# Ethnic differences in fetal growth, birth weight and infant mortality

## The Generation R Study

Ernst-Jan W.M. Troe

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# Ethnic Differences in Fetal Growth, Birth Weight and Infant Mortality

## The Generation R Study

Etnische verschillen in foetale groei, geboortegewicht en zuigelingensterfte

Het Generation R Onderzoek

**Proefschrift**

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## Manuscripts based on this thesis

***Chapter 2***

Troe EJWM, Bos V, Deerenberg IM, Mackenbach JP, Joung IMA. Ethnic differences in total and cause-specific infant mortality in the Netherlands. Paediatr Perinat Epidemiol 2006; 20: 140-7.

***Chapter 3***

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***Chapter 4***

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***Chapter 5***

Troe EJWM, Raat H, Jaddoe VWV, Hofman A, Looman CWN, Moll HA, Steegers EAP, Verhulst FC, Witteman JCM, Mackenbach JP. Explaining differences in birth weight between ethnic populations. The Generation R Study. BJOG 2007; 114: 1557-65.

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***Chapter 7***

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# 1
# Introduction

## Background

Mortality is historically the most important indicator of public health (1). Perinatal mortality is defined as the number of still births and mortality in the first week after birth. Perinatal mortality is often used as indicator of perinatal health care. Infant mortality is defined as the mortality in the first year of life of all live-born infants. Infant mortality is often used as the most objective indicator of the public health condition of a population (2). A lower birth weight (birth weight below 2500 grams) and preterm birth (< 37 weeks of gestation) are both associated with a higher perinatal and infant mortality. Birth weight is an important predictor of infant mortality. For infants of low birth weight (< 2500 grams), the risk of infant mortality is over 20 times that for infants weighing 2500 grams or more. For infants of very low birth weight (< 1500 grams) the risk is considerably higher; about 90 times that for infants weighing 2500 grams or more (3, 4). In general, subgroups of the population with a lower mean birth weight have higher infant mortality rates (5, 6). Additionally, low birth weight is associated with unfavourable health conditions later in life, like coronary heart disease and diabetes mellitus (7). (Very) preterm birth is considered as one of the most important causes of perinatal morbidity and mortality (8). Preterm birth is of major public health concern, since it is responsible for over 50% of the neonatal mortality and over 75% of neonatal morbidity (9, 10). (Very) preterm birth also contributes to long-term neurodevelopmental problems (11).

The perinatal and infant mortality in the Netherlands has rapidly declined in the last decades. However, since the 1980s the declining trend in the Netherlands has leveled off more strongly than in other European countries (12, 13), and the Netherlands therefore has lost his leading position in the international ranks of low perinatal and infant mortality. One of the factors that contribute to the leveling off of the perinatal and infant mortality rates seems to be the rapid increase in the numbers of infants born to mothers with a non-Dutch ethnic origin. In the Netherlands, the perinatal and infant mortality is higher among several large non-Dutch populations (Moroccan, Turkish, Surinamese and Antillean) compared to the Dutch native population (14, 15). This previous research indicated that the increased risk of perinatal mortality in blacks and Hindustani for large part may be attributed to an increased risk of low birth weight and/or (very) preterm birth (14, 15).

Numerous studies in other developed countries, especially in the United States and United Kingdom, have also documented ethnic differences in perinatal and infant mortality (16-26). In the United States (US) about a twofold increased risk of infant mortality exists in blacks compared to whites (16-20). In the United Kingdom (UK) the infant mortality is about 1.5 times higher in infants of mothers born in Pakistan than in infants of mothers born in the UK (21, 24). An elevated infant mortality rate is also observed in infants of mothers born in the Caribbean (23, 24). In Sweden, North-African migrant mothers have an odds ratio of 1.3 for infant death (25) and in Norway, infants of Pakistani

women have about a 1.5 times increased risk of perinatal mortality compared to infants of Norwegian women (26).

Previous studies in the United States and United Kingdom have documented substantial ethnic differences in (low) birth weight (3, 4, 9, 26, 27). A lower mean birth weight and higher rates of low birth weight are observed in blacks compared to whites in the United States (3, 4, 9, 27). Black infants had a mean birth weight that is approximately 250 grams lower than white infants (3). In Norway, mean birth weight in infants of Pakistani women was about 300 grams lower than the mean birth weight in infants of Norwegian women (26). In many industrialized countries ethnic differences in (very) preterm birth have been observed as well (28-30). In the United States several studies have shown that risk of preterm or very preterm delivery is increased in black, Mexican-American and Asian women (28, 29). In the United Kingdom an increased risk of preterm delivery is observed in Afro-Caribbean and African women (30).

## Determinants of ethnic differences in birth weight, gestational age and infant mortality.



In the international literature a multitude of determinants for low birth weight, preterm birth and perinatal and infant mortality has been described (31-33). The contributions of various of specific determinants to ethnic variations in low birth weight, preterm birth and perinatal and infant mortality have been studied. These determinants include socio-demographic determinants, lifestyle determinants, obstetrical determinants and genetic or biological determinants.

Ethnic minority populations often have a lower socio-economic status than the native population of the host country. Low socio-economic status has been shown to be associated with infant mortality, low birth weight and preterm birth (19, 34, 35). Therefore, socio-economic inequalities might partly explain ethnic differences in infant mortality, low birth weight and preterm birth. Ethnicity is also related to demographic factors such as marital status and teenage pregnancy. These factors are related to pregnancy outcomes and ethnic differences in these factors are likely to contribute to ethnic differences in infant mortality, low birth weight and preterm birth (36, 37). There are substantial differences between ethnic populations in lifestyle factors, such as smoking, alcohol consumption and obesity (38, 39). Maternal smoking and alcohol consumption during pregnancy are known to affect the risk of low birth weight, preterm birth and infant mortality (40, 41). Obesity is a known risk factor for a longer, more difficult delivery and for caesarian delivery (42). Obese women also have increased risk for macrosomic infants and hypertensive disorders, including pre-eclampsia (43). Obstetrical factors, like grande multiparity and pre-eclampsia, that are associated with low birth weight,

preterm birth and infant mortality, are related to ethnicity (44, 45). Finally, genetic/biological factors are related to pregnancy outcomes. Low maternal height increases the risk of preterm birth and consanguinity is associated with congenital abnormalities and other birth defects (46-48).

Despite prior studies, the precise explanation of the ethnic differences in low birth weight, preterm birth and infant mortality are largely unknown. Most of the previous studies on the explanation of ethnic differences in low birth weight, preterm birth and infant mortality were performed in the United States and United Kingdom. Information on the importance of these determinants on ethnic inequalities in pregnancy outcomes in the Netherlands is lacking.

## Studies on ethnic differences in infant mortality in the Netherlands

As previously stated, the perinatal and infant mortality in the Netherlands is higher among several large non-Dutch populations (Moroccan, Turkish, Surinamese and Antillean) compared to the Dutch native population (14, 15). Previous research indicated that the increased perinatal mortality in blacks and Hindustani for large part may be attributed to an increased risk of low birth weight and/or (very) preterm birth (14, 15). However, these previous studies were not able to sufficiently distinguish between ethnic populations and were not able to take into account several other determinants of perinatal and infant mortality, like maternal smoking, consanguinity, and an individual measure of socio-economic status. Additionally, these previous studies were unable to examine the magnitude of the ethnic differences in birth weight and gestational age. Finally, these studies did not examine the determinants of low birth weight and preterm birth in specific ethnic populations and therefore could not identify determinants that might be eligible for prevention strategies.

## Live-births in non-Dutch populations in the Netherlands and in Rotterdam

In 2004, 16.4% of the newborns in the Netherlands had a non-Dutch non-western ethnic background according to the definition used by Statistics Netherlands. Of the newborns with a non-Dutch non-western ethnic background, most were of Moroccan, Turkish, Surinamese or Antillean origin (figure 1). In 2004 in Rotterdam, one of the largest cities of the Netherlands, more than 50% of the newborns had a non-Dutch non-western ethnic background. Besides the large groups of Moroccan, Turkish, Surinamese or Antillean newborns, a substantial part of the newborns in Rotterdam had a Capeverdean ethnic background (figure 2).

**Figure 1.** Ethnic distribution of newborns in the Netherlands. Based on children born in 2004. (www.cbs.nl)

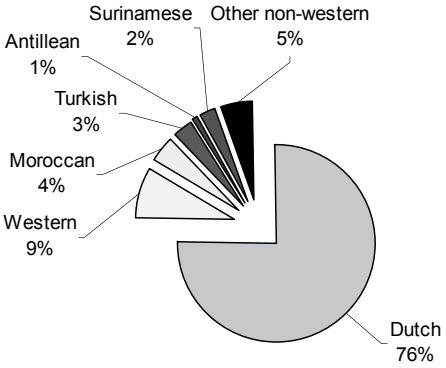
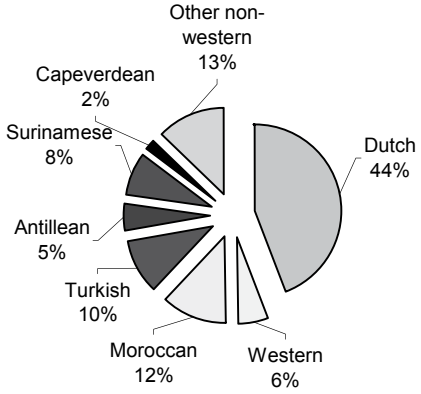



**Figure 2.** Ethnic distribution of newborns in Rotterdam. Based on children born in 2004. (www.cos.rotterdam.nl)





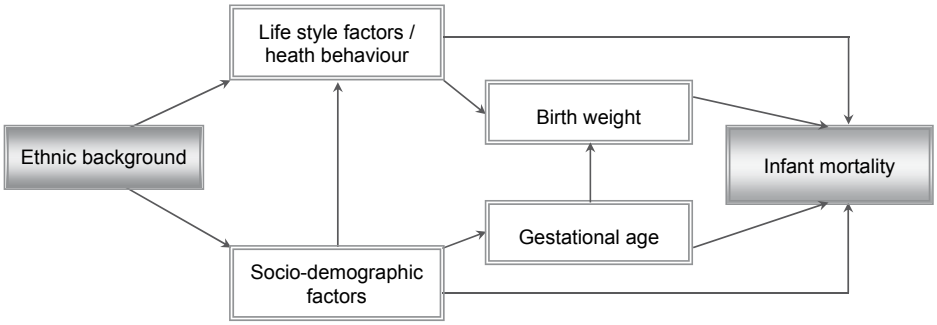

The migration histories of the non-Dutch groups differ between the populations. In the 1960s and 1970s Turkish and Moroccan men came, initially on temporary base, to the Netherlands as labour migrants. Only a small part of the labour migrants returned to their country of origin. The wives and children of the men who decided to stay permanently came to the Netherlands from the mid 1970s as a result of family reunification. In 1975, the former Dutch colony of Surinam in South America became independent, which resulted in a large migration flow of Surinamese to the Netherlands. Also in 1979/1980, many Surinamese people migrated to the Netherlands, which was related to a military coup and to perceived restrictions in obtaining residency permits for the Netherlands. The Surinamese population is ethnically diverse and consists of persons who originate from West-Africa (Creoles), India (Hindustani), Java, China and persons of mixed origin. The Dutch Antilles and Aruba are still part of the Netherlands. Between 1955 and 1985 there has been a constant and mainly work-related migration from the Dutch Antilles and Aruba to the Netherlands. After 1985 the migration from the islands increased due to an economic recession in the Dutch Antilles and Aruba. Capeverdean people migrated

to the Netherlands from the 1960s onwards. Most of the migration was work-related and most of the Capeverdean men came to the Netherlands as harbor laborers.

