily). The risk of preterm delivery and SGA became apparent when an average of three or more standard drinks per day were consumed [18,121]. This was confirmed in a study by Passaro *et al.* [122], which demonstrated a mean birth weight reduction of 150g in newborns who were exposed *in utero* to three or more standard drinks on average per day. Similar findings were documented by Mills *et al.* [123], who found a mean birth weight reduction of 165g in newborns exposed *in utero* to three to five standard drinks on average per day. Mills *et al.* [123] further noted a mean birth weight reduction of 14g compared to newborns of non-drinkers with an 11 % higher risk of LBW. Those who were exposed to moderate amounts of alcohol during pregnancy were on average 83g lighter and at a 62 % higher risk of LBW [123]. However, one needs to bear in mind that the effects of alcohol consumption are dependent on the absorption and metabolism of the mother and the fetus, which may be partially genetically determined [15]. Popova *et al.* [15], further mentions additional factors that might also influence the susceptibility of the fetus to the teratogenic effects of PAE. These factors include maternal nutritional status, stress levels during pregnancy, environmental effects to which the mom is exposed to during pregnancy, maternal smoking habits [124,125], and most likely paternal smoking and drinking habits [126].

Larkby and Day [20], found a linear correlation between PAE and growth restriction (i.e. the greater the exposure, the more distinct the effect is on growth postnatally). They further refer to the work of Smith and colleagues [127] who state that not only the amount of exposure affects birth weight, but the duration as well.

Day [128] states that one should also measure the covariates of PAE as women who consume alcohol during a specific time in pregnancy, and mainly those who continue throughout pregnancy, could be prone to other substance use as well. They are also more prone to default on prenatal care visits, have poor maternal health, and have low social class. All of these factors, on their own, carry a risk for poor pregnancy outcomes and therefore it is important to measure these with the same level of care as PAE. This should prompt further exploration not only concentrating on the effects of PAE at various stages in pregnancy but the effects of different patterns of use, and the relationship thereof on outcomes.

In the study by Olsen *et al*. [30], little effect was noted between low to moderate drinking when compared to non-smokers. However, when comparing low to moderate drinking to heavy smokers, a great reduction in mean birth weight was noted when 30 – 59g of alcohol were consumed per week. This was not apparent when comparing their findings to the study by Mills *et al.* [123] as the two studies used different standards to define exposure of alcohol and smoking. The timing of the collection of exposure data also differed. The data of Olsen *et al.* [30] were collected at 36 weeks gestation whereas that of Mills *et al.* [123] were collected somewhere in the first trimester.

Iversen *et al.* [110] and Walker *et al.* [4], reviewed risk factors associated with alcohol consumption during pregnancy including unplanned pregnancies [129,130], advanced

maternal age [131], maternal smoking [130,132], maternal alcohol consumption prior to conception [130,133,134] until confirmation thereof [130,135–138], domestic violence [129,139,140], single marital status [129,135,136], low-social economic status [141,142], and employment [134,136].

There are many conflicting views in the scientific literature. Reasons why some studies did not find any dose-response effect may include different study designs, inaccurate recollection of exposure, poor participation from the study cohort, underreporting of alcohol exposure (especially heavy exposure) due to social stigma, or use of different classifications to report maternal drinking and smoking.

Further research in this field is needed as the consequences of PAE and PCE place a heavy burden on public health resources.

Chapter 3

RESEARCH DESIGN AND METHODOLOGY

This chapter gives a brief introduction to the main SPS study and follows with an overview of the inclusion/exclusion criteria of the current study. It also maps the methods used to collect the data needed for the study as well as how the data were grouped before analysis with definitions thereof. The statistical analysis process used throughout the study is discussed and it shows that the study has met the Institution's Policy on Research ethics.

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The SPS, managed by the Prenatal Alcohol in Sudden Infant Death Syndrome (SIDS) and Stillbirth (PASS) Network, was a large, prospective, multidisciplinary study. It was designed to investigate the association between PAE, SIDS, and stillbirth [17]. Overall, 11 892 pregnant women of diverse populations (American Indians, Whites, Blacks, and mixed ancestry) [13,17,21] from well-defined geographical areas at high risk for smoking and alcohol use during pregnancy were enlisted between August 2007 and January 2015. Participants were recruited from two clinical sites (4 832 from Northern Plains in the USA and 7 060 from Bishop Lavis in Western Cape Province of SA) [17,21]. Subject to the time of recruitment, these women had up to three prenatal study visits [20-24, 28-32 (only embedded study participants) and 34-38 weeks gestation] followed by a postnatal/ newborn visit. Robust information was gathered throughout (see study design by Dukes *et al.* [17] for more information) [17].

At recruitment, written informed consent was obtained. GA was determined by a trained Research Midwife or Research Sonographer using ultrasound (crown-rump length (CRL) < 14 weeks and fetal biometry [bi-parietal diameter (BPD), head circumference (HC),

abdominal circumference (AC), and femur length (FL)) > 14 weeks gestation]. During the first prenatal study visit, self-reported maternal demographics [e.g. age, ethnicity, marital status, age at time of conception, medical (e.g. diabetes, hypertension) and obstetric history (e.g. gravidity and parity)], dietary and psychosocial information (e.g. depression based on Edinburg Depression Scale scores ≥ 13, level of education, mean household income, running water in the house or communal point, etc.) were collected by a research midwife [17,21]. This was followed by the collection of maternal anthropometric data (height in centimetres (cm), weight in kilogram (kg), body mass index (BMI) in kilogram per square metre (kg/m^2)), maternal self-report exposure to alcohol, tobacco, and illicit drugs; and fetal physiology (fetal heart rate, heart rate variability, movement, and heart rate movement coupling) [17].

PCE and PAE data was collected through maternal self-report interviews when enlisted, at subsequent prenatal study visits (up to 3) and the postnatal one-month study visit. At each of these interviews, exposure data was collected at 30-day intervals preceding the last recorded drinking and/or smoking day. This was slightly adjusted for the first prenatal interview which included exposure one year prior to pregnancy to the weeks around the last normal menstrual period (LNMP) (15 days before and 15 days after) [17,21]. The data was divided into four (4) periods; *Pre-conception* – from 15 days before to 15 days after the first day of the LNMP; *Trimester 1* – day 0 to day 97 after LNMP; *Trimester 2* – day 98 to day 195 after LNMP and *Trimester 3* – from day 196 after LNMP to delivery [21].

PCE was captured by inquiring how often the participant smoked a tobacco cigarette or chewing tobacco. Consumption was documented using grouped frequency options (i.e. none, monthly or less, 2 – 4 days per month, 2 – 3 days per week, 4 – 6 days per week, and

7 days per week) and if so the number of cigarettes smoked on a typical day, or tobacco chewed during a typical week (indicating dose per occasion) [21].

PAE was captured using the timeline follow-back (TLFB) technique of Sobell and Sobell [143]. This was adjusted slightly for the SPS population-based on feasibility findings and to capture information regarding the duration of drinking episodes, sharing, type/brand of beverages consumed as the alcohol-by-volume differs among beverages, number, container size, and iced or frozen [21,26]. Alcohol consumption was recorded during the 30-day interval ending at the last drinking day and converted to standard drinks per drinking day [117,118] (according to the WHO and National Institute of Alcohol Abuse and Alcoholism as 14g of pure alcohol) [119]. Dukes *et al.* [21] confirmed a high capture rate of PAE metrics across gestation and the meconium study by Himes *et al.* [13] confirmed the reliability of the cohort's maternal self-report.

The current study is a sub-analysis of the main SPS study. The study is a quantitative analysis based on the SA cohort only as the birth weight distributions of the two clinical sites differed significantly. Each site was therefore encouraged to analyse its data separately. Inclusion criteria were as follows: participants from the SA cohort, first enlistment into the study, and singleton pregnancy resulting in a live birth with birth weight, infant sex, and GA recorded at birth. The following were excluded: fetuses with a congenital abnormality, pregnancies that resulted in miscarriage or stillbirth, maternal use of illicit drugs (methamphetamine, marijuana, hookah, etc.), multiple pregnancies, second or further enlistment in the study, missing data necessary to calculate birth weight z-scores, and pregnancies dated by ultrasound after 24 weeks gestation.

To examine the dose-response relationship of PCE and PAE on birth (and/or fetal) weight, Brink *et al.* [144] developed a nine-level alcohol-smoking exposure grouping, as set out in Table 1:

Table 1. Nine-level alcohol-smoking exposure grouping.

No smoking or drinking over all four periods (NSND)
Low smoking only (LSND)
Heavy smoking only (HSND)
Low drinking only (NSLD)
Heavy drinking only (NSHD)
Low smoking, Low drinking (LSLD)
Heavy smoking, Low drinking (HSLD)
Low smoking, Heavy drinking (LSHD)
Heavy smoking, Heavy drinking (HSHD)

These groups could be collapsed into a four-level alcohol-smoking exposure grouping (Table 2):

Table 2. Four-level alcohol-smoking exposure grouping.

No smoking or drinking (NSND)
Smoking only (S)
Drinking only (D)
Smoking and drinking (SD)

Low smoking was defined as > 0 and < 6.5 cigarettes per day and heavy smoking as ≥ 6.5 cigarettes per day [144].

To distinguish between low and heavy alcohol exposure, both total binge episodes and total standard drinks per drinking day, from 15 days before LNMP until delivery, were considered. Binging was defined as consumption of four or more standard drinks per event [21] and a standard drink as 14g of pure alcohol [118,119]. *Low binging* was defined as < 4 binge episodes during the entire pregnancy; *low total standard drinks* was defined as < 32 standard drinks; *heavy binging* was defined as ≥ 4 but < 8 binge episodes; *heavy total standard drinks* was defined as ≥ 32 and ≤ 80 standard drinks; *very heavy binging* was defined as ≥ 8 binge episodes; *very heavy total standard drinks* was defined as > 80 standard drinks [144].

According to Brink *et al.* [144], low drinking consisted of low binging and low total standard drinks; low binging and heavy total standard drinks; heavy binging and low total standard drinks combinations. Heavy drinking consisted of heavy binging and heavy total standard drinks; very heavy binging and very heavy total standard drinks; very heavy binging and heavy total standard drinks; heavy binging and very heavy total standard drinks combinations.

The nine-level alcohol-smoking exposure grouping, as well as the four-level grouping, were used for comparison with birth weight classification according to the population-based GA and sex-specific newborn birth weight reference ranges of the INTERGROWTH-21st Project [35] and the customised individual patient characteristics growth chart of Gardosi [36] which incorporates variables such as ethnicity, maternal height, maternal weight in early pregnancy, parity as well as the sex of the newborn.

If the birth weight was > p10 the fetuses were labelled as appropriate for GA (AGA). If the birth weight was < p10 the fetuses were labelled as small for GA (SGA). These were further divided into subgroups of < p5 and < p3 (severe SGA).

Data was entered in Excel 365 (Microsoft, USA) and coded for analysis after which it was exported to STATISTICA 13 (TIBCO Software Inc. (2018). Statistica (data analysis software system), version 13. http://statistica.io.) was used for statistical analysis of the data.

The required sample sizes were calculated using a power analysis for one-way ANOVA with nine levels of alcohol-smoking exposure groups with a 5 % significance level. This determined that eighty-one (81) patients were required for each group to detect an effect size of 0.22 standard deviations with 90 % power.

Summary statistics were used to describe the variables, and the distributions were presented as histograms or frequency tables. Medians or means were used as measures of central location for ordinal and continuous responses and standard deviations and quartiles as indicators of spread.

The relationship between two continuous variables were analysed with regression analysis and the strength of the relationship was measured with Pearson correlation or Spearman correlation, the latter if the continuous variables were not normally distributed. The relationship between continuous response variables and nominal input variables were analysed using analysis of variance (ANOVA). The relationship between nominal variables were investigated with contingency tables and appropriate chi-square tests. A p-value of < 0.05 represents statistical significance in hypothesis testing and 95 % confidence intervals were used to describe the estimation of unknown parameters.

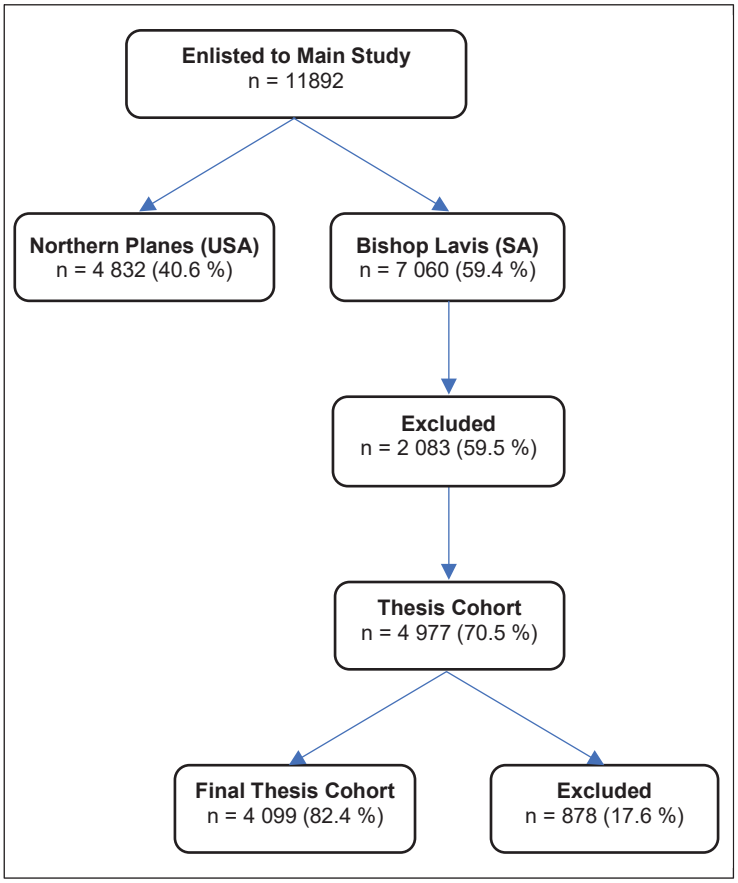
Consent to perform this quantitative analysis was obtained from the Health Research Ethics Committee of Stellenbosch University (reference number S19/09/192).

Chapter 4

RESULTS

This chapter reports on the results obtained from the data collected and displays the results by means of tables and illustrations.

In total, 7 060 pregnant women of diverse ancestry were enlisted at the SA clinical site during the main SPS, and 2 245 participants were excluded from the analysis due to various reasons: 135 withdrew from the main study; 50 had twin pregnancies; 982 had multiple listings to the main study; 150 spontaneously miscarried or had stillbirths; 7 fetuses had congenital abnormalities; 759 women reported illicit drug use during pregnancy and 112 had missing data (64 missing alcohol/smoking data and 48 missing birth weight). Another 766 women were excluded from the analysis as their GA determination was considered to be unreliable (765 participants were dated by a scan after 24 weeks, and 1 participant delivered after 44 weeks (Figure 1)). This resulted in a total of 4 099 participants for the final analysis.



(135 withdrew, 50 twin pregnancies, 982 multiple enlistments, 150 spontaneous abortions/stillbirths, 7 congenital abnormalities, 759 drug use)

(765 scanned after 24 weeks, 64 missing alcohol/smoking data, 48 missing birth weight, 1 delivered after 44 weeks)

Figure 1. Flow diagram of the study cohort.

The maternal characteristics, anthropometry, obstetric history, psychosocial background, alcohol-smoking exposure, and birth weight outcome of the final cohort are shown in Table 3.