## This thesis

The studies in this thesis are undertaken to improve the understanding of ethnic differences in perinatal and infant mortality. Ethnic differences in infant mortality at least are partly related to ethnic inequalities in fetal growth, birth weight and gestational age that are affected by specific determinants of fetal growth, birth weight and gestational age. Our conceptual model regarding the explanation of ethnic differences in infant mortality is shown in figure 3. In this model ethnic background is not assumed to have a direct effect on infant mortality but to influence birth weight, gestational age and infant mortality through life style and socio-demographic factors. Ethnic background is associated with several life style factors or health behaviours (including smoking, alcohol use, consanguineous marriage). These life style factors or health behaviours might have direct effects on infant mortality or might operate through an effect on birth weight and/or gestational age. Likewise, the socio-demographic factors (including educational level, maternal height, marital status, maternal age, parity) associated with ethnic background might have direct effects on infant mortality or operate through birth weight and/or gestational age. The socio-demographic factors might also influence life style factors / health behaviours and in this way influence birth weight, gestational age and infant mortality. With our studies we attempt to make inferences about the role of specific determinants in explaining the ethnic differences in perinatal and infant mortality.

**Figure 3.** A graphical representation of the pathways through which ethnic background is assumed to affect birth weight, gestational age, perinatal and infant mortality.



In this thesis we address the following research questions:

1) What is the magnitude of ethnic differences in total and cause-specific infant mortality?
2) What is the magnitude of ethnic differences in fetal growth, birth weight and gestational age?
3) What is the role of specific determinants in explaining ethnic differences in fetal growth, birth weight and gestational age?

The studies on the ethnic differences in infant mortality were based on nation-wide data of Statistics Netherlands and are described in part 1. We examined ethnic differences in infant mortality in the Netherlands in the four major non-Dutch populations (Turkish, Moroccan, Surinamese and Antillean) and the role of several determinants in explaining ethnic differences in infant mortality (chapter 2). Furthermore, we explored the effect of age at immigration and generational status of the mother on infant mortality in the non-Dutch populations (chapter 3). Data from the Generation R Study were used for studies presented in part 2. The Generation R Study is a multi-ethnic prospective population-based cohort study from fetal life until young adulthood. The Generation R Study is designed to identify early environmental and genetic determinants of growth, development and health in fetal life, childhood and adulthood (49, 50). We examined ethnic differences in fetal growth and birth weight and the role of specific determinants of fetal growth and birth weight (chapter 4 and 5). Furthermore, the association of consanguinity with fetal growth and birth weight, and differences in the smoking patterns during pregnancy between ethnic populations were examined (chapter 6 and 7). Finally, we examined ethnic differences in gestational age and preterm birth and their determinants (chapter 8). In the General Discussion, the main findings of this thesis are interpreted and relevant methodological aspects are discussed. Additionally, possible public health implications are discussed and suggestions for further research regarding this topic are presented.



## References

1. van der Maas PJ, Mackenbach JP. Public health and health care [In Dutch]. Maarssen: Elsevier gezondheidszorg; 1999.
2. Schulpen TW. Mortality differences between migrant and native Dutch children in the Netherlands [In Dutch]. Utrecht: Centre for migration and child health; 1996.
3. Singh GK, Yu SM. Birthweight differentials among Asian Americans. Am J Public Health. 1994 Sep; 84(9):1444-9.
4. MacDorman MF, Minino AM, Strobino DM, Guyer B. Annual summary of vital statistics--2001. Pediatrics. 2002 Dec;110(6):1037-52.

5. Wilcox AJ, Russell IT. Birthweight and perinatal mortality: II. On weight-specific mortality. Int J Epidemiol. 1983 Sep;12(3):319-25.
6. Wilcox AJ, Russell IT. Birthweight and perinatal mortality: III. Towards a new method of analysis. Int J Epidemiol. 1986 Jun;15(2):188-96.
7. Barker DJ. Fetal nutrition and cardiovascular disease in later life. Br Med Bull. 1997 Jan;53(1):96-108.
8. Wilcox AJ, Skjaerven R. Birth weight and perinatal mortality: the effect of gestational age. Am J Public Health. 1992 Mar;82(3):378-82.
9. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J. US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, hispanics, and blacks. Pediatrics. 2003 Jan; 111(1):e61-6.
10. Wen SW, Smith G, Yang Q, Walker M. Epidemiology of preterm birth and neonatal outcome. Semin Fetal Neonatal Med. 2004 Dec;9(6):429-35.
11. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med. 2005 Jan 6;352(1):9-19.
12. Achterberg PW, Kramers PGN. A healthy start? Mortality around birth in the Netherlands: trends and causes from an international perspective [In Dutch]. Bilthoven: National Institute for Public Health and the Environment; 2001.
13. Mackenbach JP. The Dutch infant mortality in the 80s [In Dutch]. Ned Tijdschr Geneeskd. 1992 Jun 13;136(24):1140-3.
14. van Enk A, Buitendijk SE, van der Pal KM, van Enk WJ, Schulpen TW. Perinatal death in ethnic minorities in The Netherlands. J Epidemiol Community Health. 1998 Nov;52(11):735-9.
15. Schulpen TW, van Steenbergen JE, van Driel HF. Influences of ethnicity on perinatal and child mortality in the Netherlands. Arch Dis Child. 2001 Mar;84(3):222-6.
16. Differences in infant mortality between blacks and whites--United States, 1980-1991. MMWR Morb Mortal Wkly Rep. 1994 Apr 29;43(16):288-9.
17. Infant mortality and low birth weight among black and white infants--United States, 1980-2000. MMWR Morb Mortal Wkly Rep. 2002 Jul 12;51(27):589-92.
18. Racial and ethnic disparities in infant mortality rates--60 largest U.S. cities, 1995-1998. MMWR Morb Mortal Wkly Rep. 2002 Apr 19;51(15):329-32, 43.
19. Din-Dzietham R, Hertz-Picciotto I. Infant mortality differences between whites and African Americans: the effect of maternal education. Am J Public Health. 1998 Apr;88(4):651-6.
20. Singh GK, Yu SM. Infant mortality in the United States: trends, differentials, and projections, 1950 through 2010. Am J Public Health. 1995 Jul;85(7):957-64.
21. Balarajan R, Soni Raleigh V, Botting B. Sudden infant death syndrome and postneonatal mortality in immigrants in England and Wales. BMJ. 1989 Mar 18;298(6675):716-20.
22. Bacon CJ. Infant mortality in ethnic minorities in Yorkshire, UK. Early Hum Dev. 1994 Sep 15;38(3): 159-60.
23. Griffiths R, White M. Ethnic differences in postneonatal mortality. BMJ. 1989 Apr 22;298(6680): 1099-100.
24. Smith GD, Chaturvedi N, Harding S, Nazroo J, Williams R. Ethnic inequalities in health: a review of UK epidemiological evidence. 2000;10(4):375-408.
25. Oldenburg CEM, Rasmussen F, Cotten NU. Ethnic differences in rates of infant mortality and sudden infant death in Sweden, 1978-1990. Eur J Publ Health. 1997 Mar;7(1):88-94.
26. Vangen S, Stoltenberg C, Skjaerven R, Magnus P, Harris JR, Stray-Pedersen B. The heavier the better? Birthweight and perinatal mortality in different ethnic groups. Int J Epidemiol. 2002 Jun;31(3): 654-60.
27. David RJ, Collins JW, Jr. Differing birth weight among infants of U.S.-born blacks, African-born blacks, and U.S.-born whites. N Engl J Med. 1997 Oct 23;337(17):1209-14.
28. Schieve LA, Handler A. Preterm delivery and perinatal death among black and white infants in a Chicago-area perinatal registry. Obstet Gynecol. 1996 Sep;88(3):356-63.

29. Shiono PH, Klebanoff MA. Ethnic differences in preterm and very preterm delivery. Am J Public Health. 1986 Nov;76(11):1317-21.
30. Aveyard P, Cheng KK, Manaseki S, Gardosi J. The risk of preterm delivery in women from different ethnic groups. BJOG. 2002 Aug;109(8):894-9.
31. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ. 1987;65(5):663-737.
32. Kramer MS. Intrauterine growth and gestational duration determinants. Pediatrics. 1987 Oct;80(4): 502-11.
33. Kramer MS, Olivier M, McLean FH, Dougherty GE, Willis DM, Usher RH. Determinants of fetal growth and body proportionality. Pediatrics. 1990 Jul;86(1):18-26.
34. Kramer MS, Goulet L, Lydon J, Seguin L, McNamara H, Dassa C, et al. Socio-economic disparities in preterm birth: causal pathways and mechanisms. Paediatr Perinat Epidemiol. 2001 Jul;15 Suppl 2:104-23.
35. Kramer MS, Seguin L, Lydon J, Goulet L. Socio-economic disparities in pregnancy outcome: why do the poor fare so poorly? Paediatr Perinat Epidemiol. 2000 Jul;14(3):194-210.
36. Lee KS, Corpuz M. Teenage pregnancy: trend and impact on rates of low birth weight and fetal, maternal, and neonatal mortality in the United States. Clin Perinatol. 1988 Dec;15(4):929-42.
37. Raatikainen K, Heiskanen N, Heinonen S. Marriage still protects pregnancy. BJOG. 2005 Oct;112(10): 1411-6.
38. Teagle SE, Brindis CD. Substance use among pregnant adolescents: A comparison of self-reported use and provider perception. Journal of Adolescent Health. 1998 1998/3;22(3):229-38.
39. Rosenberg TJ, Garbers S, Lipkind H, Chiasson MA. Maternal obesity and diabetes as risk factors for adverse pregnancy outcomes: differences among 4 racial/ethnic groups. Am J Public Health. 2005 Sep;95(9):1545-51.
40. Jaddoe VW, Verburg BO, de Ridder MA, Hofman A, Mackenbach JP, Moll HA, et al. Maternal smoking and fetal growth characteristics in different periods of pregnancy: the generation R study. Am J Epidemiol. 2007 May 15;165(10):1207-15.
41. Kleinman JC, Pierre MB, Jr., Madans JH, Land GH, Schramm WF. The effects of maternal smoking on fetal and infant mortality. Am J Epidemiol. 1988 Feb;127(2):274-82.
42. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. Obesity, obstetric complications and cesarean delivery rate--a population-based screening study. Am J Obstet Gynecol. 2004 Apr;190(4):1091-7.
43. Rosenberg TJ, Garbers S, Chavkin W, Chiasson MA. Prepregnancy weight and adverse perinatal outcomes in an ethnically diverse population. Obstet Gynecol. 2003 Nov;102(5 Pt 1):1022-7.
44. Bai J, Wong FW, Bauman A, Mohsin M. Parity and pregnancy outcomes. Am J Obstet Gynecol. 2002 Feb;186(2):274-8.
45. Caughey AB, Stotland NE, Washington AE, Escobar GJ. Maternal ethnicity, paternal ethnicity, and parental ethnic discordance: predictors of preeclampsia. Obstet Gynecol. 2005 Jul;106(1):156-61.
46. Mohanty C, Prasad R, Srikanth Reddy A, Ghosh JK, Singh TB, Das BK. Maternal anthropometry as predictors of low birth weight. J Trop Pediatr. 2006 Feb;52(1):24-9.
47. Grant JC, Bittles AH. The comparative role of consanguinity in infant and childhood mortality in Pakistan. Ann Hum Genet. 1997 Mar;61(Pt 2):143-9.
48. Stoltenberg C, Magnus P, Lie RT, Daltveit AK, Irgens LM. Birth defects and parental consanguinity in Norway. Am J Epidemiol. 1997 Mar 1;145(5):439-48.
49. Hofman A, Jaddoe VW, Mackenbach JP, Moll HA, Snijders RF, Steegers EA, et al. Growth, development and health from early fetal life until young adulthood: the Generation R Study. Paediatr Perinat Epidemiol. 2004 Jan;18(1):61-72.
50. Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, et al. The Generation R Study: Design and cohort profile. Eur J Epidemiol. 2006;21(6):475-84.

# Ethnic differences in infant mortality

# 2

# Ethnic differences in total and cause-specific infant mortality in the Netherlands

## Summary

*Objective:* We examined ethnic differences in infant mortality and the contribution of several explanatory variables.
*Methods:* Data of Statistics Netherlands from 1995 - 2000 were studied (1,178,949 live-borns). We used proportional hazard analysis to show ethnic differences in total and cause-specific infant mortality. Obstetric, demographic, geographic variables and socio-economic status were considered as possible determinants.
*Results:* The four major ethnic minority groups showed an elevated risk of infant mortality ranging from 1.28 in Turkish infants to 1.50 in Antillean/Aruban infants. In the early neonatal period risks were elevated for Surinamese (Hazard Ratio 1.48, 95% CI 1.23, 1.78) and Antilleans/Arubans (HR 1.43, 95% CI 1.06, 1.92). In the post neonatal period risks were only elevated for Turkish (HR 2.20, 95% CI 1.80, 2.69) and Moroccan infants (HR 2.06, 95% CI 1.67, 2.55). Surinamese and Antillean/Aruban infants had an elevated risk of dying from perinatal causes (HR 1.62, 95% CI 1.33, 1.98 and 1.69, 95% CI 1.24, 2.29 respectively), Turkish and Moroccan infants had an elevated risk of dying from congenital anomalies (HR 1.42, 95% CI 1.16, 1.73 and 1.46, 95% CI 1.20, 1.79 respectively). Inequalities as a result of socio-economic position and demographic factors, such as marital status and maternal age, partially explain the ethnic differences in infant mortality.
*Conclusions:* We conclude that ethnic minority groups in the Netherlands have a higher infant mortality than the native population, which in part seems preventable by reducing inequalities in socio-economic status. Marital status and age of the mother are important other risk factors of infant mortality.

## Introduction

In many western countries differences in infant mortality rates between populations with different ethnic backgrounds have been studied. Despite reductions in infant mortality in the last decades, still ethnic disparities exist (1). Most studies carried out in the United States (US) focus on mortality differences between blacks and whites, with blacks having a 2.5 times higher infant mortality rate than white, non-hispanics (2). In England and Wales infants of Pakistani mothers have a 1.7 greater risk of infant mortality compared to infants of mothers born in the United Kingdom (3).

For the US it has been shown that blacks have higher proportions of preterm and low birthweight births which contributes to the differences in infant mortality (4). That other risk factors could make an important contribution to infant mortality is illustrated by a study of Schulpen et al. (5). They showed that Moroccan and Turkish infants living in the Netherlands, who do not have a higher risk on preterm delivery and low birthweight, have none the less a 1.5 times higher risk of infant mortality. Potential factors for the explanation of ethnic differences, for which also evidence has been found, are parity, maternal age, pregnancy interval, education and family income (6-10).

Because in the US the focus is on black-white disparities, looking at other ethnic groups may give insight in how other risk factors contribute to infant mortality. The contribution of risk factors to ethnic mortality differences may inform policy makers about possible pathways for preventive policies in specific ethnic groups and their potential health gains. Studying cause of death will give insight in the major causes of infant mortality among minority groups and could further inform us about prevention strategies.

In the Netherlands live four major immigrant groups: Turks, Moroccan, Surinamese and Antillean/Aruban. They comprise almost 7% of the total population and 30 – 50% of these immigrants live in the four major cities. These minority groups bear some important similarities and differences with ethnic minority groups in other countries. Compared to the native population, they have for instance a unfavourable socio-economic position, live mainly in the major cities, have poorer housing conditions. On the other hand, in the Netherlands minority groups do have good access to health care services because of the Dutch health insurance system. The infant mortality for these minority groups in the Netherlands has not been extensively studied. Previous studies were carried out at the local level resulting in a lack of power for certain minority groups (5, 11).

We studied the following research questions:

1. Were there ethnic differences in infant mortality in the Netherlands from 1995-2000?
2. Were there ethnic differences in early, late and post neonatal mortality in the Netherlands from 1995-2000?

3. Were there ethnic differences in cause-specific infant mortality in the Netherlands from 1995-2000?
4. To which extent could the available obstetric, demographic, geographic and socio-economic variables explain ethnic differences in total infant mortality?

## Methods

### Design and study population

We analyzed the linked data of the birth registry, cause of death registry and the Municipal Population Registers of Statistics Netherlands over the period 1995-2000. The birth registry contained data of postal code, marital status, age and parity of the mother, date of birth and gender of all live born infants from which the parents were registered as inhabitants of the Netherlands at time of birth (1,178,949 live-borns). The cause of death registry consisted of all deceased inhabitants of the Netherlands and contained date of mortality and cause of death according to the International Classification of Diseases (ICD). The Municipal Population Registers contained data on the parents' country of birth. The registries were linked by the national personal identification number of infants and parents.

Infants that emigrated under the age of 1 year were censored at the date of emigration (4,628 infants). Infant mortality was defined as those live-born infants who died before reaching the age of 1 year (5,980 cases). As a result of unsuccessful linkage of the data, of 101 cases (1.7%) the age at death could not be correctly assessed. These 101 cases were excluded from analysis. The causes of death were classified according to the ICD-9 for 1995 and according to the ICD-10 for the years 1996-2000 (12). Because of small numbers in certain categories, causes of death were categorized as follows: infectious and parasitic diseases; diseases of the nervous system; conditions originating in the perinatal period; congenital anomalies; symptoms, signs and ill-defined diseases (including Sudden Infant Death Syndrome (SIDS)); external causes of injury and poisoning; and other causes (ICD-9 and ICD-10 codes are provided in table 4.).

In addition, distinctions were made between early, late and post neonatal mortality. Early neonatal mortality was defined as death in the first week of life (0 till 7 days). Late neonatal mortality was death occurring from day 7 until day 28 of life. Post neonatal mortality was death occurring from day 28 of life until day 365.

We compared infants of Turkish, Moroccan, Surinamese and Antillean/Aruban ethnicity with native Dutch. As a proxy of ethnicity we used the country of birth of the parents. An infant was not native Dutch if one of the parents was born abroad. If both parents were born abroad the country of birth of the mother decided on the infants' ethnicity (definition of Statistics Netherlands).

### Explanatory variables

The role of four types of explanatory variables has been examined.

*Obstetric variables* Parity was the number of children a woman gave birth to. If the index infant in the data set was the first born parity was zero. The following categories were defined for parity: 0, 1, 2, 3, 4, 5, 6 and 7 or more. The pregnancy-interval was calculated by subtracting the date of birth of the previous infant born to the mother from the date of birth of the infant in the dataset. Pregnancy-interval was categorised in the following categories: <1year, 1-2 years, 2-3 years, 3-4 years, 4-5 years and >5 years.

*Demographic variables* Maternal age was calculated at the date of birth of the infant and divided in five-year categories, with under 20 years as lowest and over 40 as highest category. Marital status was divided into born to married versus unmarried mothers.

*Socio-economic status* With 6-position postal code, our data were linked to another file, the Regional Income Register 1993, which is a national study that contains information on income-levels of neighbourhoods based on fiscal information of its inhabitants. This study provided information on mean equivalent household income of neighbourhoods in the Netherlands, which we used as an indicator of socio-economic status in our study. We ranked the total population according to mean neighbourhood income and distributed them into quintiles in such a manner that each quintile contained 20% of the observed person years.

The characteristics of the live borns in the dataset are shown in table 1.

**Table 1.** Characteristics of live-borns in the dataset in percentages.

| | Dutch | Turkish | Moroccan | Surinamese | Antillean |
|---|---|---|---|---|---|
| male gender (%) | 51.2 | 51.4 | 50.8 | 51.1 | 50.5 |
| maternal age (%) | | | | | |
| *< 20 years* | 0.9 | 5.8 | 3.7 | 2.7 | 6.9 |
| marital status (%) | | | | | |
| *unmarried* | 18.9 | 6.7 | 7.3 | 51.1 | 58.7 |
| pregnancy interval (%) | | | | | |
| *< 1 year* | 0.2 | 0.6 | 0.9 | 0.3 | 0.2 |
| parity (%) | | | | | |
| *0* | 46.8 | 36.0 | 34.1 | 45.3 | 43.5 |
| *≥4* | 1.4 | 2.4 | 11.4 | 2.5 | 2.5 |
| SES (quintiles, %) | | | | | |
| *highest* | 21.0 | 2.7 | 4.4 | 11.1 | 12.0 |
| *lowest* | 14.2 | 57.4 | 56.0 | 49.2 | 44.4 |

SES = socio-economic status

### Data Analysis

Cox proportional hazard analysis was used to estimate ethnic differences in infant mortality. Infant death was the outcome. Ethnicity of the infant was the independent variable. Although we did not expected (large) variations in the distribution of gender in the ethnic groups, we adjusted for gender because of the elevated infant mortality risk in male infants. Obstetric and demographic variables and socio-economic status were considered as possible explanatory variables. We adjusted for the different variables groupwise and for all the variables together. Proportional hazard analysis was also used to estimate the ethnic differences in mortality in the early, late and post neonatal period and in cause-specific mortality (adjusted for gender). A separate analysis was done studying ethnic differences in SIDS.