Table 3. Maternal and newborn characteristics, obstetric history, and prenatal alcohol and cigarette exposures of the study cohort.

	n (%)	Mean ± Std. Dev.	Median (Range)
Ultrasound dating - GA (days)	4 099 (100)	106.66 ± 33.53	107 (35 – 167)
0 - 97	1 707 (41.6)		
98 - 125	1 021 (24.9)		
126 - 167	1 371 (33.4)		
Maternal age (years)	4 099 (100)	24.78 ± 5.96	24 (16 – 44)
≤ 20	1 158 (28.3)		
21 - 35	2 690 (65.6)		
≥ 36	251 (6.1)		
Body Mass Index (kg/m^2)	3 987 (97.3)	25.68 ± 5.84	24.41 (13.70 – 55.89)
< 18.5	200 (5.0)		
18.5 - < 25	1 950 (48.9)		
25 - < 30	975 (24.5)		
≥ 30	862 (21.6)		
Gravidity	4 091 (99.8)	2.09 ± 1.23	2 (1 – 10)
Primigravida	1 698 (41.5)		
Parity	4 091 (99.8)	0.91 ± 1.09	1 (0 – 7)
Nulliparous	1 908 (46.6)		
Edinburgh depression score	4 024 (98.2)	12.56 ± 5.92	12 (0 – 30)
≥ 13	1 990 (49.5)		
Employment status	3 555 (86.7)		
Employed	1 357 (38.2)		
Education completed (years)	4 093 (99.9)	10.18 ± 1.71	10 (2 – 13)
Primary School	4 010 (98.0)		
High School	1 021 (24.9)		
Tertiary	180 (4.4)		
People living in a house	4 019 (98.1)	5.12 ± 2.49	5 (1 – 30)
Number of rooms in a house	4 003 (99.6)	3.78 ± 1.42	4 (1 – 11)
Number of people per room	4 000 (97.6)	1.50 ± 0.85	1.25 (0.25 – 10)
Household income per month (ZAR)	3 008 (73.4)	930.95 ± 621.57	800 (50 – 6000)
< 1000	1 666 (55.4)		
1000 – 2000	1 251 (41.6)		
> 2000	91 (3.0)		

Table 3. (continued).

	n (%)	Mean ± Std. Dev.	Median (Range)
Electricity	3 958 (98.4)		
Phone	3 698 (91.9)		
Running water	3 312 (82.3)		
Toilet	2 713 (67.4)		
GA at enlisting (days)	4 099 (100)	128.60 ± 40.50	130 (38 – 270)
0 – 97	1 014 (24.7)		
98 -125	892 (21.8)		
126 – 167	1 493 (36.4)		
≥ 168	700 (17.1)		
GA at birth (days)	4 099 (100)	273.36 ± 14.50	276 (167 – 307)
< 26 weeks	8 (0.2)		
26 - 32 weeks	62 (1.5)		
33 - < 37 weeks	730 (17.8)		
≥ 37 weeks	3 299 (80.5)		
Birth weight (grams)	4 099 (100)	3030.94 ± 561.24	3040 (410 – 5740)
< 1 500	51 (1.2)		
1 500 - < 2 500	504 (12.3)		
2 500 - < 4 000	3 379 (82.4)		
≥ 4 000	165 (4.0)		
Males	2 025 (49.4)		
INTERGROWTH-21st birth weight Z-score	4 077 (99.5)	- 0.35 ± 1.04	- 0.37 (- 3.58 – 4.11)
INTERGROWTH-21st percentile	4 077 (99.5)	40.19 ± 28.69	35.56 (0.12 – 99.99)
INTERGROWTH-21st < p10	739 (18.1)		
INTERGROWTH-21st < p5	412 (10.1)		
INTERGROWTH-21st < p3	266 (6.5)		
Gardosi birth weight Z-score	4 098 (100)	- 0.17 ± 1.06	- 0.18 (- 3.80 – 3.80)
Gardosi percentile	4 098 (100)	45.09 ± 28.94	42.80 (0 – 100)
Gardosi < p10	543 (13.3)		
Gardosi < p5	296 (7.2)		
Gardosi < p3	201 (4.9)		

Table 3. (continued).

	n (%)	Mean ± Std. Dev.	Median (Range)
9-level alcohol-smoking exposure grouping	4 099 (100)	3.36 ± 2.39	3 (0 – 8)
No smoking or drinking (NSND)	739 (18)		
Low smoking, No drinking (LSND)	593 (14.5)		
Heavy smoking, No drinking (HSND)	111 (2.7)		
No smoking, Low drinking (NSLD)	710 (17.3)		
No smoking, Heavy drinking (NSHD)	70 (1.7)		
Low smoking, Low drinking (LSLD)	1 216 (29.7)		
Heavy smoking, Low drinking (HSLD)	266 (6.5)		
Low smoking, Heavy drinking (LSHD)	270 (6.6)		
Heavy smoking, Heavy drinking (HSHD)	124 (3)		
4-level alcohol-smoking exposure grouping	4 099 (100)	1.93 ± 1.16	2 (0 – 3)
No smoking or drinking (NSND)	739 (18)		
Smoking only (S)	704 (17.2)		
Drinking only (D)	780 (19)		
Smoking and drinking (SD)	1 876 (45.8)		

n: number of available data; %: percentage of available data; ZAR: South African Rand

Table 4 shows the basic obstetric information compared against overall PCE and PAE and the significance thereof.

Table 4. Comparison of basic obstetric information against PCE and PAE.

	n (%)	No smoking or drinking	Smoking only	Drinking only	Smoking & Drinking	*P*
GA - recruitment (days)*	4 099 *(100)*	739 *(18)*	704 *(17.2)*	780 *(19)*	1 876 *(45.8)*	0.1
0 – 97^	1 014 *(24.7)*	196 *(26.5)*	177 *(25.1)*	188 *(24.1)*	453 *(24.1)*	
98 – 125^	892 *(21.8)*	151 *(20.4)*	163 *(23.2)*	181 *(23.2)*	397 *(21.2)*	
126 – 167^	1 493 *(36.4)*	276 *(37.3)*	256 *(36.4)*	266 *(34.1)*	695 *(37)*	
≥ 168^	700 *(17.1)*	116 *(15.7)*	108 *(15.3)*	145 *(18.6)*	331 *(17.6)*	
GA - ultrasound dating (days)*	4 099 *(100)*	739 *(18)*	704 *(17.2)*	780 *(19)*	1 876 *(45.8)*	0.2
0 – 97^	1 707 *(41.6)*	324 *(43.8)*	286 *(40.6)*	328 *(42.1)*	769 *(41)*	
98 – 125^	1 021 *(24.9)*	199 *(26.9)*	175 *(24.9)*	196 *(25.1)*	451 *(24)*	
126 – 167^	1 371 *(33.4)*	216 *(29.2)*	243 *(34.5)*	256 *(32.8)*	656 *(35)*	
GA - delivery (days)*	4 099 *(100)*	739 *(18)*	704 *(17.2)*	780 *(19)*	1 876 *(45.8)*	0.1
< 26 weeks^	8 *(0.2)*	1 *(0.1)*	3 *(0.4)*	2 *(0.3)*	2 *(0.1)*	
26 – 32 weeks^	62 *(1.5)*	8 *(1.1)*	14 *(2)*	7 *(0.9)*	33 *(1.8)*	
33 - < 37 weeks^	730 *(17.8)*	119 *(16.1)*	139 *(19.7)*	122 *(15.6)*	350 *(18.7)*	
≥ 37 weeks^	3 299 *(80.5)*	611 *(82.7)*	548 *(77.8)*	649 *(83.2)*	1491 *(79.5)*	
Birth weight (grams)*	4 099 *(100)*	739 *(18)*	704 *(17.2)*	780 *(19)*	1 876 *(45.8)*	< 0.01
< 1 500^	51 *(1.2)*	4 *(0.5)*	13 *(1.9)*	6 *(0.8)*	28 *(1.5)*	
1 500 - < 2 500^	504 *(12.3)*	66 *(8.9)*	84 *(11.9)*	66 *(8.5)*	288 *(15.4)*	
2 500 - < 4 000^	3 379 *(82.4)*	622* *(84.2)*	576* *(81.8)*	674* *(86.4)*	1 507* *(80.3)*	
≥ 4 000^	165 *(4)*	47 *(6.4)*	31 *(4.4)*	34 *(4.4)*	53 *(2.8)*	

*GA: gestational age; n: number of available data; %: percentage of available data; *: percentage within the row; ^: percentage within the column; P: p-value*

The data reveal a substantial number of late bookings among all drinkers, earlier delivery among all smokers, and more LBW among all smokers.

A. ***Growth according to the INTERGROWTH-21st project reference***

1. Proportion of SGA

Of the 4 099 participants, 4 077 had birth weights which were converted to z-scores and centiles according to the population-based GA and sex-specific newborn birth weight reference ranges of the INTERGROWTH-21st Project [35]. Twenty-two could not be converted as 13 had birth weight z-scores which plotted in infinity (meaning that the z-scores were well above the 3rd standard deviations of the mean with the centile on p100) and five delivered outside the GA-reference range borders of the INTERGROWTH-21st study [35]. The INTERGROWTH-21st Project's [35] calculator only calculates GA between 24 weeks 0 days and 42 weeks 6 days. Even though they could not be included in the conversion for z-scores and centiles, they could be included in calculating the percentage of newborns who were considered SGA. Seven hundred thirty-nine (18 %) newborns were SGA, 412 (10.1 %) had a birth weight below p5 and 266 (6.5 %) below p3.

The Chi-square test shows that there are significant differences between the nine-level alcohol-smoking exposure groups in terms of the percentage of infants whose birth weight falls below p10, p5, and p3 according to this reference (Table 5). The same is observed in the four-level alcohol-smoking exposure groups.

Table 5. Percentage of SGA infants according to the INTERGROWTH-21st birth weight reference range in the 9-level and 4-level exposure groupings.

9-level	n (%)	NSND n (%)	LSND n (%)	HSND n (%)	NSLD n (%)	NSHD n (%)	LSLD n (%)	HSLD n (%)	LSHD n (%)	HSHD n (%)	*P*
IG-21st	4 099 (100)	739 (18)	593 (14.5)	111 (2.7)	710 (17.3)	70 (1.7)	1216 (29.7)	266 (6.5)	270 (6.6)	124 (3)	
< p10	739 (18)	102* (13.8)	102* (17.2)	18* (16.2)	95* (13.4)	9 (12.9)	236* (19.4)	77* (29)	66* (24.4)	34* (27.4)	< 0.01
< p5	412 (10.1)	55* (7.4)	52* (8.8)	8 (7.2)	48* (6.8)	5 (7.1)	137* (11.3)	40* (15)	46* (17)	21* (16.9)	< 0.01
< p3	266 (6.5)	34* (4.6)	35* (5.9)	5 (4.5)	29* (4.1)	2 (2.9)	92* (7.6)	24* (9)	32* (11.9)	13* (10.5)	< 0.01

4-level		NSND n (%)	S n (%)	D n (%)	SD n (%)	*P*
IG-21st		739 (18)	704 (17.2)	780 (19)	1 876* (45.8)	
< p10	739 (18)	102 (13.8)	120* (17.1)	104 (13.3)	413* (22)	< 0.01
< p5	412 (10.1)	55 (7.4)	60 (8.5)	53 (6.8)	244* (13)	< 0.01
< p3	266 (6.5)	34 (4.6)	40 (5.7)	31 (4)	161* (8.6)	< 0.01

*IG-21st: INTERGROWTH-21st Project; n: number of available data; %: percentage of available data; NSND: no smoking or drinking; LSND: low smoking, no drinking; HSND: heavy smoking, no drinking; NSLD: no smoking, heavy drinking; LSLD: low smoking, low drinking; HSLD: heavy smoking, low drinking; LSHD: low smoking, heavy drinking; HSHD: heavy smoking, heavy drinking; S: smoking only; D: Drinking only; SD: smoking and drinking; P: p-value; *, significance*

2. *Distribution of z-scores and comparison according to the nine-level and four-level alcohol-smoking exposure groupings.*

The distribution of the birth weight z-scores according to this reference was fairly normal (Figure 2).

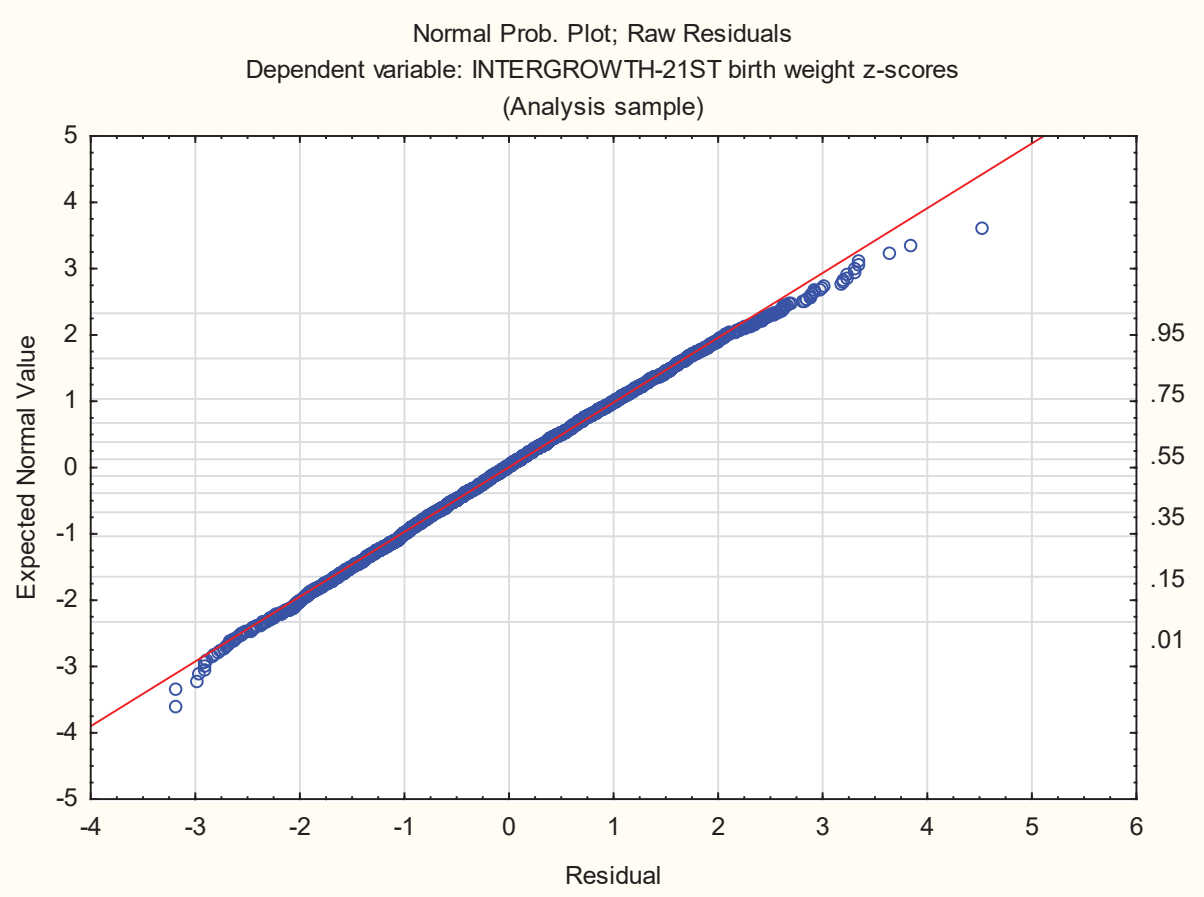


Figure 2. Normal probability plot for the INTERGROWTH-21st project's birth weight z-scores.

ANOVA was used to compare the INTERGROWTH-21st project's [35] newborn birth weight z-scores against the nine-level alcohol-smoking exposure grouping. The mean, standard deviation, and confidence intervals for the different groups are shown in Table 6.

Table 6. Mean, standard deviation, and confidence intervals of the INTERGROWTH-21st birth weight z-scores for the 9-level alcohol-smoking exposure grouping.

9-level grouping	n	Mean ± Std. Dev.	95 % CI
NSND	736	- 0.12 ± 1.06	- 0.20 to - 0.04
LSND	589	- 0.34 ± 1.04	- 0.43 to - 0.26
HSND	110	- 0.26 ± 1.00	- 0.45 to - 0.07
NSLD	708	- 0.23 ± 0.99	- 0.30 to - 0.16
NSHD	69	- 0.32 ± 0.91	- 0.54 to - 0.10
LSLD	1206	- 0.40 ± 1.03	- 0.46 to - 0.35
HSLD	266	- 0.60 ± 1.04	- 0.72 to - 0.47
LSHD	270	- 0.65 ± 1.00	- 0.77 to - 0.53
HSHD	123	- 0.66 ± 0.98	- 0.84 to - 0.49

n: number of available data; Std. Dev.: standard deviation; CI: confidence interval

Table 7 shows the significant differences across the groups. This is also presented in Figure 3.

- Combined use with high exposures (HSLD, LSHD, and HSHD) but not single use (HSND or NSHD) independently differed significantly from all other groups
- No exposure (NSND) differed significantly from low single or dual exposure (LSND, NSLD, and LSLD)
- NSLD also differed significantly from LSND and LSLD

Table 7. LSD test shows significant differences in INTERGROWTH-21st birth weight z-scores across the 9-level alcohol-smoking groups.