## Results

In total there were 1,178,848 live births from which 5,879 died under the age of 1 year resulting in an overall infant mortality of 5.0 per 1,000. The ethnic specific mortality rates are shown in table 2.

In table 3 outcomes of the proportional hazard analysis of total infant mortality are shown. After adjustment for gender (model 1) the four major ethnic minority groups showed an elevated risk of infant mortality ranging from 1.28 in Turkish infants to 1.50 in Antillean/Aruban infants. Groupwise adjustment for the different intermediary factors all showed a decline in the hazard ratios.

Adjustment for the demographic variables (model 2) resulted in a 10 until 30 % lower risk. Teenage pregnancies and infants born to unmarried mothers were associated with an elevated risk for infant mortality (HR 1.63 [95% CI 1.37, 1.94] and 1.20 [1.13, 1.28] respectively, results not shown). Teenage pregnancies were more frequently seen in all ethnic minority groups, especially among Turks and Antilleans/Arubans. Infants born to unmarried mothers are common in the Surinamese and Antillean/Aruban popula-



**Table 2.** Number of live births, early neonatal mortality (ENM), late neonatal mortality (LNM), post neonatal mortality (PNM), number of deaths and infant mortality rates (IMR) per ethnic group and of the total dataset.

| | Live births | ENM | LNM | PNM | Deaths | IMR (95 % CI) |
|---|---|---|---|---|---|---|
| **Dutch** | 935,858 | 2,715 | 718 | 1,089 | 4,522 | 4.8 (4.7, 4.9) |
| **Turkish** | 41,348 | 105 | 44 | 106 | 255 | 6.2 (5.5, 7.0) |
| **Moroccan** | 39,210 | 135 | 34 | 94 | 263 | 6.7 (5.9, 7.5) |
| **Surinamese** | 27,313 | 117 | 27 | 32 | 176 | 6.4 (5.5, 7.4) |
| **Antillean** | 10,654 | 44 | 15 | 18 | 77 | 7.2 (5.6, 8.8) |
| **Total** | 1,178,848 | 3,455 | 931 | 1,493 | 5,879 | 5.0 (4.9, 5.0) |

**Table 3.** Crude and adjusted hazard ratios (HR) of infant mortality in different ethnic groups.

| | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
|---|---|---|---|---|---|
| | HR (95 % CI) | HR (95 % CI) | HR (95 % CI) | HR (95 % CI) | HR (95 % CI) |
| **Dutch** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **Turkish** | 1.28 (1.12, 1.45) | 1.23 (1.08, 1.40) | 1.25 (1.10, 1.43) | 1.16 (1.02, 1.32) | 1.16 (1.01, 1.33) |
| **Moroccan** | 1.39 (1.23, 1.57) | 1.35 (1.19, 1.53) | 1.31 (1.15, 1.48) | 1.28 (1.13, 1.46) | 1.23 (1.07, 1.41) |
| **Surinamese** | 1.34 (1.15, 1.55) | 1.24 (1.07, 1.45) | 1.27 (1.09, 1.48) | 1.24 (1.07, 1.45) | 1.24 (1.06, 1.46) |
| **Antillean** | 1.50 (1.20, 1.88) | 1.35 (1.07, 1.69) | 1.43 (1.14, 1.80) | 1.41 (1.13, 1.77) | 1.36 (1.09, 1.72) |

HR = Hazard Ratio

Model 1: adjusted for gender of infant.

Model 2: adjusted for gender and marital status of infant and maternal age (demographic variables).

Model 3: adjusted for gender of infant, parity and pregnancy interval (obstetric variables).

Model 4: adjusted for gender of infant and socio economic status.

Model 5: adjusted for gender and marital status of infant, maternal age, parity, pregnancy interval and socio economic status.

tions. More than 50% of the infants in these populations are born to unmarried mothers compared to 20% in the native Dutch population and 10% in the Turkish and Moroccan populations.

Adjustment for the obstetric variables (model 3) led to a decline in risk up to 5%. A short pregnancy interval (<1 year) was rare, but associated with an elevated risk for infant mortality (HR 5.10 [4.00, 6.50], results not shown). Primiparity and grande multiparity (parity 4 or higher) also were associated with a higher risk for infant mortality (HR 1.27 [1.20, 1.34] and 1.34 [1.06, 1.69] respectively, results not shown).

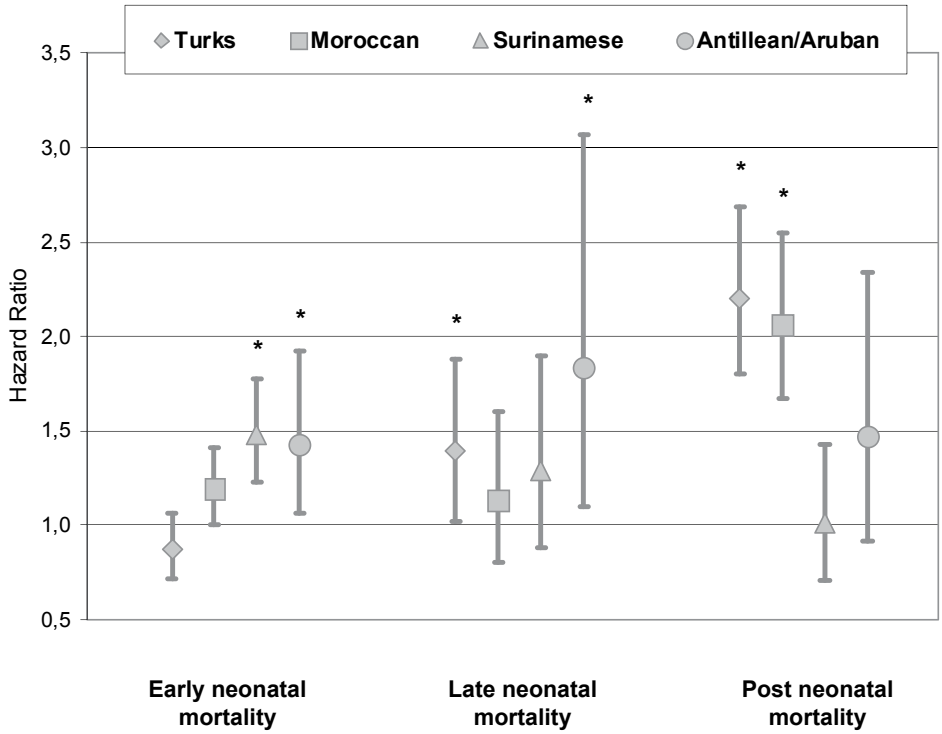
All ethnic minority groups had an unfavourable socio-economic position compared to the Dutch population. After adjustment for socio-economic status 18 until 43% lower mortality risks were seen (model 4).

After adjustment for all variables (model 5) infant mortality risks of the ethnic minority groups decreased by 28 until 43%, but remained significantly higher compared to the Dutch.

In a separate analysis we studied ethnic differences in mortality in the early, late and post neonatal period (figure 1). This showed that in the early neonatal period the mortality risk is elevated for the Surinamese and Antillean/Aruban groups. In the late neonatal period we see an elevated ratio in the Turkish and Antillean group. In the post neonatal period risks were elevated for the Turkish and Moroccan groups.

Finally, we studied ethnic differences in cause-specific infant mortality. The two major causes of death were conditions originating in the perinatal period (2,828 cases, 48.1%) and congenital anomalies (2,073 cases, 35.3%) (table 4). Turkish infants had a higher risk of dying of all the causes except conditions originating in the perinatal period. The risk of dying from congenital anomalies, ill-defined causes and other causes was elevated for the Moroccan. Surinamese infants had a higher ratio for infectious causes, conditions

**Figure 1.** Hazard Ratios and 95% confidence intervals of early neonatal, late neonatal and post neonatal mortality among ethnic minority groups compared to the Dutch native population (specific number of cases are provided in table 2).




* p < 0,05

originating in the perinatal period and other causes. Finally, Antillean/Aruban infants had an elevated risk for dying from conditions originating in the perinatal period and other causes. Turkish infants were the only group with an elevated risk of dying from SIDS (HR 2.13 [1.21, 3.76], results not shown).

## Discussion

Infant mortality was raised in all four ethnic minority groups. The unfavourable socio-economic position of immigrants made an important contribution to the observed differences in infant mortality. Demographic variables also contributed to these differences. Although parity and pregnancy interval were associated with infant mortality, their contribution to the differences was small because of the small proportions of women with short pregnancy interval and high parity. Even after adjustment for all intermedi-

**Table 4.** Hazard ratios (HR) of causes of infant mortality in different ethnic groups (95% CI between brackets, bold ratios are significant).

| | Infectious causes (n=155) | Neurological causes (n=153) | Perinatal causes (n=2828) | Congenital causes (n=2073) | Ill-defined causes (n=290) | External causes (n=93) | Other causes (n=288) |
|---|---|---|---|---|---|---|---|
| **Dutch** (n=4,522) | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **Turkish** (n=255) | **2.73 (1.53, 4.85)** | **2.22 (1.20, 4.13)** | **0.79 (0.63, 1.00)** | **1.42 (1.16, 1.73)** | **2.41 (1.54, 3.78)** | **2.33 (1.07, 5.07)** | **2.68 (1.74, 4.13)** |
| **Moroccan** (n=263) | 1.11 (0.45, 2.71) | 1.92 (0.97, 3.79) | 1.11 (0.91, 1.35) | **1.46 (1.20, 1.79)** | **2.79 (1.81, 4.30)** | 1.41 (0.51, 3.85) | **2.46 (1.56, 3.91)** |
| **Surinamese** (n=176) | **2.23 (1.04, 4.78)** | 1.23 (0.45, 3.33) | **1.62 (1.33, 1.98)** | 0.85 (0.63, 1.16) | 1.05 (0.46, 2.36) | **2.52 (1.02, 6.26)** | 1.59 (0.82, 3.11) |
| **Antillean** (n=77) | 1.64 (0.41, 6.65) | 2.38 (0.76, 7.48) | **1.69 (1.24, 2.29)** | 1.12 (0.73, 1.73) | 0.90 (0.22, 3.63) | 1.30 (0.18, 9.39) | **2.74 (1.22, 6.18)** |

*ICD-10 codes for different categories:*
Infectious causes: A00-B99, Neurological causes: G00-H95, Perinatal causes: P00-P96, Congenital causes: Q00-Q99, Ill-defined causes: R00-R99, External causes: V01-Y89, Other causes: C00-F99, I00-O99.
*ICD-9 codes for different categories:*
Infectious causes: 001-139, 279.8, Neurological causes: 320-389, Perinatal causes: 760-779, Congenital causes: 740-759, Ill-defined causes: 780-799, External causes: E800-E999, Other causes: 140-319, 390-676.

ary variables there remained a significantly elevated risk on infant mortality for ethnic minority groups.