LSD test; variable INTERGROWTH-21st birth weight z-scores Probabilities for Post Hoc Tests Error: Between MS = 1.0479, df = 4068.0									
9-level grouping	1 - 0.12	2 - 0.34	3 - 0.26	4 - 0.23	5 - 0.32	6 - 0.40	7 - 0.60	8 - 0.65	9 - 0.66
NSND		< 0.01	0.17	0.04	0.13	< 0.01	< 0.01	< 0.01	< 0.01
LSND	< 0.01		0.45	0.05	0.84	0.23	< 0.01	< 0.01	< 0.01
HSND	0.17	0.45		0.76	0.73	0.17	< 0.01	< 0.01	< 0.01
NSLD	0.04	0.05	0.76		0.50	< 0.01	< 0.01	< 0.01	< 0.01
NSHD	0.13	0.84	0.73	0.50		0.49	0.04	0.02	0.03
LSLD	< 0.01	0.23	0.17	< 0.01	0.49		0.01	< 0.01	0.02
HSLD	< 0.01	< 0.01	< 0.01	< 0.01	0.04	0.01		0.58	0.56
LSHD	< 0.01	< 0.01	< 0.01	< 0.01	0.02	< 0.01	0.58		0.88
HSHD	< 0.01	< 0.01	< 0.01	< 0.01	0.03	0.01	0.56	0.88	

NSND: no smoking or drinking; LSND: low smoking, no drinking; HSND: heavy smoking, no drinking; NSLD: no smoking, low drinking; NSHD: no smoking, heavy drinking; LSLD: low smoking, low drinking; HSLD: heavy smoking, low drinking; LSHD: low smoking, heavy drinking; HSHD: heavy smoking, heavy drinking.

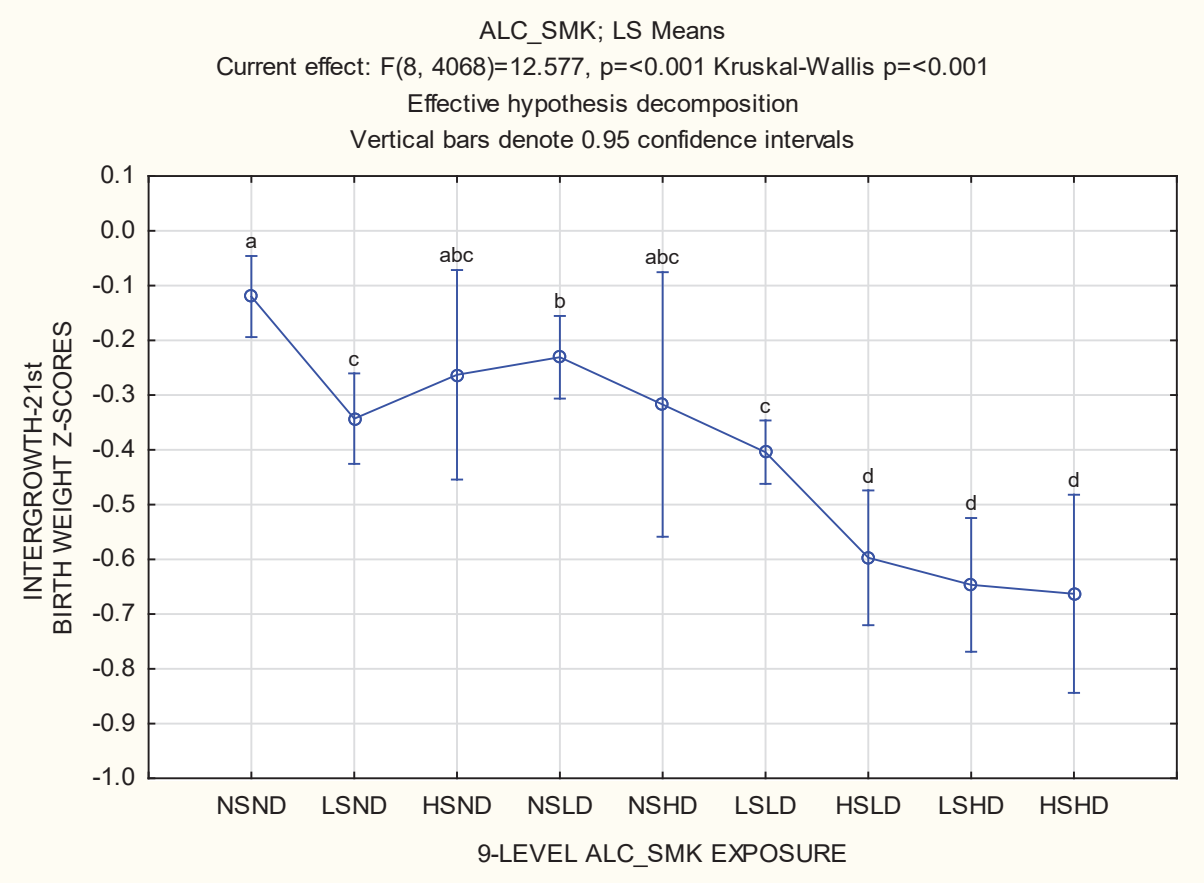


Figure 3. Relationship between the 9-level alcohol-smoking exposure grouping and the birth weight z-scores according to the INTERGROWTH-21st project reference.

The above was repeated for the four-level alcohol-smoking exposure grouping. Table 8 refers to the mean, standard deviation, and confidence intervals of the groups.

Table 8. Mean, standard deviation, and confidence intervals of the INTERGROWTH-21st birth weight z-scores for the 4-level alcohol-smoking exposure grouping.

4-level grouping	n	Mean ± Std. Dev.	95 % CI
N	736	- 0.12 ± 1.06	- 0.20 to - 0.04
S	699	- 0.33 ± 1.03	- 0.41 to - 0.25
D	777	- 0.24 ± 0.98	- 0.31 to - 0.17
SD	1865	- 0.48 ± 1.03	- 0.53 to - 0.44

n: number of data available; Std. Dev.: standard deviation; CI: confidence interval

The significant differences of birthweight z-scores across the four groups are tabulated in Table 9 and illustrated in Figure 4. Significant differences were seen between no use (NSND) and all other groups, and also between dual use (SD) and all other groups but not between S and D (trend only).

Table 9. Significant differences in INTERGROWTH-21st birth weight z-scores across the 4-level alcohol-smoking groups are shown with the LSD test.

LSD test; variable INTERGROWTH-21st birth weight z-scores Probabilities for Post Hoc Tests Error: Between MS = 1.0523, df = 4073.0				
4-level grouping	1 - 0.12	2 - 0.33	3 - 0.24	4 - 0.48
NSND		< 0.01	0.03	< 0.01
S	< 0.01		0.09	< 0.01
D	0.03	0.09		< 0.01
SD	< 0.01	< 0.01	< 0.01	

NSND: no smoking or drinking; S: smoking only; D: drinking only; SD: smoking and drinking

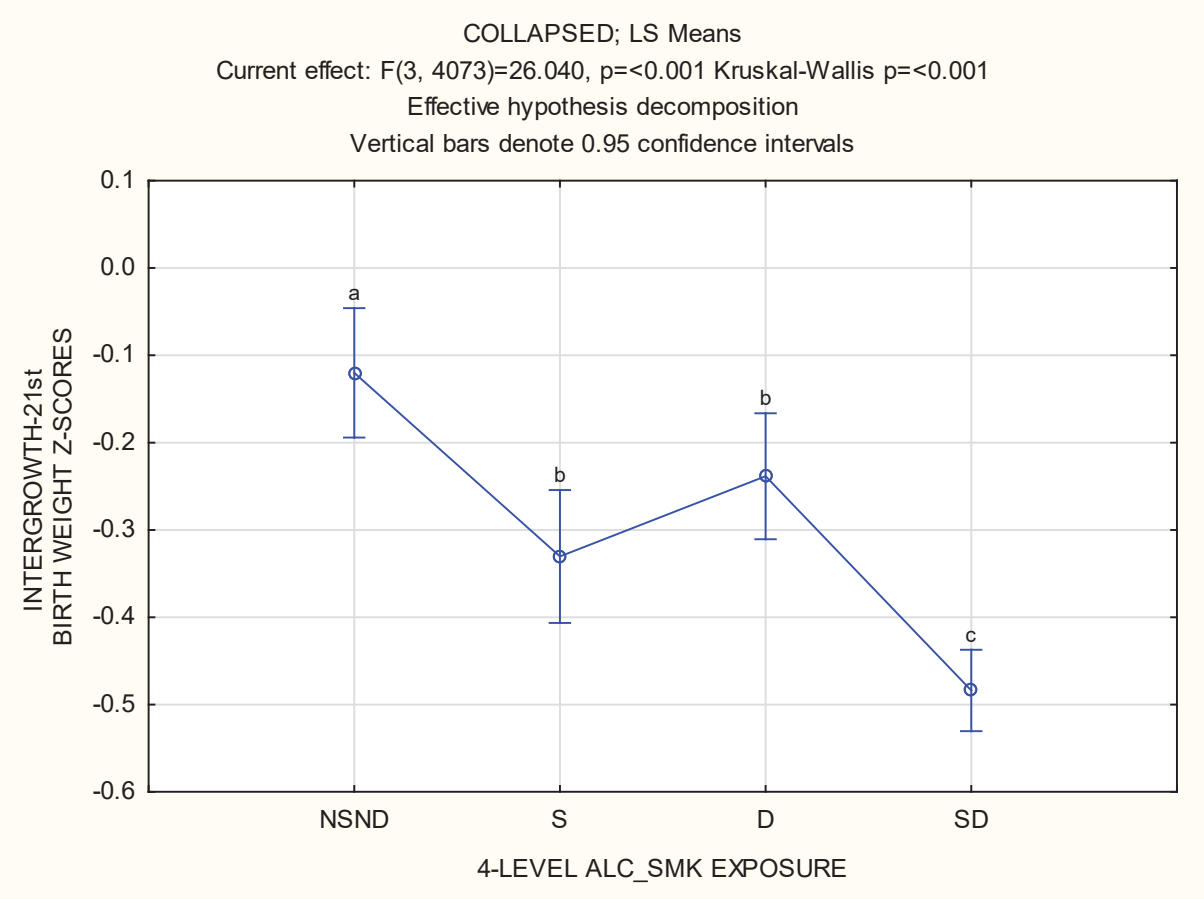


Figure 4. Comparison between the 4-level alcohol-smoking exposure grouping and the birth weight z-scores of the INTERGROWTH-21st project.

3. *Distribution of centiles and comparison according to the nine-level and four-level alcohol-smoking exposure groupings.*

The birth weight centiles according to the INTERGROWTH-21st project [35] were not normally distributed, therefore non-parametric testing i.e. Kruskal-Wallis was used (Figure 5).

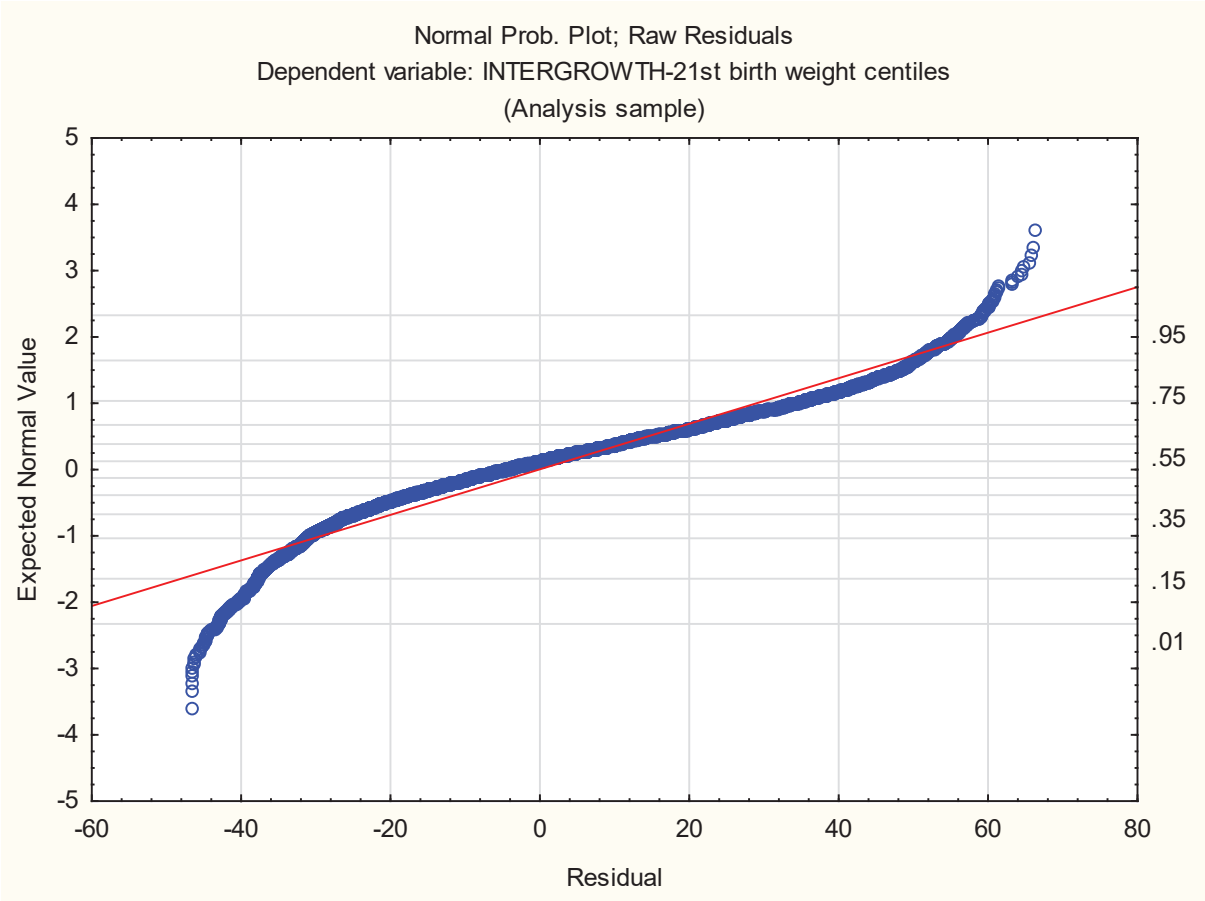


Figure 5. Probability plot demonstrating the non-normal distribution of the birth weight centiles according to the INTERGROWTH-21st project.

The INTERGROWTH-21st project's [35] birth weight centiles were compared against the nine-level alcohol-smoking grouping with the use of ANOVA. Table 10 shows the mean, standard deviation, and confidence intervals.

Table 10. Mean, standard deviation, and confidence intervals of the INTERGROWTH-21st birth weight centiles for the 9-level alcohol-smoking exposure grouping.

9-level grouping	n	Mean ± Std. Dev.	95 % CI
NSND	736	46.66 ± 29.51	44.53 – 48.80
LSND	589	39.82 ± 28.79	37.49 – 42.15
HSND	110	42.01 ± 29.38	36.46 – 47.56
NSLD	708	43.22 ± 27.91	41.17 – 45.28
NSHD	69	40.69 ± 26.96	34.21 – 47.16
LSLD	1206	38.53 ± 28.39	36.92 – 40.13
HSLD	266	33.22 ± 28.29	29.80 – 36.63
LSHD	270	32.47 ± 26.29	29.32 – 35.62
HSHD	123	32.11 ± 26.46	27.38 – 36.83

n: number of data available; Std. Dev.: standard deviation; CI: confidence interval

The birth weight centiles differed significantly across the groups. This is shown in Table 11 and expressed graphically in Figure 6.

- Dual use with high exposure (HSLD, LSHD, and HSHD) but not single high exposure (HSND and NSHD) independently differed significantly from all other groups
- No exposure (NSND) also differed from low single or dual exposure (LSND, NSLD, LSLD)
- NSLD further differed significantly from LSND and LSLD

Table 11. The LSD test shows significant differences in INTERGROWTH-21st birth weight centiles between the 9-level alcohol-smoking groups.

LSD test; variable INTERGROWTH-21st birth weight percentiles
Probabilities for Post Hoc Tests
Error: Between MS = 805.32, df = 4068.0

9-level grouping	1 46.66	2 39.82	3 42.01	4 43.22	5 40.69	6 38.53	7 33.22	8 32.47	9 32.11
NSND		< 0.01	0.11	0.02	0.09	< 0.01	< 0.01	< 0.01	< 0.01
LSND	< 0.01		0.46	0.03	0.81	0.36	< 0.01	< 0.01	0.01
HSND	0.11	0.46		0.68	0.76	0.22	0.01	< 0.01	0.01
NSLD	0.02	0.03	0.68		0.48	< 0.01	< 0.01	< 0.01	< 0.01
NSHD	0.09	0.82	0.76	0.48		0.54	0.05	0.03	0.04
LSLD	< 0.01	0.36	0.22	< 0.01	0.54		0.01	0.01	0.02
HSLD	< 0.01	< 0.01	0.01	< 0.01	0.05	0.01		0.76	0.72
LSHD	< 0.01	< 0.01	< 0.01	< 0.01	0.03	< 0.01	0.76		0.91
HSHD	< 0.01	0.01	0.01	< 0.01	0.04	0.02	0.72	0.91	

NSND: no smoking or drinking; LSND: low smoking, no drinking; HSND: heavy smoking, no drinking; NSLD: no smoking, low drinking; NSHD: no smoking, heavy drinking; LSLD: low smoking, low drinking; HSLD: heavy smoking, low drinking; LSHD: low smoking, heavy drinking; HSHD: heavy smoking, heavy drinking.

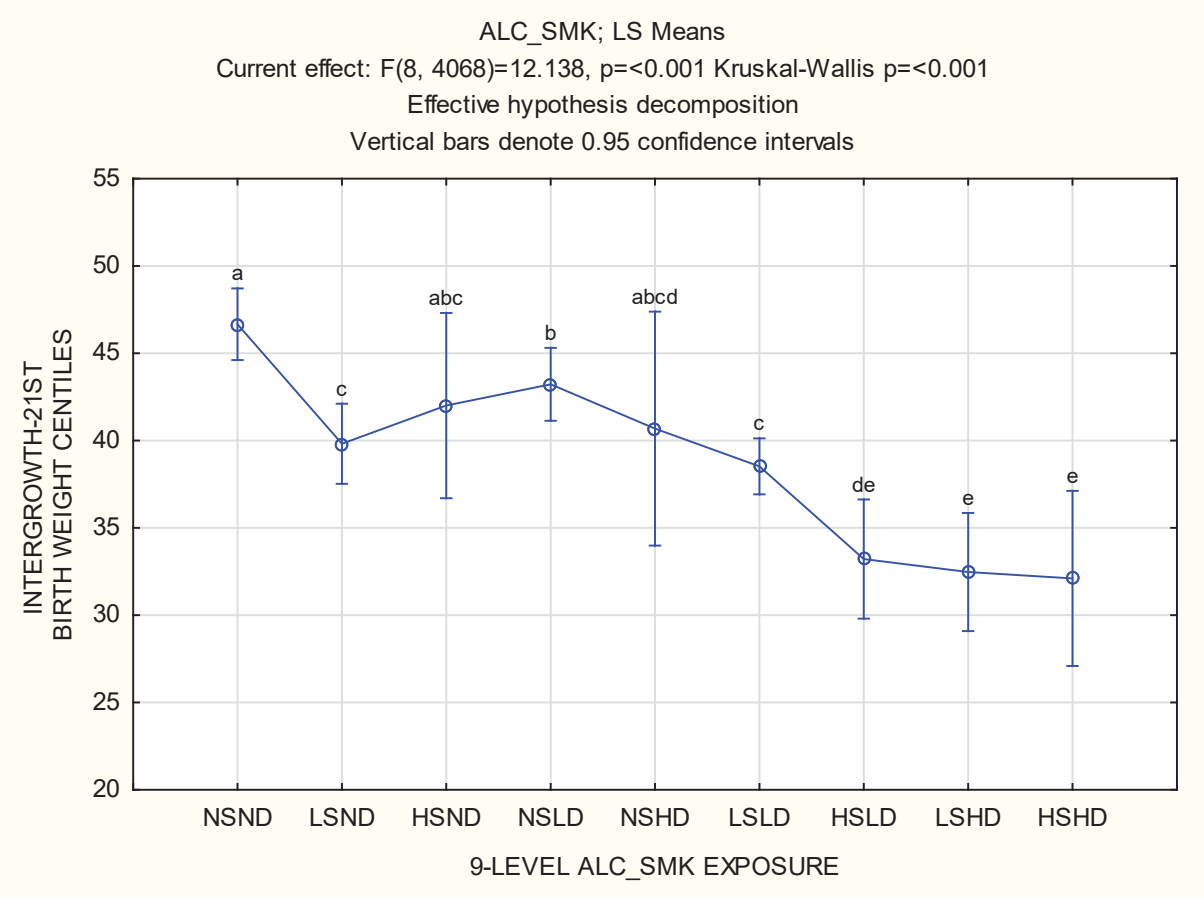


Figure 6. Comparison between the 9-level alcohol-smoking exposure grouping and the birth weight centiles of the INTERGROWTH-21st project.

The above was repeated for the four-level alcohol-smoking exposure grouping. Table 12 shows the mean, standard deviation, and confidence intervals between the groups.

Table 12. Mean, standard deviation, and confidence intervals of the INTERGROWTH-21st birth weight centiles for the 4-level alcohol-smoking exposure grouping.

4-level grouping	n	Mean ± Std. Dev.	95 % CI
NSND	736	46.66 ± 29.51	44.53 – 48.80
S	699	40.17 ± 28.87	38.01 – 42.31
D	777	43.00 ± 27.82	41.04 – 44.96
SD	1865	36.47 ± 28.07	35.19 – 37.74

n: number of data available; Std. Dev.: standard deviation; CI: confidence interval

Significant differences in birth weight centiles across the groups are seen in Table 13 and illustrated in Figure 7. Significant differences were noted between NSND and all other groups, and between SD and all other groups, but not between groups S and D (trend only).

Table 13. Significant differences in INTERGROWTH-21st birth weight centiles across the 4-level alcohol-smoking groups are shown with the LSD test.

LSD test; variable INTERGROWTH-21st birth weight percentiles Probabilities for Post Hoc Tests Error: Between MS = 808.12, df = 4073.0				
4-level grouping	1 46.66	2 40.17	3 43.00	4 36.47
NSND		< 0.01	0.01	< 0.01
S	< 0.01		0.06	< 0.01
D	0.01	0.06		< 0.01
SD	< 0.01	< 0.01	< 0.01	

NSND: no smoking or drinking; S: smoking only; D: drinking only; SD: smoking and drinking

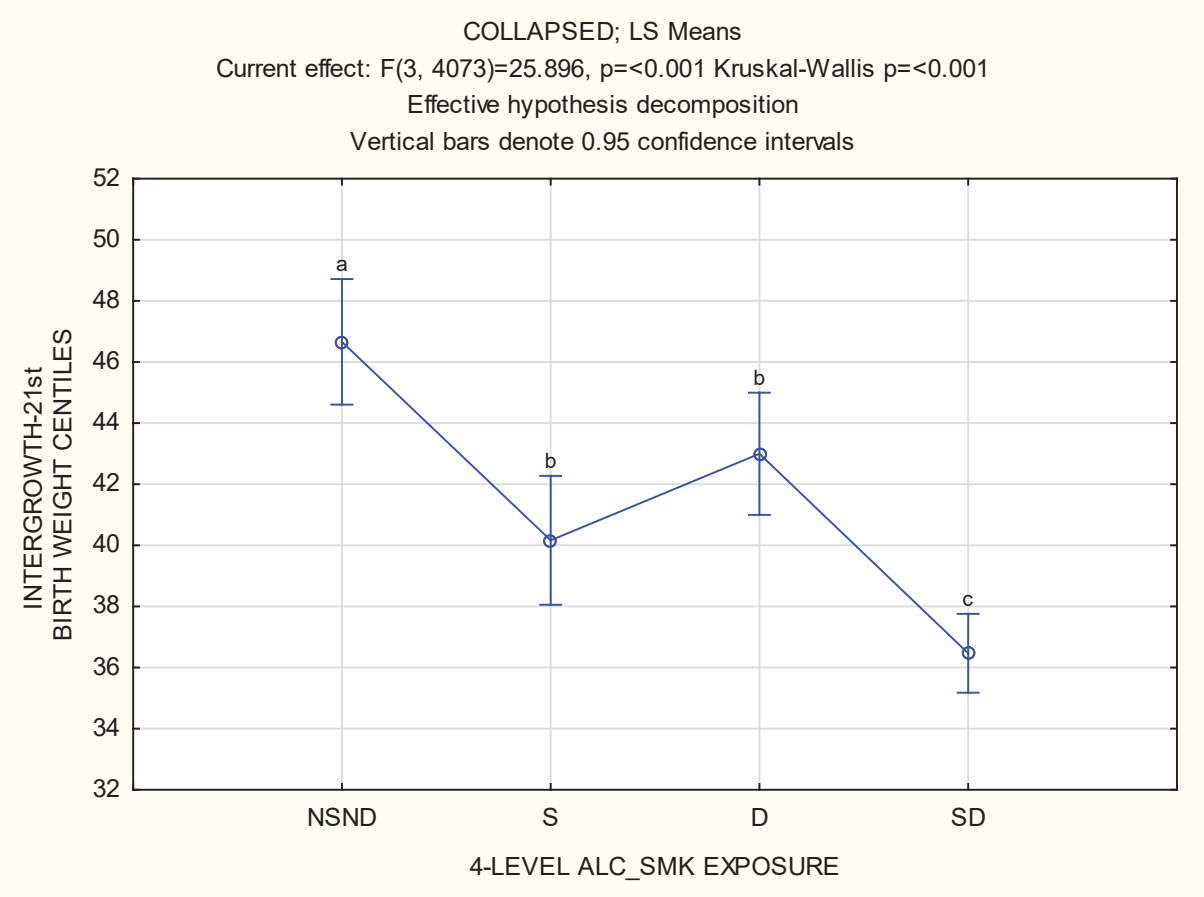


Figure 7. Relationship between the 4-level alcohol-smoking exposure grouping and the birth weight centiles of the INTERGROWTH-21st project.

B. ***Growth according to Gardosi's growth charts customised for individual patient characteristics***

1. Proportion of SGA

Of the 4 099 participants, only one had a birth weight that could not be converted to a z-score and centile according to Gardosi's [36] customised individual growth charts as the maternal height was missing.

When comparing the newborn birth weight to that of the growth chart of Gardosi customised for individual patient characteristics [36], 543 (13.3 %) newborns

were SGA and 296 (7.2 %) had a birth weight below p5 and 201 (4.9 %) below p3.

The Chi-square test shows that there are significant differences between the nine-level alcohol-smoking exposure groups in terms of the percentage of infants whose birth weight falls below p10, p5, and p3 according to this reference. The same is seen for the four-level alcohol-smoking exposure groups (Table 14).

Table 14. Percentage of SGA infants according to Gardosi's customised individual birth weight reference ranges in the 9-level and 4-level exposure groupings.

9-level	n (%)	NSND n (%)	LSND n (%)	HSND n (%)	NSLD n (%)	NSHD n (%)	LSLD n (%)	HSLD n (%)	LSHD n (%)	HSHD n (%)	*P*
Gardosi	4098 (100)	739 (18)	592 (14.4)	111 (2.7)	710 (17.3)	70 (1.7)	1216 (29.7)	266 (6.5)	270 (6.6)	124 (3)	
< p10	543 (13.3)	75* (10.2)	75* (12.7)	11* (9.9)	62* (8.7)	7 (10)	169* (13.9)	58* (21.8)	56* (20.7)	30* (24.2)	< 0.01
< p5	296 (7.2)	36* (4.9)	41* (6.9)	7 (6.3)	32* (4.5)	3 (4.3)	92* (7.6)	35* (13.2)	37* (13.7)	13* (10.5)	< 0.01
< p3	201 (4.9)	23* (3.1)	28* (4.7)	5 (4.5)	23* (3.2)	1 (1.4)	67* (5.5)	24* (9)	23* (8.5)	7 (5.7)	< 0.01

4-level		NSND n (%)	S n (%)	D n (%)	SD n (%)	*P*
Gardosi	4098 (100)	739 (18)	703 (17.2)	780 (19)	1876 (45.8)	
< p10	543 (13.3)	75 (10.2)	86* (12.2)	69* (8.9)	313* (16.7)	< 0.01
< p5	296 (7.2)	36 (4.9)	48 (6.8)	35 (4.5)	177* (9.4)	< 0.01
< p3	201 (4.9)	23 (3.1)	33 (4.7)	24 (3.1)	121* (6.5)	< 0.01

*n: number of available data; %: percentage of available data; NSND: no smoking or drinking; LSND: low smoking, no drinking; HSND: heavy smoking, no drinking; NSLD: no smoking, heavy drinking; LSLD: low smoking, low drinking; HSLD: heavy smoking, low drinking; LSHD: low smoking, heavy drinking; HSHD: heavy smoking, heavy drinking; S: smoking only; D: Drinking only; SD: smoking and drinking; P: p-value; *, significance*

2. *Distribution of z-scores and comparison according to the nine-level and four-level alcohol-smoking exposure groupings.*

Figure 8 shows that the birth weight z-scores according to Gardosi's [36] birth weight reference range were fairly normally distributed.

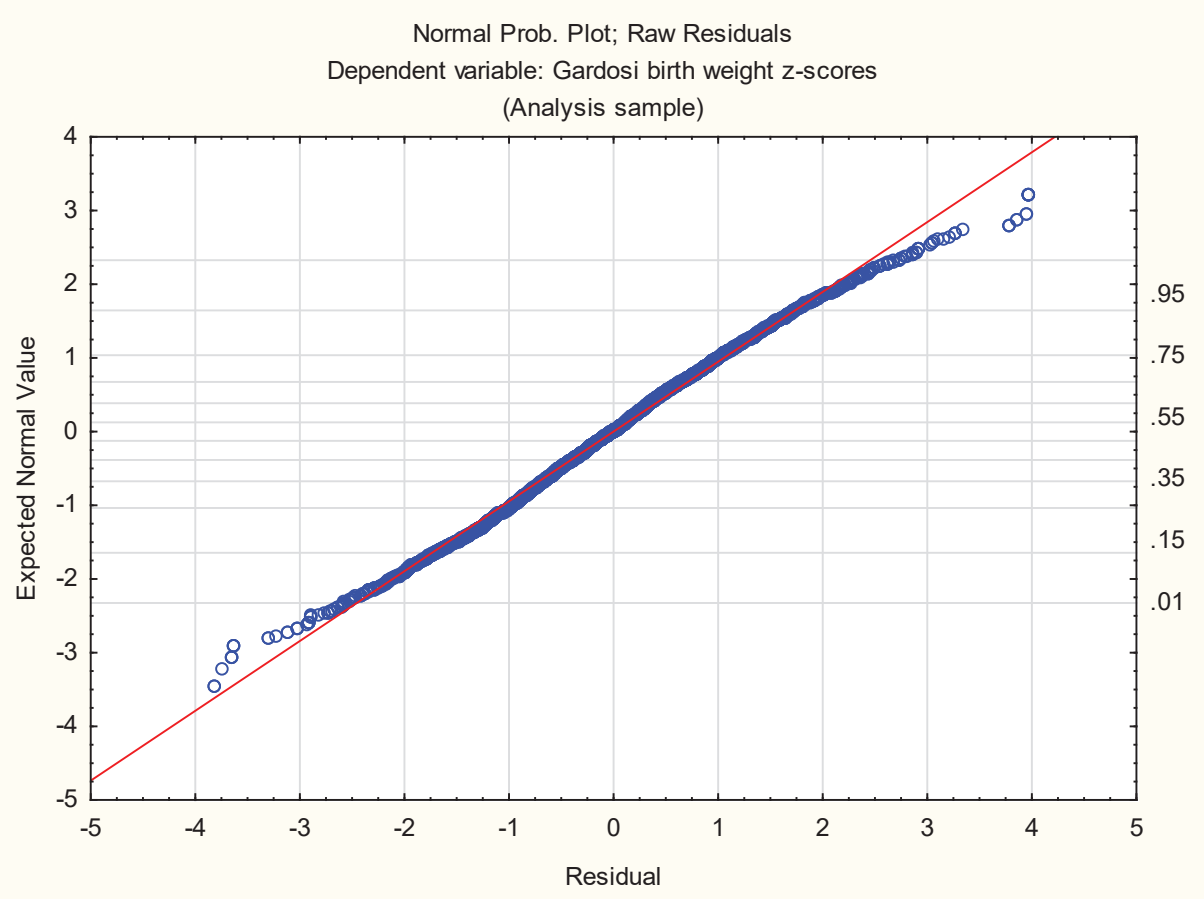


Figure 8. Probability plot showing normal distribution of birth weight z-scores according to Gardosi's reference ranges.

ANOVA was used to compare Gardosi's [36] birth weight z-scores against the nine-level alcohol-smoking grouping. Table 15 shows the mean, standard deviation, and confidence intervals of the groups.

Table 15. Mean, standard deviation, and confidence intervals of the Gardosi's birth weight z-scores for the 9-level alcohol-smoking exposure grouping.

9-level grouping	n	Mean ± Std. Dev.	95 % CI
NSND	736	0.02 ± 1.07	- 0.05 to - 0.10
LSND	589	- 0.16 ± 1.09	- 0.24 to - 0.07
HSND	110	- 0.16 ± 1.02	- 0.35 to 0.03
NSLD	708	- 0.06 ± 0.98	- 0.14 to 0.01
NSHD	69	- 0.20 ± 0.87	- 0.41 to 0.01
LSLD	1206	- 0.17 ± 1.07	- 0.23 to - 0.11
HSLD	266	- 0.46 ± 1.10	- 0.59 to - 0.32
LSHD	270	- 0.50 ± 1.05	- 0.63 to - 0.38
HSHD	123	- 0.57 ± 0.99	- 0.74 to - 0.39

n: number of data available; Std. Dev.: standard deviation; CI: confidence interval

The significant differences across the groups are shown in Table 16 and illustrated in Figure 9.