Surinamese and Antillean/Aruban live-borns had an almost 1.5 times higher risk of dying in the early neonatal period. Turkish and Moroccan infants had a more than 2 times higher risk of dying in the post neonatal period. The most important causes of death were conditions originating in the perinatal period for Surinamese and Antillean/Aruban infants and congenital anomalies for Turkish and Moroccan infants.

Several factors should be taken into account when interpreting the results. First, we analysed registry data in which we had information on several risk factors for infant mortality. But information on several other important risk factors was lacking (birthweight, gestational age, smoking habits). Also, no information was available on utilisation of prenatal care, maternity care, or child health centres. In the Netherlands prenatal care is based on risk selection. Midwives are the primary care givers in case of uncomplicated pregnancies and deliveries; mothers can express a preference for either a home or hospital delivery. In case of medical need women are referred to specialist care. In the first week after delivery mothers are entitled to maternity care. There is only sparse information on ethnic differences in utilisation of these health services in the Netherlands. A recent study on the quality of perinatal care showed no differences in scores of substandard care between midwives and gynaecologists and home and hospital deliveries (13). A study on vaccination coverage found a lower coverage of ethnic minority children, but these were predominantly ethnic minority children born abroad (14), which indicates no

large ethnic differences in access to child health centres. On the other hand, differences in the utilisation of care are conceivable and might increase the risks of ethnic minorities on infant mortality.

Second, we adjusted for socio-economic status by making use of an ecological measure. Although this is an indicator at the ecological level, it is able to exemplify socio-economic differences in mortality and is relatively robust for confounding (15, 16). Adjustment with an individual measure of socio-economic status would have been preferable. However, Bos et al showed that this ecological measure is a good indicator of individual socio-economic differences (15, 17).

Third, unwed motherhood might be a proxy marker for several different cultural and socio-economic aspects, which vary between ethnic groups, and which might not all be detrimental. In Surinamese and Antilleans/Arubans unwed motherhood is rather common (over 50%). Possibly, unwed motherhood is more culturally accepted in these populations, and consequently less stigmatizing and less stress enhancing. Thus, the effects of unwed motherhood might be less detrimental for Surinamese and Antillean/Aruban than for native Dutch mothers. Therefore, in a separate analysis we tested for an interaction effect between ethnicity and marital status on infant mortality. Since no interaction effect could be demonstrated (p-value 0.60), it can be concluded that the high prevalence of unwed motherhood partially explains the increased infant mortality among Surinamese and Antilleans/Arubans.



Finally, we defined ethnicity by country of birth. Especially the Surinamese and Antillean/Aruban populations are of mixed ethnic origin. E.g. the Surinamese population consists mainly of Hindustanis originating from India and Creoles from Africa. This may lead to an underestimation of differences in infant mortality among certain ethnic groups. However, these ethnic diverse populations have some social and cultural characteristics in common, which in our opinion makes the definition by country of birth acceptable.

The Surinamese and Antillean/Aruban live-borns had a higher risk of dying in the early neonatal period. From previous studies it is known that Surinamese and Antilleans have a higher prevalence of low birthweight infants and preterm births (18). The higher proportion of infants dying from conditions originating in the perinatal period together with the higher risk of early neonatal mortality suggests that preterm births and low birthweight are important risk factors in these groups. In our study low socio-economic status, teenage pregnancy and unwed motherhood were the most important risk factors in these minority groups. Unfavourable socio-economic status increases the likelihood of unhealthy behaviours, exposure to stress and living in unfavourable material condition, which in turn increases the risk of preterm birth and low birthweight (19). Teenage and single motherhood, which are more common in Surinamese and Antillean/Aruban women are also associated with a lower socio-economic position, more

unhealthy behaviours (smoking, drug use), more stress and unfavourable material conditions. Additionally, teenage and single mothers might engage in more risk full sexual behaviour, which may lead to a higher prevalence of urogenital infections. Urogenital infections have been shown to be a risk factor for preterm delivery (20).

In the post neonatal period Turkish and Moroccan infants had an elevated risk on mortality. The higher risk for SIDS in the Turkish group partially explained their elevated ratio in the post neonatal period. Other studies have shown that smoking at home, prone sleeping position and use of a duvet or pillow is more frequent among Turkish infants (21). A further reduction in the Turkish group should be possible by paying attention to risk factors relevant to SIDS.

In the Turkish and Moroccan groups congenital anomalies were of importance. The causes for this elevated risk are reason for speculation. It has been suggested that this is caused by the higher frequency of consanguine marriages in these populations (22). We were unable to find studies on the percentages consanguine marriages in these populations and on the risk of (lethal) congenital anomalies these marriages would lead to. Besides, studies using excess mortality to study the effects of consanguine marriages are scarce and have several methodological problems (23). It is therefore hard to say if consanguine marriages explain the elevated risk, but it is likely that they contribute to the elevated mortality. Another explanation could be that immigrant women in the Netherlands, like black women in the US, less frequently make use of antenatal diagnostics (24). Differences in practice of prenatal screening and termination of pregnancy contribute to the variations in perinatal mortality between European countries (25). The same could account for differences between ethnic groups within countries. It could be that this feature is less frequently used by minority groups because of lack of knowledge or a different attitude towards prenatal screening or pregnancy termination. More awareness of the risks of consanguine marriages and greater emphasis on genetic counselling and antenatal diagnosis might reduce the incidence of congenital disorders and, consequently, reduce infant mortality.

Our findings could be of interest for many other Western-European countries, given the similarities between the migrant populations. E.g. Germany also has a large Turkish migrant population; France has a large Moroccan migrant population; and Great Britain has a large population from former colonies, e.g. the Indian / Pakistani and Afro-Caribbean population.

This study showed that the four minority groups had an elevated infant mortality, and that perinatal causes and congenital anomalies were important causes of infant mortality. Socio-economic and demographic factors were associated with higher infant mortality in the minority groups. To reduce differences in infant mortality, inequalities as a result of socio-economic position should be reduced. Attention to the risks of marital status and age of the mother could probably help to further diminish ethnic differences

in infant mortality. Research on determinants of preterm delivery, low birthweight and congenital anomalies will give more insight in the causal pathways, and might lead to specific prevention strategies.