- Dual consumption with high exposure (HSLD, LSHD, and HSHD) but not single high exposure (HSND and NSHD) independently differed significantly from all other groups (except for HSLD not differing from NSHD)
- No exposure (NSND) also differed significantly from low smoking (LSND and LSLD)
- NSLD differed from LSLD

Table 16. The LSD test shows significant differences in Gardosi's birth weight z-scores between the 9-level alcohol-smoking groups.

LSD test; variable Gardosi birth weight z-scores Probabilities for Post Hoc Tests Error: Between MS = 1.1079, df = 4089.0									
9-level grouping	1 .02	2 - 0.16	3 - 0.16	4 - 0.06	5 - 0.20	6 - 0.17	7 - 0.46	8 - 0.50	9 - 0.57
NSND		< 0.01	0.09	0.12	0.09	< 0.01	< 0.01	< 0.01	< 0.01
LSND	< 0.01		0.99	0.11	0.74	0.76	< 0.01	< 0.01	< 0.01
HSND	0.09	0.99		0.38	0.79	0.89	0.01	< 0.01	< 0.01
NSLD	0.12	0.11	0.38		0.30	0.03	< 0.01	< 0.01	< 0.01
NSHD	0.09	0.74	0.79	0.30		0.82	0.07	0.03	0.02
LSLD	< 0.01	0.76	0.89	0.03	0.82		< 0.01	< 0.01	< 0.01
HSLD	< 0.01	< 0.01	0.01	< 0.01	0.07	< 0.01		0.60	0.34
LSHD	< 0.01	< 0.01	< 0.01	< 0.01	0.03	< 0.01	0.60		0.59
HSHD	< 0.01	< 0.01	< 0.01	< 0.01	0.02	< 0.01	0.34	0.59	

NSND: no smoking or drinking; LSND: low smoking, no drinking; HSND: heavy smoking, no drinking; NSLD: no smoking, low drinking; NSHD: no smoking, heavy drinking; LSLD: low smoking, low drinking; HSLD: heavy smoking, low drinking; LSHD: low smoking, heavy drinking; HSHD: heavy smoking, heavy drinking.

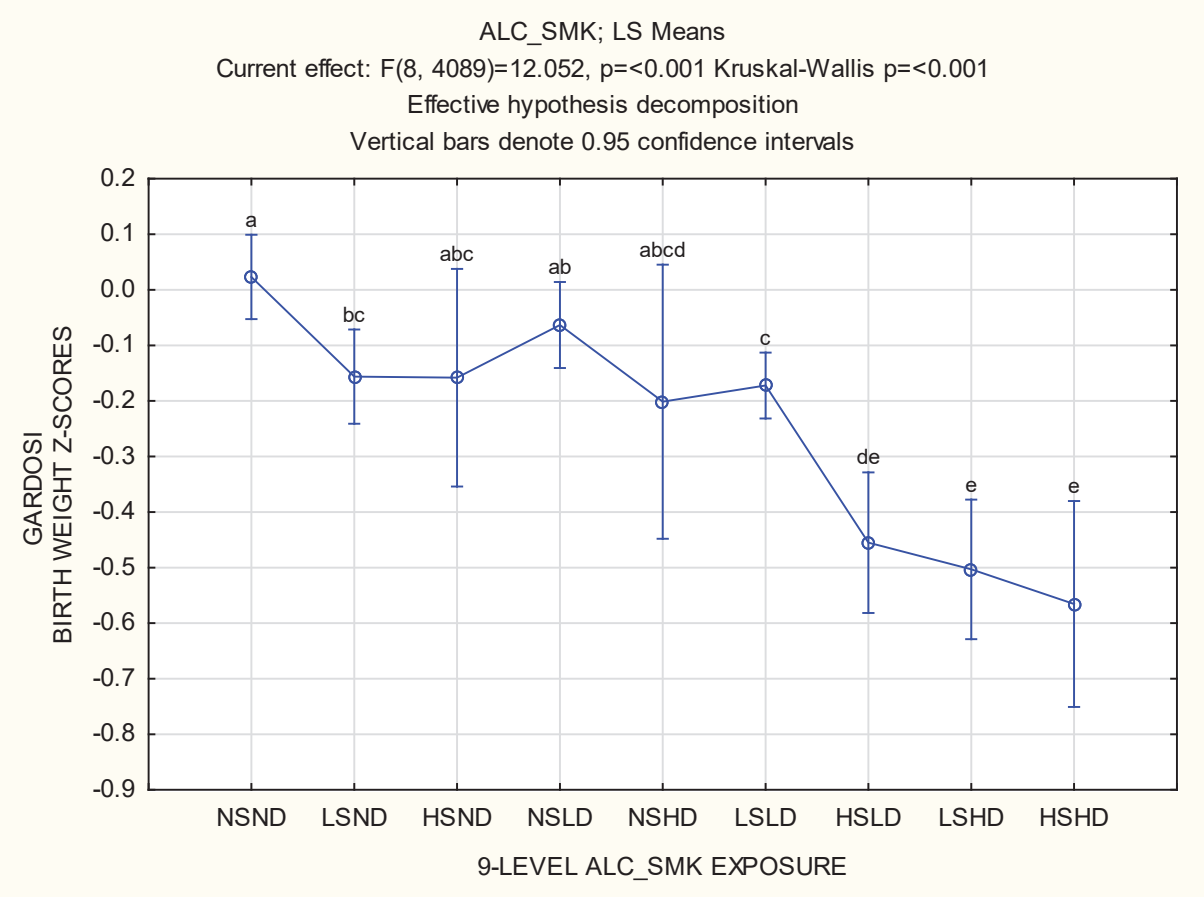


Figure 9. The association between the 9-level alcohol-smoking exposure groups and Gardosi's birth weight z-scores.

The above was repeated for the four-level alcohol-smoking exposure grouping. The mean, standard deviation, and confidence intervals are tabulated in Table 17.

Table 17. Mean, standard deviation, and confidence intervals of Gardosi's birth weight z-scores for the 4-level alcohol-smoking exposure grouping.

4-level grouping	n	Mean ± Std. Dev.	95 % CI
NSND	739	0.02 ± 1.07	- 0.05 to 0.10
S	703	- 0.16 ± 1.08	- 0.24 to - 0.08
D	780	- 0.08 ± 0.97	- 0.14 to - 0.01
SD	1876	- 0.29 ± 1.08	- 0.34 to - 0.24

n: number of data available; Std. Dev.: standard deviation; CI: confidence interval

Table 18 shows the significant differences in birth weight z-scores across the groups. This is demonstrated in Figure 10, with significant differences seen between group SD and all others, and also between NSND and S. No difference is seen between NSND and D (trend only).

Table 18. Significant differences in Gardosi's birth weight z-scores across the 4-level alcohol-smoking groups are shown with the LSD test.

LSD test; variable Gardosi's birth weight z-scores Probabilities for Post Hoc Tests Error: Between MS = 1.1180, df = 4094.0				
4-level grouping	1 46.66	2 40.17	3 43.00	4 36.47
NSND		0.01	0.07	< 0.01
S	0.01		0.14	0.01
D	0.07	0.14		< 0.01
SD	< 0.01	0.01	< 0.01	

NSND: no smoking or drinking; S: smoking only; D: drinking only; SD: smoking and drinking

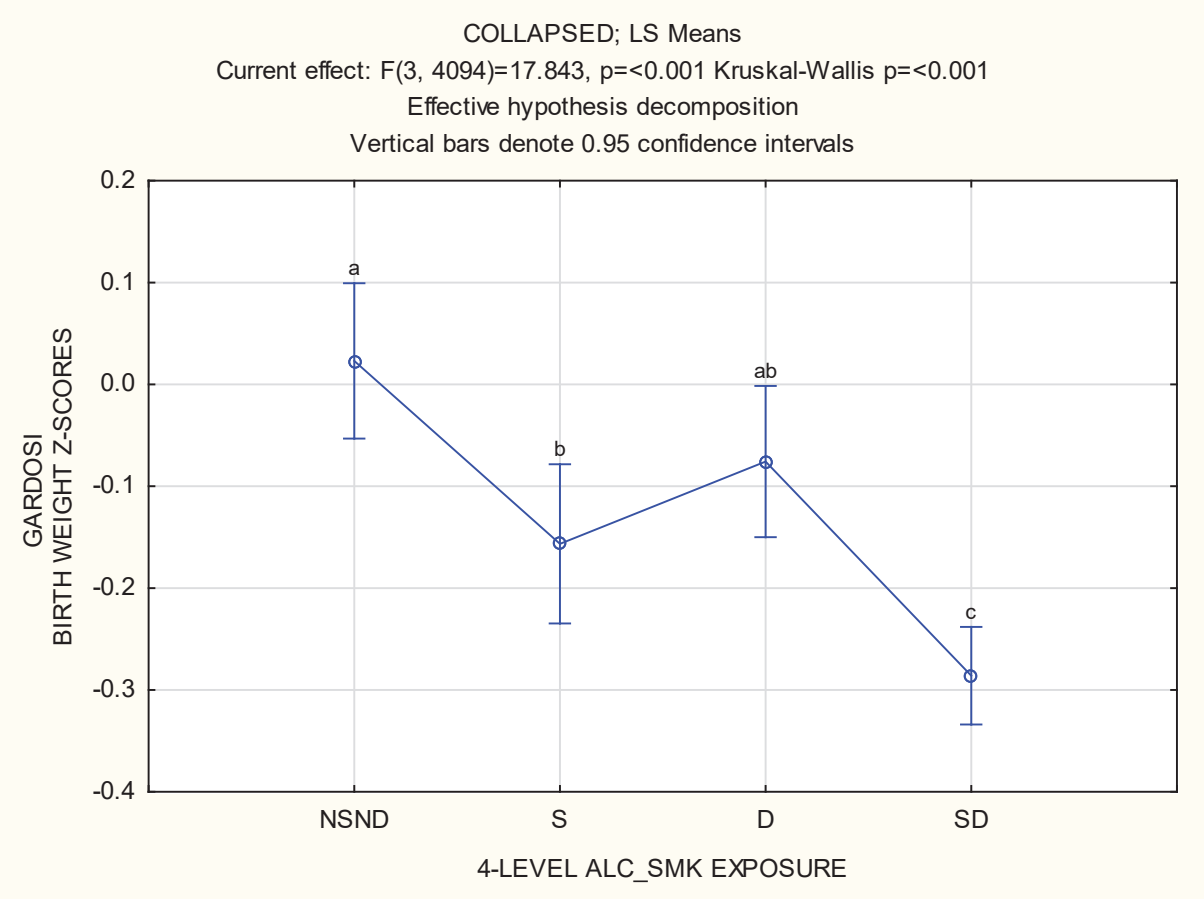


Figure 10. Gardosi's birth weight z-scores compared to 4-level alcohol-smoking exposure grouping.

3. Distribution of centiles and comparison according to exposure groupings

The distribution of birth weight centiles according to the Gardosi [36] reference range was not normal, therefore non-parametric testing (i.e. Kruskal-Wallis) was used (Figure 11).

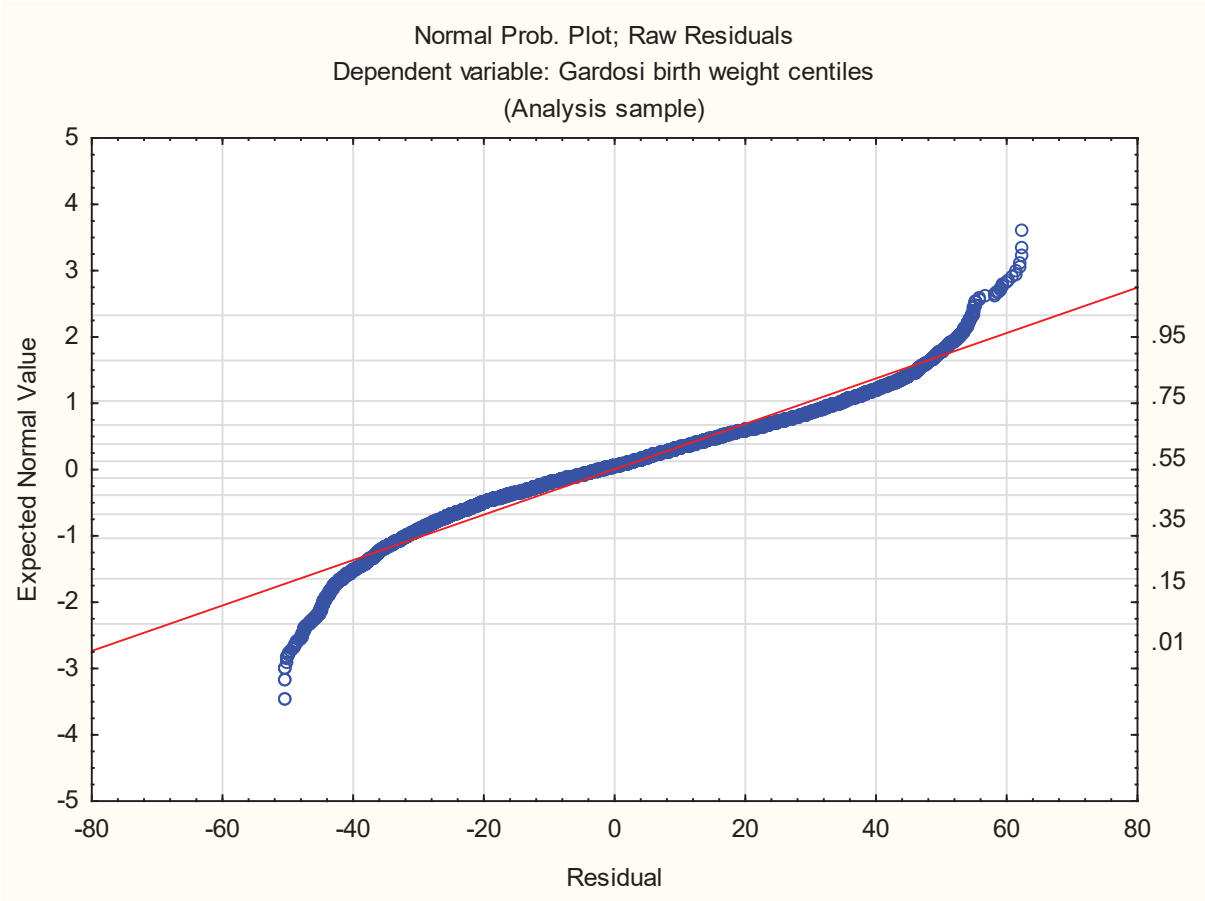


Figure 11. Probability plot showing the non-normal distribution of the birth weight centiles according to Gardosi.

The nine-level alcohol-smoking grouping was compared to Gardosi's [36] birth weight centiles with the use of ANOVA. Table 19 refers to the mean, standard deviation, and confidence intervals.

Table 19. Mean, standard deviation, and confidence intervals of Gardosi's birth weight centiles for the 9-level alcohol-smoking exposure grouping.

9-level grouping	n	Mean ± Std. Dev.	95 % CI
NSND	739	50.54 ± 28.90	48.46 – 52.63
LSND	592	45.13 ± 29.32	42.77 – 47.50
HSND	111	44.61 ± 29.55	39.05 – 50.17
NSLD	710	47.99 ± 27.57	45.95 – 50.02
NSHD	70	44.43 ± 26.68	38.07 – 50.79
LSLD	1216	44.78 ± 28.98	43.15 – 46.41
HSLD	266	37.49 ± 29.29	33.95 – 41.03
LSHD	270	36.67 ± 27.65	33.35 – 39.98
HSHD	124	34.36 ± 27.38	29.49 – 39.22

n: number of data available; Std. Dev.: standard deviation; CI: confidence interval

The significant differences across the groups when compared to the above reference are shown in Table 20 and illustrated in Figure 12.

- Dual consumption with high exposure (HSLD, LSHD, and HSHD) but not single high exposure (HSND and NSHD) independently differed significantly from all others (except for HSLD not differing from NSHD)
- No exposure (NSND) also differed significantly from LSND, HSND, and LSLD
- LSLD differed from NSLD
- HSND also differed significantly from NSND

Table 20. The LSD test shows significant differences in Gardosi's birth weight centiles between the 9-level alcohol-smoking groups.

LSD test; variable Gardosi's birth weight percentiles Probabilities for Post Hoc Tests Error: Between MS = 1.1079, df = 4089.0									
9-level grouping	1 50.54	2 45.13	3 44.61	4 47.99	5 44.43	6 44.78	7 37.49	8 36.67	9 34.36
NSND		< 0.01	0.04	0.09	0.09	< 0.01	< 0.01	< 0.01	< 0.01
LSND	< 0.01		0.86	0.07	0.85	0.81	< 0.01	< 0.01	< 0.01
HSND	0.04	0.86		0.25	0.97	0.95	0.03	0.01	< 0.01
NSLD	0.09	0.07	0.25		0.32	0.02	< 0.01	< 0.01	< 0.01
NSHD	0.09	0.85	0.97	0.32		0.92	0.07	0.04	0.02
LSLD	< 0.01	0.81	0.95	0.02	0.92		< 0.01	< 0.01	< 0.01
HSLD	< 0.01	< 0.01	0.03	< 0.01	0.07	< 0.01		0.74	0.32
LSHD	< 0.01	< 0.01	0.01	< 0.01	0.04	< 0.01	0.74		0.46
HSHD	< 0.01	< 0.01	< 0.01	< 0.01	0.02	< 0.01	0.32	0.46	

NSND: no smoking or drinking; LSND: low smoking, no drinking; HSND: heavy smoking, no drinking; NSLD: no smoking, low drinking; NSHD: no smoking, heavy drinking; LSLD: low smoking, low drinking; HSLD: heavy smoking, low drinking; LSHD: low smoking, heavy drinking; HSHD: heavy smoking, heavy drinking.

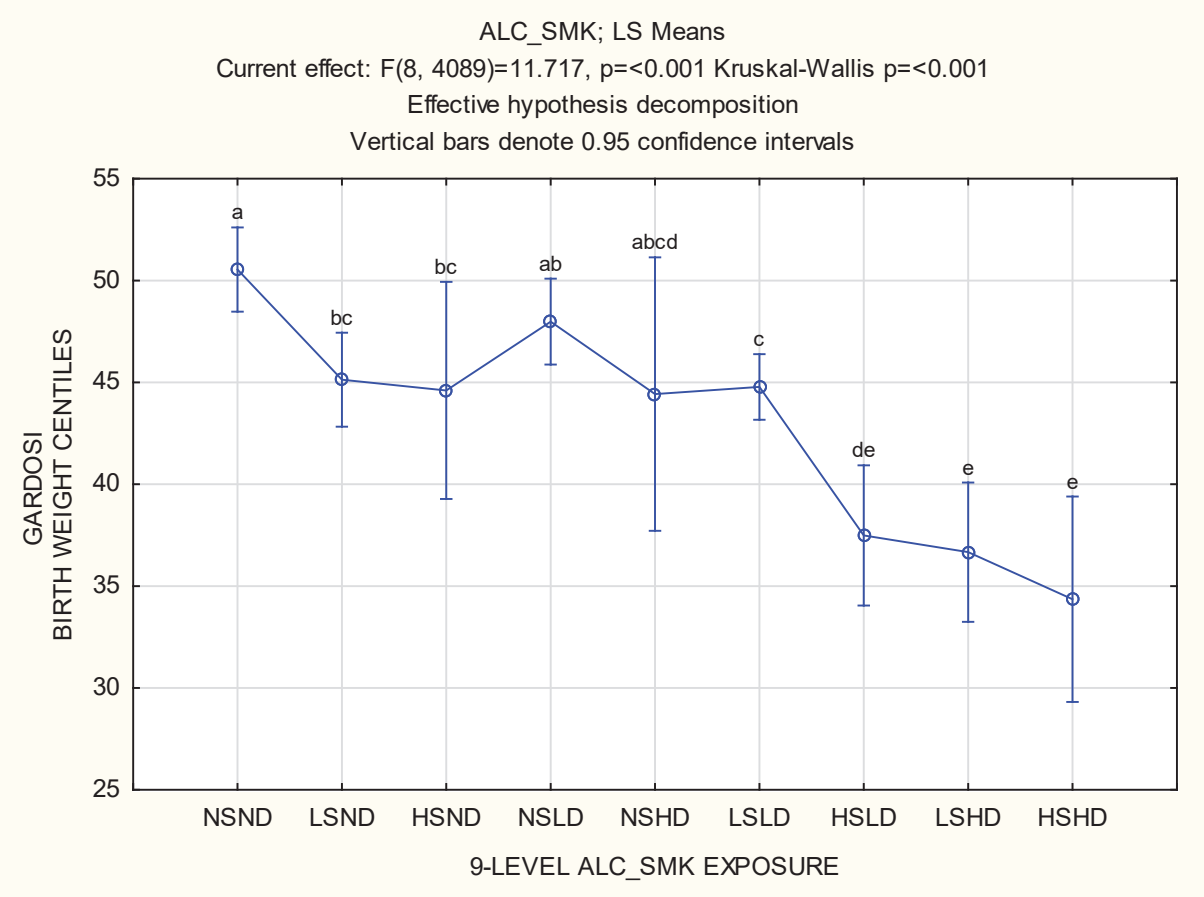


Figure 12. Comparison of Gardosi's birth weight centiles between the 9-level alcohol-smoking exposure groups.

The above was repeated for the four-level alcohol-smoking exposure grouping. The mean, standard deviation, and confidence intervals are shown in Table 21.

Table 21. Mean, standard deviation, and confidence intervals of Gardosi's birth weight centiles for the 4-level alcohol-smoking exposure grouping.

4-level grouping	n	Mean ± Std. Dev.	95 % CI
NSND	739	50.54 ± 28.90	48.46 – 52.63
S	703	45.05 ± 29.34	42.88 – 47.22
D	780	47.67 ± 27.50	45.73 – 49.60
SD	1876	41.89 ± 28.99	40.58 – 43.20

n: number of data available; Std. Dev.: standard deviation; CI: confidence interval

Table 22 depicts the significant differences in birth weight centiles across the groups. This is also shown in Figure 13, with significant differences seen between group SD and all others, and between NSND and S, but not D (trend only).

Table 22. Significant differences in Gardosi's birth weight centiles across the 4-level alcohol-smoking groups.

LSD test; variable Gardosi birth weight percentiles Probabilities for Post Hoc Tests Error: Between MS = 826.89, df = 4094.0				
4-level grouping	1 50.54	2 45.05	3 47.67	4 41.89
NSND		<.001	0.051	<.001
S	<.001		0.080	0.013
D	0.051	0.080		<.001
SD	<.001	0.013	<.001	

NSND: no smoking or drinking; S: smoking only; D: drinking only; SD: smoking and drinking

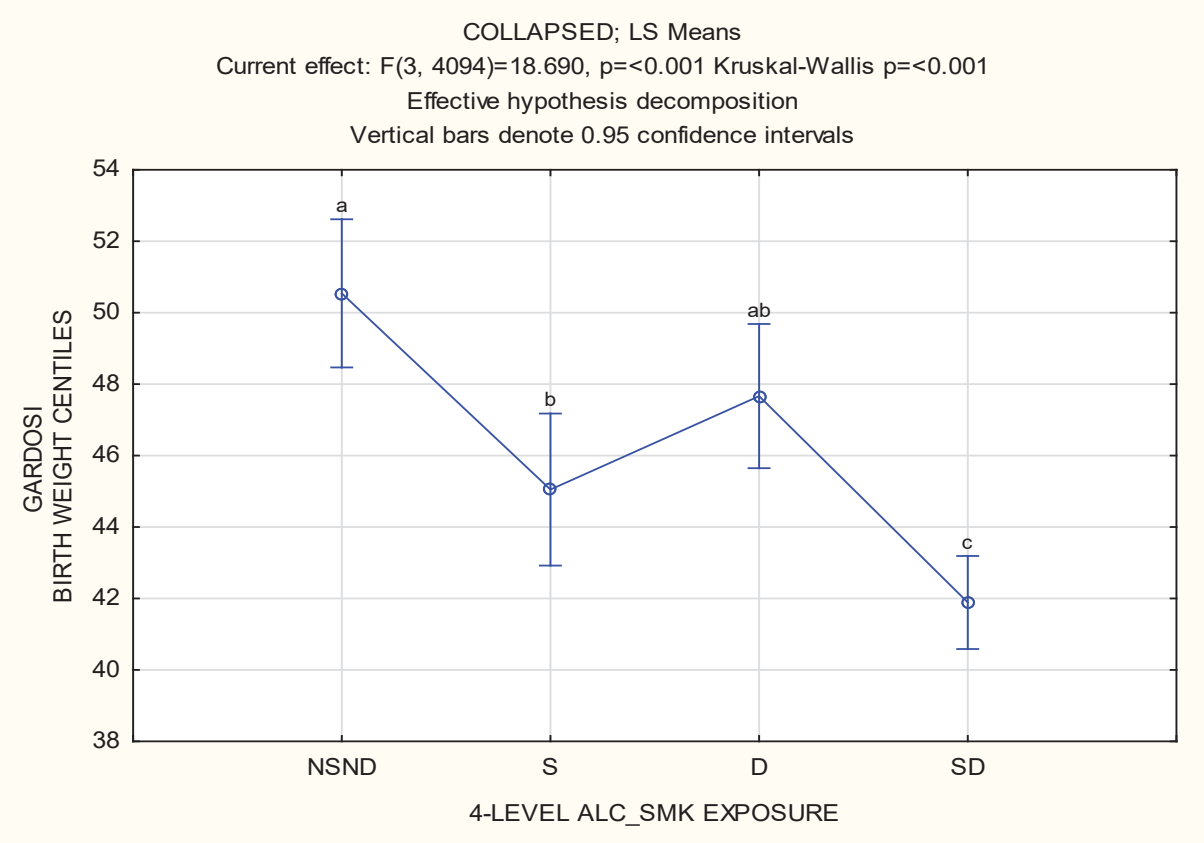


Figure 13. The association between the 4-level alcohol smoking exposure grouping and the birth weight centiles of Gardosi.

Chapter 5

DISCUSSION

During this chapter, the results will be discussed in-depth and compared to the literature.

The main aim of the study was to determine if there is a combined dose-response effect of PCE and PAE on birth weight by converting the birth weight to z-scores and centiles according to the population-based GA and sex-specific newborn reference ranges from the INTERGROWTH-21st Project [35] and those of Gardosi [36] which are customised to individual patient characteristics. The data was compared between the nine-level and four-level alcohol-smoking exposure groups.

When comparing the basic obstetric information of our study against PCE and PAE, it was clear that a substantial number of late bookings (GA ≥ 98 days [14 weeks]) is seen among all drinkers, earlier delivery (< 266 days [37 weeks]) among all smokers and LBW among all smokers.

1. Proportion of SGA

The percentage of newborns identified in our study as SGA is significantly higher than expected (approximately 10 % [72]) with different proportions for both references: 739 (18 %) newborns were < p10 according to the INTERGROWTH-21st project's [35] reference and 543 (13.3 %) according to the reference of Gardosi [36]; < p5: 412 (10.1 %) and 296 (7.2 %) respectively; and < p3: 266 (6.5 %) and 201 (4.9 %) respectively. The question arises whether this is due to the socioeconomic status of our study group.

Significant differences were found between the nine-level alcohol-smoking exposure groups in the percentage of infants whose birth weight was below p10, p5, and p3 when compared to the INTERGROWTH-21st project [35] and Gardosi's [36] references. The results for the two references were essentially the same. The highest percentage of SGA was found in the HSLD, LSHD, and HSHD groups that consisted of dual exposure with either or both exposures being heavy. This finding is supported by Okah *et al.* [145] who found that women who smoke during pregnancy are sevenfold more likely to consume alcohol compared to non-smokers. In our study, the majority of women reported dual exposure (45.8 %) versus 17.2 % who reported to smoke only and 19 % who reported consuming alcohol only. A smaller, but still significant, effect was noted for smoking (with or without low drinking) and < p10 but no effect of HSND for birth weight below p5 and p3, probably due to small numbers. No significant differences were noted for group NSHD (whether using p10, p5, or p3). This could be due to the small sample size rather than the absence of a true effect (which would be biologically counterintuitive) but the percentage in all drinkers was also the same as non-users. The combined dose-response effect was greater, especially when exposure to one or both was heavy.

When compared to the four-level alcohol-smoking exposure grouping, the lowest percentage of SGA was found in group D, but not significantly different from NSND. Similar findings were noted in the study of Brink *et al.* [144] where they found that heavy drinking during pregnancy without smoking was highly related to an increase in birth weight. This varied from other studies [18,146] that found alcohol exposure during pregnancy to have a decreasing effect on birth weight. Group SD was significantly different from the rest with the highest percentage of SGA. The S group only showed significance compared to the other groups in the below p10 range. No significance was

noted for < p5 or < p3 when compared to the INTERGROWTH-21st project [35]. A smaller effect, but still significant was found in the below p10 group when compared to Gardosi [36].

The results from our study conflict with the reviews of Henderson *et al.* [16] and Patra *et al.* [18] who found no dose-response relationship between low PAE and adverse birth outcomes. This may be due to different study designs and methods used. Most of the studies did not adjust for ethnicity. Some studies included only white women in their study and others only black women [16]. The other difference found is the way in which a standard drink and low, moderate, or heavy drinking was defined. According to Patra *et al.* [18], this differs among countries. In another review by Henderson *et al.* [14] the definition of binge drinking included consumption of small as well as substantial amounts of alcohol.

Our findings correlate with the work by Yang *et al.* [147], who found an increased risk for SGA when heavy PAE was combined with pre-existing smoking.

2. *Distribution of birth weight z-scores and centiles according to the reference ranges of the INTERGROWTH-21st project and Gardosi*

The distribution of the birth weight z-scores, according to both reference ranges, differed significantly between the nine-level alcohol-smoking exposure groups, except for single heavy exposures (HSND and NSHD) which showed no significance. This could be due to the small sample size.

The results from both reference ranges were very similar. The lowest distribution was noted in the dual consumption with high exposure groups (HSLD, LSHD, and HSHD). The highest distribution was found in the NSND group which differed significantly from LSND and LSLD (low single or dual exposure). NSND also differed significantly from NSLD when compared to the INTERGROWTH-21st project [35], but no significance was noted when compared to Gardosi [36]. The second highest distribution was noted in the NSLD group which differed significantly from LSLD in both references as well as from LSND when compared to the INTERGROWTH-21st project [35].

When compared to the four-level alcohol-smoking exposure grouping, the lowest distribution was noted in the SD group (dual exposure). With the INTERGROWTH-21st project [35], the highest distribution was found in the NSND group which differed significantly from all the other groups (single or dual exposure), followed by group D (not significant). When compared with Gardosi [36], the highest distribution was found in the NSND with no significant difference noted from group D.

A recent paper from the main SPS study studied maternal habits in subsequent pregnancies after a previous enrolment. They noted that even though the patients received adequate information on adverse effects of PAE and PCE at first enlistment, it had little effect on limiting exposure as a substantial number of women in the SPS smoked (68.4 – 73.7 %) and used alcohol (54.6 – 63.8 %) in their subsequent pregnancy [11].

The study by Brooke *et al.* [81] found a strong correlation between PAE and PCE on birth weight. No differences were seen among women who have never smoked and those who stopped smoking before falling pregnant. A significant trend was seen towards LBW with increasing consumption of alcohol among smokers. We agree that a clear dose-response

effect of PAE on birth weight was noted among smokers with a significant trend towards decreased birth weight with increased drinking. Furthermore, earlier studies [148–151] highlighted the significance of social class and other factors relating to it such as income, housing, and education as these factors could affect birth weight due to stress.

Our findings are in agreement with that of Olsen *et al.* [30] who found a dose-response relationship between smoking and alcohol use during pregnancy on fetal growth, especially when comparing low to moderate amounts of alcohol consumption to heavy smoking. This is one of the first studies that investigated the effect of dual exposure compared to the systematic reviews of Patra *et al.* [18] and Henderson *et al.* [16] who only investigated the effect of single exposures. The reason why our data might differ from studies not finding a dose-response is the fact that most studies only collected singular exposure data (i.e. smoking or drinking) or when combined they only collected exposure data in the third trimester whereas our study collected PCE and PAE data 15 days prior to the first day of the LNMP up to a month postnatal.

Chapter 6

CONCLUSION

This chapter will highlight our study's findings and learned points.

With the use of the INTERGROWTH-21st project's [35] newborn birth weight reference ranges and the GA sex-specific birth weight reference ranges, customised to individual patient characteristics of Gardosi [36] our study revealed that alcohol-smoking exposure has a combined dose-response effect on birth weight and the proportion of SGA infants, especially when one or both exposures are high. A smaller effect was seen for single high exposures or low smoking exposures (with or without low drinking). With low alcohol exposure without smoking, birth weight distributions were always lower than with no exposure, but the difference was only significant when using the INTERGROWHT-21 project's reference and not when using that of Gardosi. Single PCE had a larger effect than single PAE, but the combination thereof had a significant effect on fetal growth.