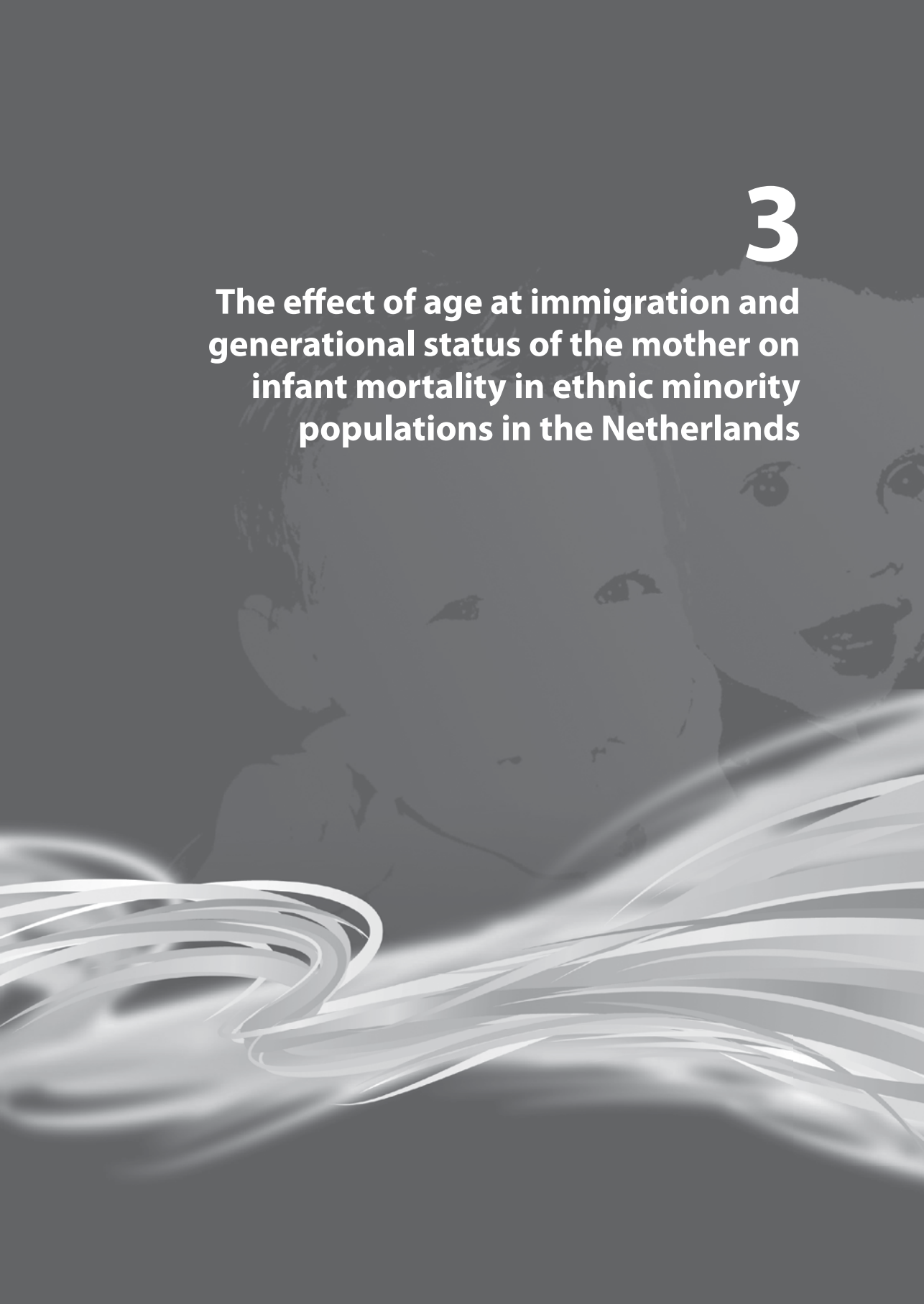
## References


1. Infant mortality and low birth weight among black and white infants--United States, 1980-2000. MMWR Morb Mortal Wkly Rep. 2002 Jul 12;51(27):589-92.
2. MacDorman MF, Minino AM, Strobino DM, Guyer B. Annual summary of vital statistics--2001. Pediatrics. 2002 Dec;110(6):1037-52.
3. Smith GD, Chaturvedi N, Harding S, Nazroo J, Williams R. Ethnic inequalities in health: a review of UK epidemiological evidence. 2000;10(4):375-408.
4. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J. US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, hispanics, and blacks. Pediatrics. 2003 Jan; 111(1):e61-6.
5. Schulpen TW, van Enk A. [Mortality according to ethnicity in children in The Netherlands] Mortaliteit naar etniciteit bij kinderen in Nederland. Ned Tijdschr Geneeskd. 1996 Dec 14;140(50):2489-92.
6. Bai J, Wong FW, Bauman A, Mohsin M. Parity and pregnancy outcomes. Am J Obstet Gynecol. 2002 Feb;186(2):274-8.
7. Din-Dzietham R, Hertz-Picciotto I. Infant mortality differences between whites and African Americans: the effect of maternal education. Am J Public Health. 1998 Apr;88(4):651-6.
8. Phipps MG, Blume JD, DeMonner SM. Young maternal age associated with increased risk of postneonatal death. Obstet Gynecol. 2002 Sep;100(3):481-6.
9. Rawlings JS, Rawlings VB, Read JA. Prevalence of low birth weight and preterm delivery in relation to the interval between pregnancies among white and black women. N Engl J Med. 1995 Jan 12;332(2): 69-74.
10. Singh GK, Yu SM. Infant mortality in the United States: trends, differentials, and projections, 1950 through 2010. Am J Public Health. 1995 Jul;85(7):957-64.
11. Nijhuis HGJ, Nordbeck HJ, Belleman SJM. Perinatal and infant mortality in Amsterdam and The Hague [In Dutch]. Tijdschrift voor Sociale Gezondheidszorg, 1985;63(10):409-14.
12. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, 1989 Revision. Geneva; 1992.
13. Wolleswinkel-van den Bosch JH, Vredevoogd CB, Borkent-Polet M, van Eyck J, Fetter WP, Lagro-Janssen TL, et al. Substandard factors in perinatal care in The Netherlands: a regional audit of perinatal deaths. Acta Obstet Gynecol Scand. 2002 Jan;81(1):17-24.
14. van der Wal MF, Diepenmaat AC, Pauw-Plomp H, van Weert-Waltman ML. High vaccination rates among children of Amsterdam [In Dutch]. Ned Tijdschr Geneeskd. 2001 Jan 20;145(3):131-5.
15. Bos V, Kunst AE, Mackenbach JP. The size of socio-economic mortality differences on neighbourhood level: a comparison with estimations on basis of information on individual level [In Dutch]. In: Socio-economic differences in health: from explanations to reductions. Editor: Stronks K. The hague: ZonMw, 2001:8-20.
16. Bos V, Kunst AE, Mackenbach JP. Socio-economic mortality differences in the Netherlands: an analysis on basis of neigbourhood characterisitcs [In Dutch]. Tijdschrift voor Gezondheidswetenschappen. 2002;80(3):158-65.
17. Bos V, Kunst AE, Garssen J, Mackenbach JP. Socioeconomic inequalities in mortality within ethnic groups in the Netherlands, 1995-2000. J Epidemiol Community Health. 2005 Apr;59(4):329-35.
18. van Enk A, Buitendijk SE, van der Pal KM, van Enk WJ, Schulpen TW. Perinatal death in ethnic minorities in The Netherlands. J Epidemiol Community Health. 1998 Nov;52(11):735-9.

19. Kramer MS, Seguin L, Lydon J, Goulet L. Socio-economic disparities in pregnancy outcome: why do the poor fare so poorly? Paediatr Perinat Epidemiol. 2000 Jul;14(3):194-210.
20. Fiscella K. Racial disparities in preterm births. The role of urogenital infections. Public Health Rep. 1996 Mar-Apr;111(2):104-13.
21. van der Wal MF, de Jonge GA, Pauw-Plomp H. Ethnic origin and care giving styles relevant to cot death [In Dutch]. Ned Tijdschr Geneeskd. 1999 Oct 23;143(43):2141-6.
22. Schulpen TW, van Steenbergen JE, van Driel HF. Influences of ethnicity on perinatal and child mortality in the Netherlands. Arch Dis Child. 2001 Mar;84(3):222-6.
23. Bennett RL, Motulsky AG, Bittles A, Hudgins L, Uhrich S, Doyle DL, et al. Genetic counseling and screening of consanguineous cuoples and their offspring: recommendations of the national society of genetic counselors. J Genetic Couns. 2002 April;11(2):97-119.
24. Brett KM, Schoendorf KC, Kiely JL. Differences between black and white women in the use of prenatal care technologies. Am J Obstet Gynecol. 1994 Jan;170(1 part 1):41-6.
25. van der Pal-de Bruin KM, Graafmans W, Biermans MC, Richardus JH, Zijlstra AG, Reefhuis J, et al. The influence of prenatal screening and termination of pregnancy on perinatal mortality rates. Prenat Diagn. 2002 Nov;22(11):966-72.

# 3

# The effect of age at immigration and generational status of the mother on infant mortality in ethnic minority populations in the Netherlands



## Abstract

*Background:* Migrant populations consist of migrants with differences in generational status and length of residence. Several studies suggest that health outcomes differ by generational status and duration of residence. We examined the association of generational status and age at immigration of the mother with infant mortality in migrant populations in the Netherlands.

*Methods:* Data from Statistics Netherlands were obtained from 1995 through 2000 for infants of mothers with Dutch, Turkish and Surinamese ethnicity. Mothers were categorised by generational status (Dutch-born and foreign-born) and by age at immigration (0-16 years and > 16 years). The associations of generational status and age at immigration of the mother with total and cause-specific infant mortality were examined.

*Results:* The infant mortality rate in Turkish mothers rose with lower age at immigration (from 5.5/1000 to 6.4/1000) and was highest for Dutch-born Turkish mothers (6.8/1000). Infant death from perinatal and congenital causes increased with lower age at immigration and was highest in the Dutch-born Turkish women. In contrast, in Surinamese mothers infant mortality declined with lower age at immigration (from 8.0/1000 to 6.3/1000) and was lowest for Dutch-born Surinamese mothers (5.5/1000). Generational status and lower age at immigration of Surinamese women were associated with declining mortality of congenital causes.

*Conclusions:* Total and cause-specific infant mortality seem to differ according to generational status and age at immigration of the mother. The direction of these trends however differs between ethnic populations. This may be related to acculturation and selective migration.

## Introduction

In the Netherlands, as in more Western countries, infant mortality risk is elevated in migrant populations (1). These populations consist of migrants with differences in generational status and length of residence. Several studies in the United States (US) suggest that health outcomes differ by generational status and duration of residence. Foreign-born black and Hispanic mothers have, despite their socio-economic disadvantaged status, more favourable birth outcomes compared to US-born blacks and Hispanics (2-6). A lower infant mortality risk is also observed in foreign-born black mothers compared to US-born blacks (7). North African immigrant women in France and Belgium have good birth outcomes compared to the native populations (4). However, the effect of generational status on birth outcomes seems to be different in ethnic populations. In contrast with the foreign-born black and Hispanic women, foreign-born Asian women in the US have an increased risk for low birth weight (8, 9). Length of residence might also be related to changes in the risk profiles of migrant mothers. Longer length of residence in Mexican immigrants is associated with a change in health status and birth outcomes (10, 11).

Previous studies indicate that the favourable birth and health outcomes of foreign-born migrant women might be explained by the "healthy migrant effect" and by the relatively healthy life styles that these mothers maintained from the country of origin. A change to an unhealthier life style could contribute to the decreased health outcomes of native-born migrants and migrants with longer residence duration. It is uncertain, however, whether selection effects and health behaviour play a role in migrant groups in other industrialised countries.

In the present paper, we conducted an explorative study to the association of generational status and age at immigration of the mother with total and cause-specific infant mortality in the Turkish and Surinamese populations. We described the total and cause-specific infant mortality levels in relation to generational status and age at migration of the mother and we explored to what extent these associations could be explained by obstetric, demographic and socio-economic variables.

## Methods

### Design and study population

We analyzed the linked data of the birth registry, cause of death registry and the Municipal Population Registers of Statistics Netherlands for the period 1995-2000. The birth registry contained the date of birth and sex of all live born infants from which the parents were registered as inhabitants of the Netherlands at time of birth (1,178,949 live

borns). It also contained data of postal code, marital status, age and parity of the mother. The cause of death registry consisted of all deceased inhabitants of the Netherlands and contained the date of mortality and cause of death according to the International Classification of Diseases (ICD). The Municipal Population Registers contained data on the country of birth of the parents and grandparents. The registries were linked by the national personal identification number of infants and parents.

We compared live borns of mothers of Dutch, Turkish and Surinamese descent (973,162 live borns). A mother was considered non-native Dutch if one of the parents was born abroad (definition of Statistics Netherlands). We made a distinction within each ethnic minority population according to generational status and age at immigration of the mother. Mothers from Turkish and Surinamese descent were classified as Dutch-born if she was born in the Netherlands and as foreign-born if the mother was born abroad. Foreign-born mothers were subdivided by their age at immigration (0-16 years and > 16 years). This cut-off point was chosen because children in the Netherlands are obliged to go to school until they reach the age of 16 years. Of 1,959 live borns (3.7% of the studied foreign-born population) the age at immigration of the mother could not be assessed, because of lack of data on date of immigration. These mothers were excluded from analysis.

The causes of death were classified according to the ICD-9 for 1995 and according to the ICD-10 for the years 1996-2000 (12). Because of small numbers of deaths, causes of death were categorized into broad groups: conditions originating in the perinatal period (ICD-9 codes: 760-779, ICD-10 codes: P00-P96); congenital anomalies (ICD-9 codes: 740-759, ICD-10 codes: Q00-Q99) and other causes (ICD-9 codes: 001-676, 780-799, E800-E999, ICD-10 codes: A00-O99, R00-R99, V01-Y89). Of one case the cause of death was missing in the dataset. This case was omitted from the cause-specific mortality regression analysis.



**Covariates**

The following types of variables were used in the data-analysis.

*Obstetric variables* Parity was defined as the number of children a woman gave birth to. If the index infant in the data set was the first-born parity was zero. Parity was divided into categories ranging from zero to more than eight.

*Demographic variables* Maternal age was calculated at the date of birth of the infant and divided in five-year categories, with under 20 years as lowest and over 40 as highest category. Marital status of the mother was categorised as married or unmarried.