It further revealed that with heavier combinations of exposure, there was a greater effect on birth weight. Therefore, our study concurs with that of Day [128] and Larkby and Day [20] who state that while there is a dose-response relationship of PAE and PCE during pregnancy, there is no level of exposure that is safe during pregnancy as the smallest amount of exposure could produce an adverse effect.

RECOMMENDATIONS

This study population with low socioeconomic status is considered to be a high-risk community that warrants more direct health awareness campaigns. It is important to develop appropriate health education programs with “dual messages” on PCE and PAE as combined exposure in pregnancy could lead to harmful effects. Furthermore, it is important to stress that no level of PCE and PAE during pregnancy is safe.

Chapter 7

LIMITATIONS OF THE STUDY

This chapter will address the limitations of the study.

Firstly, many factors could contribute to the underreporting of PAE and PCE during pregnancy. Women might incorrectly recollect their exposure, feel embarrassed, or underreport due to social stigma [21,22]. The design of the SPS tried to reduce recollection error by obtaining information at 30-day intervals using the TLFB technique [143] This is seen as the gold standard for assessing alcohol exposure over long periods, as alcohol has a short half-life [22] making it difficult to validate chronic exposure (especially timing, frequency and amount of exposure [17]) with the use of non-invasive biomarkers in samples such as maternal saliva, - urine, - hair and infant meconium or hair [22]. Infant meconium has the advantage of identifying moderate drinking and binging as it is most sensitive for identifying amounts of alcohol and nicotine that crossed the placental barrier to the fetus in the third trimester [13,23,152]. In a small sample (n = 108) of infants from the main SPS, meconium was tested and successfully validated for PCE and PAE by self-report in this study [13]. The study design further created a sense of trust between the participants, the community, and the study staff by using certificates of confidentiality to reduce embarrassment and social stigma [21].

Secondly, it was challenging to collect exposure information at specific periods in pregnancy as gaps may have arisen due to late enlistment or missing assessments, which is quite problematic as it may bias research findings, especially if the data are not missing completely at random [21].

Thirdly, passive maternal exposure or environmental tobacco exposure due to 'second-hand' tobacco smoke was not documented and is known to affect birth weight [6]. A study by Martinez *et al.* [153] found a decrease of 88g in mean birth weight with paternal smoking of 20 cigarettes per day during pregnancy, whereas a study by Hegaard *et al*. [154] found a decrease of 79g in mean birth weight from passive maternal exposure in and outside the home.

REFERENCES

[1] Ward C, Lewis S, Coleman T. Prevalence of maternal smoking and environmental tobacco smoke exposure during pregnancy and impact on birth weight: Retrospective study using Millennium Cohort. BioMed Central Public Health. 2007;7(1):1–7.

[2] Cornelius MD, Day NL. The effects of tobacco use during and after pregnancy on exposed children: Relevance of findings for alcohol research. Alcohol Research and Health. 2000;24(4):242–9.

[3] Aliyu M, Wilson R, Zoorob R, Brown K, Alio A, Clayton H, et al. Prenatal alcohol consumption and fetal growth restriction: Potentiation effect by concomitant smoking. Nicotine and Tobacco Research. 2009;11(1):36–43.

[4] Walker MJ, Al-Sahab B, Islam F, Tamim H. The epidemiology of alcohol utilization during pregnancy: An analysis of the Canadian Maternity Experiences Survey (MES). BioMed Central Pregnancy and Childbirth. 2011;11(52):1–9.

[5] Knopik V, Maccani M, Francazio S, McGeary J. The epigenetics of maternal cigarette smoking during pregnancy and effects on child development. Development and Psychopathology. 2012;24(4):1377–90.

[6] Reeves S, Bernstein I. Effects of maternal tobacco-smoke exposure on fetal growth and neonatal size. Expert Review of Obstetrics and Gynecology. 2008;3(6):719–30.

[7] Sharma A, Cogswell M, Li R. Dose-response associations between maternal smoking during pregnancy and subsequent childhood obesity: effect modification by maternal race/ethnicity in a low-income US cohort. American Journal of Epidemiology. 2008;168(9):995–1007.

[8] Nugent K, Lester B, Greene S, Wieczorek-Deering D, O'Mahony P. The effects of maternal alcohol consumption and cigarette smoking during pregnancy on acoustic cry analysis. Child Development. 1996;67(4):1806–15.

[9] Steyn K, Yach D, Stander I, Fourie J. Smoking in urban pregnant women in South Africa. South African Medical Journal. 1997;87(4):460–3.

[10] Muckle G, Laflamme D, Gagnon J, Boucher O, Jacobson J, Jacobson S. Alcohol, smoking, and drug use among inuit women of childbearing age during pregnancy and the risk to children. Alcoholism: Clinical and Experimental Research. 2011;35(6):1081–91.

[11] Odendaal H, Brink L, Nel D, Carstens E, de Jager M, Potter M, et al. Smoking and drinking habits of women in subsequent pregnancies after specific advice about the dangers of these exposures during pregnancy. South African Medical Journal. 2020;110(11):1100–4.

[12] Powers JR, McDermott LJ, Loxton DJ, Chojenta CL. A prospective study of prevalence and predictors of concurrent alcohol and tobacco use during pregnancy. Maternal and Child Health Journal. 2013;17(1):76–84.

[13] Himes S, Dukes K, Tripp T, Petersen J, Raffo C, Burd L, et al. Clinical sensitivity and specificity of meconium fatty acid ethyl ester, ethyl glucuronide, and ethyl sulfate for detecting maternal drinking during pregnancy. Clinical Chemistry. 2015;61(3):523–32.

[14] Henderson J, Kesmodel U, Gray R. Systematic review of the fetal effects of prenatal binge-drinking. Journal of Epidemiology and Community Health. 2007;61:1069–73.

[15] Popova S, Lange S, Probst C, Gmel G, Rehm J. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: A systematic review and meta-analysis. The Lancet. 2017;5(3):e290–9.

[16] Henderson J, Gray R, Brocklehurst P. Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. British Journal of Obstetrics and Gynaecology. 2007;114:243–52.

[17] Dukes K, Burd L, Elliott A, Fifer W, Folkerth R, Hankins G, et al. The safe passage study: Design, methods, recruitment, and follow-up approach. Paediatric and Perinatal Epidemiology. 2014;28(5):455–65.

[18] Patra J, Bakker R, Irving H, Jaddoe V, Malini S, Rehm J. Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA)-a systematic review and meta-analyses. British Journal of Obstetrics and Gynaecology. 2011;118:1411–21.

[19] Odendaal H, Steyn D, Elliott A, Burd L. Combined effects of cigarette smoking and alcohol consumption on perinatal outcome. Gynecologic and Obstetric Investigation 2009;67:1–8.

[20] Larkby C, Day N. The effects of prenatal alcohol exposure. Alcohol Health and Research World. 1997;21(3):192–8.

[21] Dukes K, Tripp T, Willinger M, Odendaal H, Elliott AJ, Kinney HC, et al. Drinking and smoking patterns during pregnancy: Development of group-based trajectories in the Safe Passage Study. Alcohol. 2017;62:49–60.

[22] Bakhireva L, Savage D. Focus on: Biomarkers of fetal alcohol exposure and fetal alcohol effects. Alcohol Research and Health. 2011;34(1):56–63.

[23] Shisler S, Eiden R, Molnar D, Schuetze P, Huestis M, Homish G. Original investigation smoking in pregnancy and fetal growth: The case for more intensive assessment. Nicotine and Tobacco Research. 2017;19(5):525–31.

[24] Petersen Z. Smoking cessation during pregnancy: A person-centred approach among disadvantaged women in South Africa. Umeå Universitet, Sweden, 2011.

[25] Viljoen J, Odendaal H. Smoking in pregnancy - What does my patient know? South African Medical Journal. 2005;11(3):56–7.

[26] Dukes K, Tripp T, Petersen J, Robinson F, Odendaal H, Elliott A, et al. A modified timeline followback assessment to capture alcohol exposure in pregnant women: Application in the Safe Passage Study. Alcohol. 2017;62:17–27.

[27] May P, Gossage J, Brooke L, Snell C, Marais A, Hendricks L, et al. Maternal risk factors for fetal alcohol syndrome in the Western Cape Province of South Africa: A population-based study. American Journal of Public Health. 2005;95(7):1190–9.

[28] Fouché L, Kritzinger A, Le Roux T. Gestational age and birth weight variations in young

children with language impairment at an early communication intervention clinic. South African Journal of Communication Disorders. 2018;65(1):1–9.

[29] Peacock J, Bland M, Anderson R, Peacock J, Bland J, Anderson H, et al. Effects on birthweight of alcohol and caffeine consumption in smoking women. Journal of Epidemiology and Community Health. 1991;45(2):159–63.

[30] Olsen J, da Costa Pereira A, Olsen S. Does maternal tobacco smoking modify the effect of alcohol on fetal growth? American Journal of Public Health. 1991;81(1):69–73.

[31] Haste F, Anderson H, Brooke O, Bland J, Peacock J. The effects of smoking and drinking on the anthropometric measurements of neonates. Paediatric and Perinatal Epidemiology. 1991;5(5):83–92.

[32] Larroque B, Kaminski M, Lelong N, Subtil D, Dehaene P. Effects on birth weight of alcohol and caffeine consumption during pregnancy. American Journal of Epidemiology. 1993;137:941–50.

[33] Kariniemi V, Rosti J. Maternal smoking and alcohol consumption as determinants of birth weight in an unselected study population. Journal of Perinatal Medicine. 1988;16(3):249–52.

[34] O'Leary C, Bower C, Zubrick S, Geelhoed E, Kurinczuk J, Nassar N. A new method of prenatal alcohol classification accounting for dose, pattern and timing of exposure: Improving our ability to examine fetal effects from low to moderate alcohol. Journal of Epidemiology and Community Health. 2010;64:956–62.

[35] Villar J, Ismail L, Victora C, Ohuma E., Bertino E, Altman D, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: The newborn cross-sectional study of the INTERGROWTH-21st Project. The Lancet. 2014;384:857–68.

[36] Gardosi J. New definition of small for gestational age based on fetal growth potential. Hormone Research. 2006;65(3):15–8.

[37] Audette M, Kingdom J. Screening for fetal growth restriction and placental insufficiency. Seminars in Fetal and Neonatal Medicine. 2018;23:119–25.

[38] Miller S, Huppi P, Mallard C. The consequences of fetal growth restriction on brain structure and neurodevelopmental outcome. The Journal of Physiology. 2016;594(4):807–23.

[39] Barker D. In utero programming of chronic disease. Clinical Science. 1998;95(2):115–28.

[40] Barker DJP. Fetal origins of coronary heart disease. British Medical Journal. 1995;311(6998):171–4.

[41] Bakker H, Jaddoe V. Cardiovascular and metabolic influences of fetal smoke exposure. European Journal of Epidemiology. 2011;26(10):763.

[42] Lambers D, Clark K. The maternal and fetal physiologic effects of nicotine. Seminars in Perinatology. 1996;20(2):115–26.

[43] Gardiner HM. Intrauterine programming of the cardiovascular system. Ultrasound in Obstetrics and Gynecology. 2008;32(4):481–4.

[44] Slotkin T. Developmental cholinotoxicants: nicotine and chlorpyrifos. Environmental Health

Perspectives. 1999;107(Suppl1):71–80.

[45] Ziaei S, Nouri K, Kazemnejad A. Effects of carbon monoxide air pollution in pregnancy on neonatal nucleated red blood cells. Paediatric and Perinatal Epidemiology. 2005;19(1):27–30.

[46] Kramer M. Determinants of low birth weight: methodological assessment and meta-analysis. Bulletin of the World Health Organization. 1987;65(5):663.

[47] Easter S, Eckert L, Boghossian N, Spencer R, Oteng-Ntim E, Ioannou C, et al. Fetal growth restriction: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2017;35(48):6546–54.

[48] Cutland C, Lackritz E, Mallett-Moore T, Bardají A, Chandrasekaran R, Lahariya C, et al. Low birth weight: Case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017;35(48Part A):6492.

[49] Silverman W, Lecey J, Beard A, Brown A, Cornblath M, Grossman M, et al. Committee on fetus and newborn: Nomenclature for duration of gestation, birth weight and intra-uterine growth. Pediatrics. 1967;39(6):935–9.

[50] De Onis M, Blössner M, Villar J. Levels and patterns of intrauterine growth retardation in developing countries. European Journal of Clinical Nutrition. 1998;52:S5-15.

[51] Schlaudecker E, Munoz F, Bardají A, Boghossian N, Khalil A, Mousa H, et al. Small for gestational age: Case definition & guidelines for data collection, analysis, and presentation of maternal immunisation safety data. Vaccine. 2017;35:6518–28.

[52] Figueras F, Savchev S, Triunfo S, Crovetto F, Gratacos E. An integrated model with classification criteria to predict small-for-gestational-age fetuses at risk of adverse perinatal outcome. Ultrasound in Obstetrics and Gynecology. 2015;45(3):279–85.

[53] Godfrey K, Barker D. Fetal programming and adult health. Public Health Nutrition. 2001;4(2b):611–24.

[54] Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. British Medical Journal. 2013;346.

[55] Pilliod R, Cheng Y, Snowden J, Doss A, Caughey A. The risk of intrauterine fetal death in the small-for-gestational-age fetus. American Journal of Obstetrics and Gynecology. 2012;207(4):318-e1.

[56] von Beckerath A, Kollmann M, Rotky-Fast C, Karpf E, Lang U, Klaritsch P. Perinatal complications and long-term neurodevelopmental outcome of infants with intrauterine growth restriction. American Journal of Obstetrics and Gynecology. 2013;208(2):130-e1.

[57] Lees CC, Marlow N, Van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, et al. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. The Lancet. 2015;385(9983):2162–72.

[58] Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound in Obstetrics and Gynecology.

2013;42(4):400–8.

[59] Francis JH, Permezel M, Davey MA. Perinatal mortality by birthweight centile. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2014;54(4):354–9.

[60] Jarvis S, Glinianaia S, Torrioli M, Platt M, Miceli M, Jouk P, et al. Cerebral palsy and intrauterine growth in single births: European collaborative study. The Lancet. 2003;362(9390):1106–1011.

[61] Barker DJP. The long-term outcome of retarded fetal growth. Clinical Obstetrics and Gynecology. 1997;40(4):853–63.

[62] Pojda J, Kelley L. Low birth weight: Report of a meeting in Dhaka, Bangladesh on 14–17 June 1999. vol. 18. Geneva: 2000.

[63] Bale JR, Stoll BJ, Lucas AO. Improving birth outcomes: Meeting the challenge in the developing world Washington DC. Institute of Medicine Committee on Improving Birth Outcomes Board on Global Health. 2003:205–35.

[64] Villar J, Papageorghiou AT, Pang R, Ohuma EO, Ismail LC, Barros FC, et al. The likeness of fetal growth and newborn size across non-isolated populations in the INTERGROWTH-21st Project: the Fetal Growth Longitudinal Study and Newborn Cross-Sectional Study. The Lancet Diabetes and Endocrinology. 2014;2(10):781–92.

[65] Nardozza LMM, Caetano ACR, Zamarian ACP, Mazzola JB, Silva CP, Marçal VMG, et al. Fetal growth restriction: current knowledge. Archives of Gynecology and Obstetrics. 2017;295(5):1061–77.

[66] Dall'Asta A, Brunelli V, Prefumo F, Frusca T, Lees CC. Early onset fetal growth restriction. Maternal Health, Neonatology and Perinatology. 2017;3(1):1–2.

[67] Snijders RJM, Sherrod C, Gosden CM, Nicolaides KH. Fetal growth retardation: associated malformations and chromosomal abnormalities. American Journal of Obstetrics and Gynecology. 1993;168(2):547–55.

[68] Jaddoe VWV, Bakker R, Hofman A, Mackenbach JP, Moll HA, Steegers EAP, et al. Moderate alcohol consumption during pregnancy and the risk of low birth weight and preterm birth. The Generation R Study. Annals of Epidemiology. 2007;17(10):834–40.

[69] McCowan LME, Dekker GA, Chan E, Stewart A, Chappell LC, Hunter M, et al. Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: prospective cohort study. British Medical Journal. 2009;338:1–6.

[70] Gouin K, Murphy K, Shah PS. Knowledge synthesis group on determinants of low birth weight and preterm births. Effects of cocaine use during pregnancy on low birthweight and preterm birth: systematic review and metaanalyses. American Journal of Obstetrics and Gynecology. 2011;204(4):340.

[71] Mizuuchi M, Cindrova-Davies T, Olovsson M, Charnock-Jones DS, Burton GJ, Yung HW. Placental endoplasmic reticulum stress negatively regulates transcription of placental growth factor via ATF4 and ATF6β: implications for the pathophysiology of human pregnancy

complications. The Journal of Pathology. 2016;238(4):550–61.