*Socio-economic status* With 6-position postal code, our data were linked to another file, the Regional Income Register 1993, which is a national study that contains information on income-levels of neighbourhoods based on fiscal information of its inhabitants. This study provided information on mean equivalent household income of neighbour-

**Table 1.** Subject characteristics of live borns according to ethnicity mother and age at immigration (n=973,162).

| | Dutch ( n = 912,165) | Turks (n = 35,455) | | | Surinamese (n = 25,542) | | |
|---|---|---|---|---|---|---|---|
| | | > 16 years | 0-16 years | Dutch-born | > 16 years | 0-16 years | Dutch-born |
| Gender infant (%) | | | | | | | |
| *Boy* | 51.2 | 51.7 | 51.9 | 50.5 | 51.3 | 51.4 | 51.4 |
| Maternal age (%) | | | | | | | |
| *< 20 yrs* | 0.8 | 4.5 | 3.9 | 15.2 | 0.9 | 3.7 | 15.8 |
| *20-24 yrs* | 7.2 | 32.5 | 32.5 | 57.3 | 12.0 | 20.6 | 31.4 |
| *25-29 yrs* | 34.1 | 34.2 | 39.3 | 24.1 | 29.4 | 38.5 | 28.4 |
| *30-34 yrs* | 42.3 | 19.3 | 20.4 | 3.2 | 32.5 | 28.1 | 18.9 |
| *35-39 yrs* | 14.1 | 8.1 | 3.9 | 0.1 | 20.2 | 8.3 | 5.0 |
| *> 40 yrs* | 1.6 | 1.5 | 0.1 | 0.0 | 5.1 | 0.7 | 0.5 |
| Marital status (%) | | | | | | | |
| *Unmarried* | 16.2 | 2.1 | 3.7 | 12.4 | 28.6 | 44.0 | 61.4 |
| Mean equivalent income (%) | | | | | | | |
| *Low* | 14.2 | 61.3 | 60.0 | 57.8 | 57.5 | 53.6 | 45.7 |
| *High* | 20.9 | 2.2 | 2.4 | 4.0 | 8.5 | 10.6 | 12.3 |
| Parity (%) | | | | | | | |
| *> 4* | 1.4 | 3.2 | 1.5 | 0.1 | 3.8 | 1.7 | 0.4 |

hoods in the Netherlands, which we used as an indicator of socio-economic status in our study. Mean equivalent household income was classified into five categories. The characteristics of the live borns are shown in table 1.

### Data Analysis

We calculated the infant mortality rates (number of infant deaths / 1,000 live births) according to generational status and age at immigration of the mother. We estimated the relative total and cause-specific infant mortality risks with Cox proportional hazard regression analysis. We related the number of infant deaths, defined as those live born infants who died before reaching the age of 1 year, to the observed person time as offset variable, and to ethnic origin as independent variable. Infants that emigrated under the age of 1 year were censored at the date of emigration. Sex of the infant and age of the mother were included in all models. In additional models we adjusted for mean neighbourhood income, parity and marital status of the mother to study their effect on the observed associations. We performed a log linear trend analysis to study differences in trends in total infant mortality. In these we used generational status and age at immigration as predictors. All statistical analyses were performed using the Statistical Package of Social Sciences version 11.0 for Windows (SPSS Inc, Chicago, IL, USA).

## Results

Infant mortality rates according to generational status and age at immigration of the mother are shown in figure 1. The infant mortality rate among native Dutch mothers was 4.8/1000 live births. Among Turkish mothers the infant mortality increased from 5.5/1000 live births for Turkish-born mothers who migrated after the 16th birthday, to 6.4/1000 for Turkish-born mothers who migrated at younger ages, and to 6.8/1000 for Dutch-born Turkish mothers. Among Surinamese mothers an opposite pattern was observed. Surinamese-born mothers who immigrated at higher age had an infant mortality rate of 8.0/1000 live births. The infant mortality rate among Surinamese-born mothers who migrated under 16 years was 6.3/1000 and 5.5/1000 among Dutch-born Surinamese mothers.

The estimated hazard ratios of total infant mortality according to generational status and age at immigration (table 2) showed the same pattern as seen in the infant mortality rates, even though the differences were not statistically significant. In the Turkish mothers the infant mortality risk seemed to rise with lower age at immigration. In Surinamese mothers the opposite trend was observed, in which infant mortality risk declined with lower age at immigration. Adjustment for parity, marital status and mean neighbourhood income did not substantially change the estimated hazard ratios. The log linear trend analysis showed a significant difference in trend of generational status and age at immigration between Turkish and Surinamese mothers (p = 0.04). For Turkish mothers



**Figure 1.** Infant mortality rates of first generation migrant mothers according to age at immigration of the mother (> 16 years, 0-16 years) and Dutch-born migrant mothers.

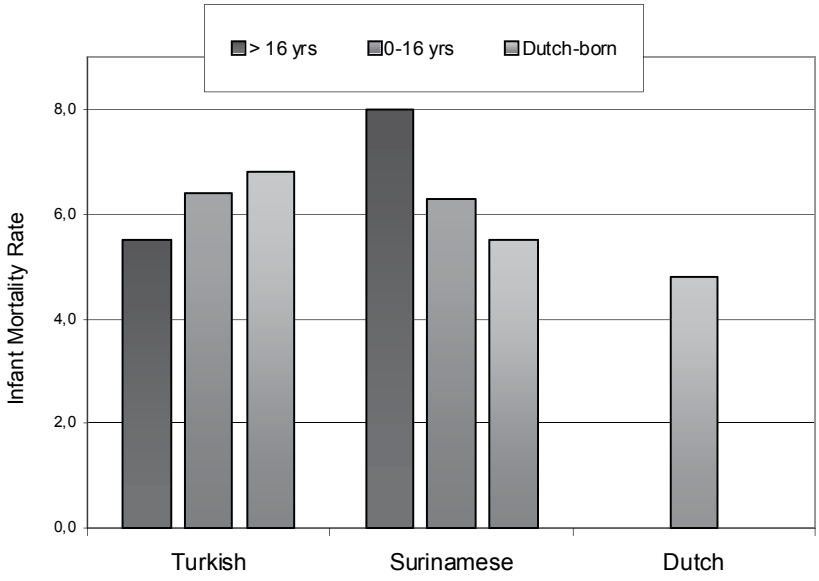


**Table 2.** Hazard Ratios (HR) for infant mortality according to generational status and age at immigration of the mother (> 16 yrs reference).

| | Turks | | | Surinamese | | |
|---|---|---|---|---|---|---|
| | **> 16 years** | **0-16 years** | **Dutch-born** | **> 16 years** | **0-16 years** | **Dutch-born** |
| **Live borns** | 18960 | 11371 | 3838 | 8797 | 11359 | 4713 |
| **Infant deaths** | 105 | 73 | 26 | 70 | 72 | 26 |
| **HR (model 1)** | 1.00 | 1.18 (0.87-1.60) | 1.35 (0.86-2.11) | 1.00 | 0.83 (0.59-1.16) | 0.69 (0.42-1.12) |
| **HR (model 2)*** | 1.00 | 1.19 (0.88-1.61) | 1.34 (0.85-2.13) | 1.00 | 0.86 (0.61-1.21) | 0.70 (0.43-1.15) |

HR = Hazard Ratio

Model 1: adjusted for sex of infant and age of the mother.

Model 2: adjusted for sex of infant and age, parity, marital status and mean neighbourhood income of the mother.

* Log linear trend analysis showed a significant difference in trend between Turkish and Surinamese mothers ($p = 0.04$)

the rate increased by a RR of 1.12 per class, for the Surinamese there was a decrease by a RR of 0.824.

Results for specific causes of death are shown in table 3. In Turkish mothers an increase in mortality with lower age at immigration was observed both for perinatal and congenital causes. In Surinamese mothers the opposite trend was observed both for congenital causes and the group other causes. The differences between the Turkish and Surinamese populations with regards to the trends for causes of death did not reach statistical significance.

Our study is limited to the Turkish and Surinamese populations because of the small number of Dutch-born live births in other migrant populations. However, for people from Moroccan descent, we could analyse the association between infant mortality and

**Table 3.** Hazard Ratios (HR) for cause specific mortality according to generational status and age at immigration of the mother (> 16 yrs reference).

| | Turks | | | Surinamese | | |
|---|---|---|---|---|---|---|
| | **> 16 years** | **0-16 years** | **Dutch-born** | **> 16 years** | **0-16 years** | **Dutch-born** |
| ***Perinatal causes (n)*** | 25 | 21 | 9 | 39 | 42 | 18 |
| **HR (model1)** | 1.00 | 1.46 (0.82-2.63) | 2.03 (0.90-4.57) | 1.00 | 0.95 (0.60-1.48) | 1.04 (0.58-1.89) |
| **HR (model2)** | 1.00 | 1.42 (0.79-2.56) | 1.60 (0.69-3.74) | 1.00 | 1.02 (0.64-1.60) | 1.08 (0.59-2.00) |
| ***Congenital causes (n)*** | 44 | 31 | 11 | 19 | 15 | 4 |
| **HR (model1)** | 1.00 | 1.17 (0.74-1.86) | 1.48 (0.75-2.94) | 1.00 | 0.60 (0.30-1.20) | 0.32 (0.10-1.04) |
| **HR (model2)** | 1.00 | 1.19 (0.75-1.89) | 1.58 (0.78-3.18) | 1.00 | 0.60 (0.30-1.22) | 0.33 (0.10-1.11) |
| ***Other causes (n)*** | 36 | 20 | 6 | 12 | 15 | 4 |
| **HR (model1)** | 1.00 | 0.95 (0.55-1.65) | 0.81 (0.33-1.96) | 1.00 | 0.80 (0.37-1.74) | 0.40 (0.12-1.32) |
| **HR (model2)** | 1.00 | 0.97 (0.56-1.69) | 0.93 (0.37-2.30) | 1.00 | 0.77 (0.35-1.71) | 0.37 (0.11-1.26) |

HR = Hazard Ratio

Model 1: adjusted for sex of infant and age of the mother.

Model 2: adjusted for sex of infant and age, parity, marital status and mean neighbourhood income of the mother.

age at immigration among Moroccan-born women. The results showed the same trend as observed among Turkish-born mothers. The infant mortality risk in Moroccan mothers with age at immigration under 16 years was elevated compared to the reference group of mothers who migrated at older age (HR 1.28, 95% CI 0.94-1.74, results not shown).