[72] Gratacós E, Figueras F. Fetal growth restriction as a perinatal and long-term health problem: clinical challenges and opportunities for future (4P) fetal medicine. Fetal Diagnosis and Therapy. 2014;36(2):85.

[73] Ego A, Subtil D, Grange G, Thiebaugeorges O, Senat M-V, Vayssiere C, et al. Customized versus population-based birth weight standards for identifying growth restricted infants: a French multicenter study. American Journal of Obstetrics and Gynecology. 2006;194(4):1042–9.

[74] Gardosi J. Customized fetal growth standards: rationale and clinical application. vol. 28(1). WB Saunders; 2004.

[75] McCowan LME, Harding JE, Stewart AW. Customised birthweight centiles predict SGA pregnancies with perinatal morbidity. British Journal of Obstetrics and Gynaecology. 2005;112(8):1026–33.

[76] Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. The Lancet. 1992;339(8788):283–7.

[77] Gardosi J, Mongelli M, Wilcox M, Chang A. An adjustable fetal weight standard. Ultrasound in Obstetrics and Gynecology. 1995;6(3):168–74.

[78] Kramer M. The epidemiology of low birthweight. Nestle Nutrition Institute Workshop Series. 2013;74:1–10.

[79] World Health Organization (WHO). Maternal anthropometry and pregnancy outcomes: a WHO collaborative study. World Health Organization Bulletin. 1995;73:1–6.

[80] Williams RL, Creasy RK, Cunningham GC, Hawes WE, Norris FD, Tashiro M. Fetal growth and perinatal viability in California. Obstetric and Gynaecology. 1982;59(5):624–32.

[81] Brooke O, Anderson H, Bland J, Peacock J, Stewart C. Effects on birth weight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. British Medical Journal. 1989;298(6676):795–801.

[82] Nordentoft M, Lou H, Hansen D, Nim J, Pryds O, Rubin P, et al. Intrauterine growth retardation and premature delivery: The influence of maternal smoking and psychosocial factors. American Journal of Public Health. 1996;86(3):347–54.

[83] Chomba E, Tshefu A, Onyamboko M, Kaseba-Sata C, Moore J, McClure EM, et al. Tobacco use and secondhand smoke exposure during pregnancy in two African countries: Zambia and the Democratic Republic of the Congo. Acta Obstetricia et Gynecologica. 2010;89(4):531–9.

[84] Caleyachetty R, Tait C, Kengne A, Corvalan C, Uauy R, Echouff o-Tcheugui J. Tobacco use in pregnant women: analysis of data from Demographic and Health Surveys from 54 low-income and middle-income countries. The Lancet. 2014;2(9):e513–20.

[85] Jones PJH, Leichter J, Lee M. Placental blood flow in rats fed alcohol before and during gestation. Life Sciences. 1981;29(11):1153–9.

[86] Cogswell ME, Weisberg P, Spong C. Cigarette smoking, alcohol use and adverse pregnancy

outcomes: implications for micronutrient supplementation. The Journal of Nutrition. 2003;133(5):1722S-1731S.

[87] Hamid A, Kaur J. Long-term alcohol ingestion alters the folate-binding kinetics in intestinal brush border membrane in experimental alcoholism. Alcohol. 2007;41(6):441–6.

[88] Thomson AD. Alcohol and nutrition. Clinics in Endocrinology and Metabolism. 1978;7(2):405–28.

[89] Hebel R, Fox N, Sexton M. Dose-response of birth weight to smoking during pregnancy. Journal of Clinical Epidemiology. 1988;41(5):483–9.

[90] Bernstein I, Mongeon J, Badger G, Solomon L, Heil S, Higgins S. Maternal smoking and its association with birth weight. Obstetrics and Gynecology. 2005;106(5):986–91.

[91] Backe B. Maternal smoking and its association with birth weight. Acta Obstetricia et Gynecologica. 1993;72(3):172–6.

[92] Martin LT, McNamara M, Milot A, Bloch M, Hair EC, Halle T. Correlates of smoking before, during, and after pregnancy. American Journal of Health Behavior. 2008;32(3):272–82.

[93] Floyd LR, Decouflé P, Hungerford DW. Alcohol use prior to pregnancy recognition. American Journal of Preventative Medicine. 1999;17(2):101–7.

[94] IARC Monographs on the evaluation of carcinogenic risks to humans. Alcohol Drinking. 1988;44.

[95] Windham G, Fenster L, Hopkins B, Swan S. The association of moderate maternal and paternal alcohol consumption with birthweight and gestational age. Epidemiology. 1995;6(6):591–7.

[96] Polygenis D, Wharton S, Malmberg C, Sherman N, Kennedy D, Koren G, et al. Moderate alcohol consumption during pregnancy and the Incidence of fetal malformations: A Meta-Analysis. Neorotoxicology and Teratology. 1998;20(1):61–7.

[97] O'Leary C. The association between prenatal alcohol exposure, fetal growth and preterm birth: evidence from a systematic review and meta-analyses. Evidence-Based Nursing. 2012;15(3):77–8.

[98] Malet L, De Chazeron I, Llorca PM, Lemery D. Alcohol consumption during pregnancy: A urge to increase prevention and screening. European Journal of Epidemiology. 2006;21(10):787–8.

[99] Green JH. Fetal Alcohol Spectrum Disorders: Understanding the effects of prenatal alcohol exposure and supporting students. Journal of School Health. 2007;77(3):103–8.

[100] Chudley AE, Conry J, Cook JL, Loock C, Rosales T, LeBlanc N. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. Canadian Medical Association Journal. 2005;172(5 supp:S1–21.

[101] Kelly YJ, Sacker A, Gray R, Kelly J, Wolke D, Head J, et al. Light drinking during pregnancy: still no increased risk for socioemotional difficulties or cognitive deficits at 5 years of age? Journal of Epidemiology and Community Health. 2012;66(1):41–8.

[102] Barr HM, Bookstein FL, O'Malley KD, Connor PD, Huggins JE, Streissguth AP. Binge drinking during pregnancy as a predictor of psychiatric disorders on the structured clinical interview for DSM-IV in young adult offspring. American Journal of Psychiatry. 2006;163(6):1061–5.

[103] Abel EL. Fetal Alcohol Abuse Syndrome 1998.

[104] Allebeck P, Olsen J. Alcohol and fetal damage. Alcoholism: Clinical and Experimental Research. 1998;22:3295–325.

[105] Clarren SK, Astley SJ, Gunderson VM, Spellman D. Cognitive and behavioral deficits in nonhuman primates associated with very early embryonic binge exposures to ethanol. The Journal of Pediatrics. 1992;121(5):789–96.

[106] Astley SJ, Magnuson SI, Omnell LM, Clarren SK. Fetal alcohol syndrome: changes in craniofacial form with age, cognition, and timing of ethanol exposure in the macaque. Teratology. 1999;59(3):163–72.

[107] Skagerström J, Alehagen S, Häggström-Nordin E, Årestedt K, Nilsen P. Prevalence of alcohol use before and during pregnancy and predictors of drinking during pregnancy: A cross sectional study in Sweden. BioMed Central Public Health. 2013;13(1):1–10.

[108] Tough S, Tofflemire K, Clarke M, Newburn-Cook C. Do women change their drinking behaviors while trying to conceive? An opportunity for preconception counseling. Clinical Medicine and Research. 2006;4(2):97–105.

[109] Lange S, Probst C, Quere M, Rehm J, Popova S. Alcohol use, smoking and their co-occurrence during pregnancy among Canadian women, 2003 to 2011/12. Addictive Behaviors. 2015;50:102–9.

[110] Iversen M, Sorensen N, Broberg L, Damm P, Hedegaard M, Tabor A, et al. Alcohol consumption and binge drinking in early pregnancy. A cross-sectional study with data from the Copenhagen pregnancy cohort. BioMed Central Pregnancy and Childbirth. 2015;15(327):1–10.

[111] Sokol R, Delaney-Black V, Jama BN-, 2003 U. Fetal alcohol spectrum disorder. Journal of American Medical Association. 2003;290(2):2996–9.

[112] Little RE. Moderate alcohol use during pregnancy and decreased infant birth weight. American Journal of Public Health. 1977;67(12):1154–6.

[113] Hanson JW, Streissguth AP, Smith DW. The effects of moderate alcohol consumption during pregnancy on fetal growth and morphogenesis. The Journal of Pediatrics. 1978;92(3):457–60.

[114] Lazzaroni F, Bonassi S, Magnani M, Calvi A, Repetto E, Serra G, et al. Moderate maternal drinking and outcome of pregnancy. European Journal of Epidemiology. 1993;9(6):599–606.

[115] Lundsberg L, Illuzzi J, Belanger K, Triche E, Bracken M. Low to moderate prenatal alcohol consumption and the risk of selected birth outcomes: A prospective cohort study. Annals of Epidemiology. 2015;25(1):46.

[116] McDonald A, Armstrong B, Sloan M. Cigarette, alcohol, and coffee consumption and

prematurity. American Journal of Public Health. 1992;82(1):87–90.

[117] Brick J. Standardization of alcohol calculations in research. Alcoholism. 2006;30(8):1276–87.

[118] International Center for Alcohol Policies. What is a “standard drink”? ICAP Reports. 1998;5:1–6.

[119] World Health Organization. International guide for monitoring alcohol consumption and related harm. World Health Organization. 2000.

[120] Ouellette E, Rosett H, Rosman N, Weiner L. Adverse effects on offspring of maternal alcohol abuse during pregnancy. New England Journal of Medicine. 1977;297(10):528–30.

[121] Chiaffarino F, Parazzini F, Chatenoud L, Ricci E, Sandretti F, Cipriani S, et al. Alcohol drinking and risk of small for gestational age birth. European Journal of Clinical Nutrition. 2006;60(9):1062–6.

[122] Passaro KT, Little RE, Savitz DA, Noss J. The effect of maternal drinking before conception and in early pregnancy on infant birthweight. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. Epidemiology. 1996;7(4):377–83.

[123] Mills J, Graubard B, Harley E, Rhoads G, Berendes H. Maternal alcohol consumption and birth weight: How much drinking during pregnancy is safe? Journal of American Medical Association. 1984;252(14):1875–9.

[124] Eberhart JK, Parnell SE. The genetics of Fetal Alcohol Spectrum Disorders (FASD). Alcoholism, Clinical and Experimental Research.. 2016;40(6):1165.

[125] May PA, Gossage JP. Maternal risk factors for Fetal Alcohol Spectrum Disorders: Not as simple as it might seem. Alcohol Research and Health 2011;34(1):26.

[126] Day J, Savani S, Krempley B, Nguyen M, Kitlinska J. Influence of paternal preconception exposures on their offspring: through epigenetics to phenotype. American Journal of Stem Cells. 2016;5(1):11.

[127] Smith I E, Coles C D, Lancaster J, Fernhoff P M, Falec A. The effect of volume and duration of prenatal ethanol exposure on neonatal physical and behavioral development. Neurobehavioral Toxicology and Teratology. 1986;8(4):375–81.

[128] Day N. Editorial: Research on the effects of prenatal alcohol exposure - A new direction. American Journal of Public Health. 1995;85(12):1614–5.

[129] Perham-Hester KA, Gessner BD. Correlates of drinking during the third trimester of pregnancy in Alaska. Maternal and Child Health Journal. 1997;1(3):165–72.

[130] Ethen MK, Ramadhani TA, Scheuerle AE, Canfield MA, Wyszynski DF, Druschel CM, et al. Alcohol consumption by women before and during pregnancy. Maternal and Child Health Journal. 2009;13(2):274–85.

[131] Murphy DJ, Mullally A, Cleary BJ, Fahey T, Barry J. Behavioural change in relation to alcohol exposure in early pregnancy and impact on perinatal outcomes - A prospective cohort study. BioMed Central Pregnancy and Childbirth. 2013;13(1):1–8.

[132] Salihu HM, Wilson RE. Epidemiology of prenatal smoking and perinatal outcomes. Early

Human Development. 2007;83(11):713–20.

[133] McNamara TK, Orav EJ, Wilkins-Haug L, Chang G. Social support and prenatal alcohol use. Journal of Women's Health. 2006;15(1):70–6.

[134] Chang G, McNamara TK, Orav EJ, Wilkins-Haug L. Alcohol use by pregnant women: Partners, knowledge, and other predictors. Journal of Studies on Alcohol. 2006;67(2):245–51.

[135] Gladstone J, Levy M, Nulman I, Koren G. Characteristics of pregnant women who engage in binge alcohol consumption. Canadian Medical Association Journal. 1997;156(6):789–94.

[136] Ebrahim S, Luman E, Floyd R, Murphy C, Bennett EM, Boyle CA. Alcohol consumption by pregnant women in the United States during 1988–1995. Obstetrics and Gynaecology. 1998;92(2):187–92.

[137] Flynn HA, Marcus SM, Barry KL, Blow FC. Rates and correlates of alcohol use among pregnant women in obstetrics clinics. Alcoholism: Clinical and Experimental Research. 2003;27(1):81–7.

[138] Crome I, Kumar M. Epidemiology of drug and alcohol use in young women. Seminars in Fetal and Neonatal Medicine. 2007;12(2):98–105.

[139] Perreira K, Cortes K. Race/ethnicity and nativity differences in alcohol and tobacco use during pregnancy. American Journal of Public Health. 2006;96(9):1629–36.

[140] Martin SL, Beaumont JL, Kupper LL. Substance use before and during pregnancy: Links to intimate partner violence. American Journal of Drug and Alcohol Abuse. 2003;29(3):599–617.

[141] Day N, Cottreau C, Richardson G. The epidemiology of alcohol, marijuana, and cocaine use among women of childbearing age and pregnant women. Clinical Obstetrics and Gynecology. 1993;36(2):232–45.

[142] McLeod D, Pullon S, Cookson T, Cornford E. Factors influencing alcohol consumption during pregnancy and after giving birth. The New Zealand Medical Journal (Online). 2002;115(1157).

[143] Sobell L, Sobell M. Timeline follow-back: A technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP, editors. Measuring Alcohol Consumption. 17th ed., Totowa, NJ: Humana Press; 1992, p. 41–72.

[144] Brink LT, Nel DG, Hall DR, Odendaal HJ. The Intricate Interactions between Maternal Smoking and Drinking During Pregnancy and Birthweight Z-Scores of Preterm Births. Journal of Womens Health Care and Management. 2021;2:1–7.

[145] Okah F, Cai J, Hoff G. Term-gestation low birth weight and health-compromising behaviors during pregnancy. Obstetrics and Gynecology. 2005;105(3):543–50.

[146] Addila A, Azale T, Gete Y, Yitayal M. The effects of maternal alcohol consumption during pregnancy on adverse fetal outcomes among pregnant women attending antenatal care at public health facilities in Gondar town, Northwest Ethiopia: a prospective cohort study. Substance Abuse: Treatment, Prevention, and Policy. 2021;16(1):1–15.

[147] Yang Q, Witkiewicz B, Olney R, Liu Y, Davis M, Khoury M, et al. A case-control study of maternal alcohol consumption and intrauterine growth retardation. Annals of Epidemiology.

2001;11(7):497–503.

[148] Stein A, Campbell EA, Day A, Mcpherson K, Cooper PJ. Social adversity, low birth weight, and preterm delivery. British Medical Journal. 1987;295(6593):291–3.

[149] Norbeck JS, Tilden VP. Life stress, social support, and emotional disequilibrium in complications of pregnancy: A prospective, multivariate study. Journal of Health and Social Behavior. 1983;24(1):30–46.

[150] Chalmers B. Psychosocial factors and obstetric complications. Psychological Medicine. 1983;13(2):333–9.

[151] Picone TA, Allen LH, Olsen PN, Ferris ME. Pregnancy outcome in North American women. II. Effects of diet, cigarette smoking, stress, and weight gain on placentas, and on neonatal physical and behavioral characteristics. The American Journal of Clinical Nutrition. 1982;36(6):1214–24.

[152] Gray T, Eiden R, Leonard K, Connors G, Shisler S, Huestis M. Nicotine and metabolites in meconium as evidence of maternal cigarette smoking during pregnancy and predictors of neonatal growth deficits. Nicotine and Tobacco Research. 2010;12(6):658–64.

[153] Martinez FD, Wright AL, Taussig LM. The effect of paternal smoking on the birthweight of newborns whose mothers did not smoke. Group Health Medical Associates. American Journal of Public Health. 2011;84(9):1489–91.

[154] Hegaard H, Kjærgaard H, Moller L, Wachmann H, Ottesen B. The effect of environmental tobacco smoke during pregnancy on birth weight. Acta Obstetricia et Gynecologica. 2006;85(6):675–81.