## Discussion

This study suggests that associations of infant mortality with generational status and age at immigration are different among Turkish and Surinamese mothers. Among Turkish mothers infant mortality diverged from the infant mortality level of Dutch mothers. Infant mortality increased with lower age at immigration and infant mortality was highest for Dutch-born Turkish mothers. This trend was also observed for perinatal causes and congenital causes. Among Surinamese mothers a convergence of infant mortality toward the infant mortality level of Dutch mothers was observed. Infant mortality declined with lower age at immigration of the mother and was lowest for Surinamese mothers who are born in the Netherlands. This trend was especially observed for congenital causes and the group of other causes. Adjustment for differences in parity, marital status and mean neighbourhood income did not change these associations.

Strengths of our database include complete national coverage of all births and infant deaths (including deaths abroad of babies born in the Netherlands) and accurate registry of generational status and age at immigration. The results of this study should however be evaluated against some potential data problems. First, although we had nation-wide data on infant mortality during an observation period of six years, the numbers of live-borns and infant deaths were small, resulting in rather large confidence intervals. However, also given the consistency in most of the patterns, the results may be taken as suggestions of true associations with generational status and age at immigration that should be confirmed in further studies. Second, the data that were available from national registries lack information on several important risk factors of infant mortality, such as birth weight, gestational age, prenatal care use and life-style factors. As a result, we were not able to explore the causal pathways underlying the observed patterns. In addition, our socio-economic measure was an ecological one (neighbourhood income) and therefore was only a proximate measure of individual and household level socio-economic status. It may be that fuller adjustment for socio-economic status would have shown larger effects.

We choose to use age at immigration of the mother as the key parameter of interest instead of length of residence. Other studies have described an association of duration of residence with health and birth outcomes in migrants (10, 11). Age at immigration of the mother however may be more appropriate from a life course perspective as it

allows us to locate the critical event (migration to a new country) within the life course of a woman. Women who migrate at young age receive education in the host country and may therefore be more familiar with the language, the health care system and other relevant aspects of the host society. Besides, young migrants will be more likely to have adopted the life styles prevailing in host countries than people who migrated at older ages. Despite these theoretical advantages, we found that the choice was less important in practice. In a separate analysis, we studied the effect of mothers' residence duration (classified in 10-year intervals) on infant mortality in foreign-born mothers. For both Turkish and Surinamese mothers, we observed the same pattern as observed in relationship to age at immigration of the mother (residence duration < 10 years used as reference; HR and 95% CI in Turkish mothers: residence duration > 10 years: 1.14 (0.83-1.57) Dutch-born: 1.31 (0.83-2.07); HR and 95% CI in Surinamese mothers: residence duration > 10 years 1.04 (0.73-1.49), Dutch-born 0.79 (0.48-1.31)).

A common framework for the interpretation of these patterns is provided by the acculturation theory. Acculturation is a multidimensional phenomenon from which language components, dietary intake and smoking are important indicators of their effect on birth outcomes (13). In the US, acculturation is associated with a decrease in protective cultural behaviours in Hispanics (14-16). In the Netherlands, the Turkish migrant population seems to resemble the Hispanic migrant population in the US with respect to their low socio-economic status, healthy diet and life style, and language problems [17, 18, 19]. The higher infant mortality of Turkish migrants who are more integrated into Dutch society (i.e. Dutch-born and Turkish migrants with younger age at immigration) might be due to adaptation of unhealthy western life-styles. This suggestion is supported by a Dutch report showing a rising trend of tobacco use especially among younger Turkish women (17). We hypothesize that this change to an unhealthy life-style possibly could outweigh the favourable effects of increased integration, such as better mastery of the Dutch language.

The process of acculturation of Surinamese migrants seems to differ from that of Turkish migrants. The Surinamese migrant population is much more familiar with the Dutch language and the Dutch educational system than the Dutch Turkish migrant population. Also a higher prevalence of marriages with native Dutch men is seen among Surinamese women (18). Compared to other migrant populations, Surinamese migrant women gain most profit from their education in the Netherlands (19). It is therefore likely that Surinamese migrants, including those who arrived in the Netherlands at adult age, have adequate access to and utilisation of (perinatal) health care services. This more optimal use of perinatal care, including the use of prenatal screening, might be reflected by the declining rates of infant death of congenital causes. The lack of a similar decline in infant death of perinatal causes, which is elevated in the whole Surinamese population, might be due to a higher proportion of preterm births and low birth weight infants (20).

In addition to acculturation, selective immigration might contribute to the observed patterns, such as those among the Turkish population. Turkish women that migrated above the age of 16 years for a large part consist of women who migrate to get married in the Netherlands (19). These women will have had relatively good health and their health potential may have contributed to a lower mortality risk of their children. Thus, the relatively low levels of mortality of children born to Turkish-born mother who migrated at older ages suggest that "healthy migrant effects" play a role.

In contrast, the Surinamese-born women that migrated at older age to the Netherlands are characterized especially by a relatively low socio-economic position (60% of these women are in the lowest income group compared to 45% of the Dutch-born Surinamese migrants). Thus, the high levels of mortality of children born to Surinamese-born women that migrated at older age suggest an effect of selective immigration of socio-economic disadvantaged women.

In conclusion, these results suggest that generational status and age at immigration of the mother of foreign descent are associated with infant mortality. We hypothesize that these associations might be determined by both acculturation processes and by selection upon migration. We further hypothesize that these associations may radically differ between ethnic populations. The results for Surinamese migrant women suggest that increased acculturation and social integration could result in improving health outcomes of their children. The inverse patterns observed for Turkish migrant women are worrisome as they suggest increasing inequalities in infant mortality between the Turkish and native Dutch population.

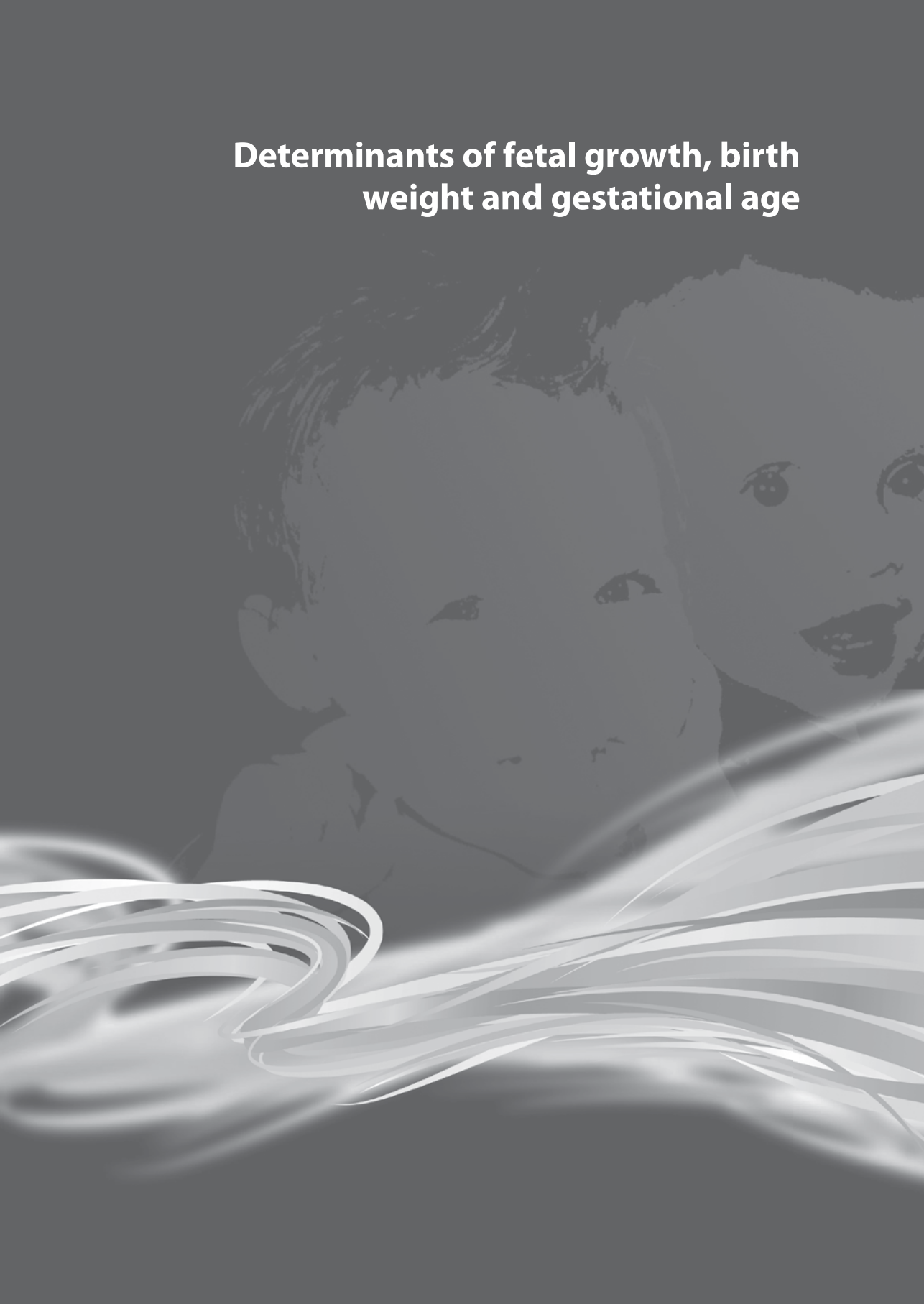


## References

1. Troe EJWM, Bos V, Deerenberg IM, Mackenbach JP, Joung IMA. Ethnic differences in total and cause-specific infant mortality in the Netherlands. Paediatric and perinatal Epidemiology. 2006 Mar; 20(2): 140-7
2. Cabral H, Fried LE, Levenson S, Amaro H, Zuckerman B. Foreign-born and US-born black women: differences in health behaviors and birth outcomes. Am J Public Health. 1990 Jan;80(1):70-2.
3. David RJ, Collins JW, Jr. Differing birth weight among infants of U.S.-born blacks, African-born blacks, and U.S.-born whites. N Engl J Med. 1997 Oct 23;337(17):1209-14.
4. Guendelman S, Buekens P, Blondel B, Kaminski M, Notzon FC, Masuy-Stroobant G. Birth outcomes of immigrant women in the United States, France, and Belgium. Matern Child Health J. 1999 Dec;3(4): 177-87.
5. Guendelman S, Gould JB, Hudes M, Eskenazi B. Generational differences in perinatal health among the Mexican American population: findings from HHANES 1982-84. Am J Public Health. 1990 Dec;80 Suppl:61-5.
6. Singh GK, Yu SM. Adverse pregnancy outcomes: differences between US- and foreign-born women in major US racial and ethnic groups. Am J Public Health. 1996 Jun;86(6):837-43.
7. Kleinman JC, Fingerhut LA, Prager K. Differences in infant mortality by race, nativity status, and other maternal characteristics. Am J Dis Child. 1991 Feb;145(2):194-9.

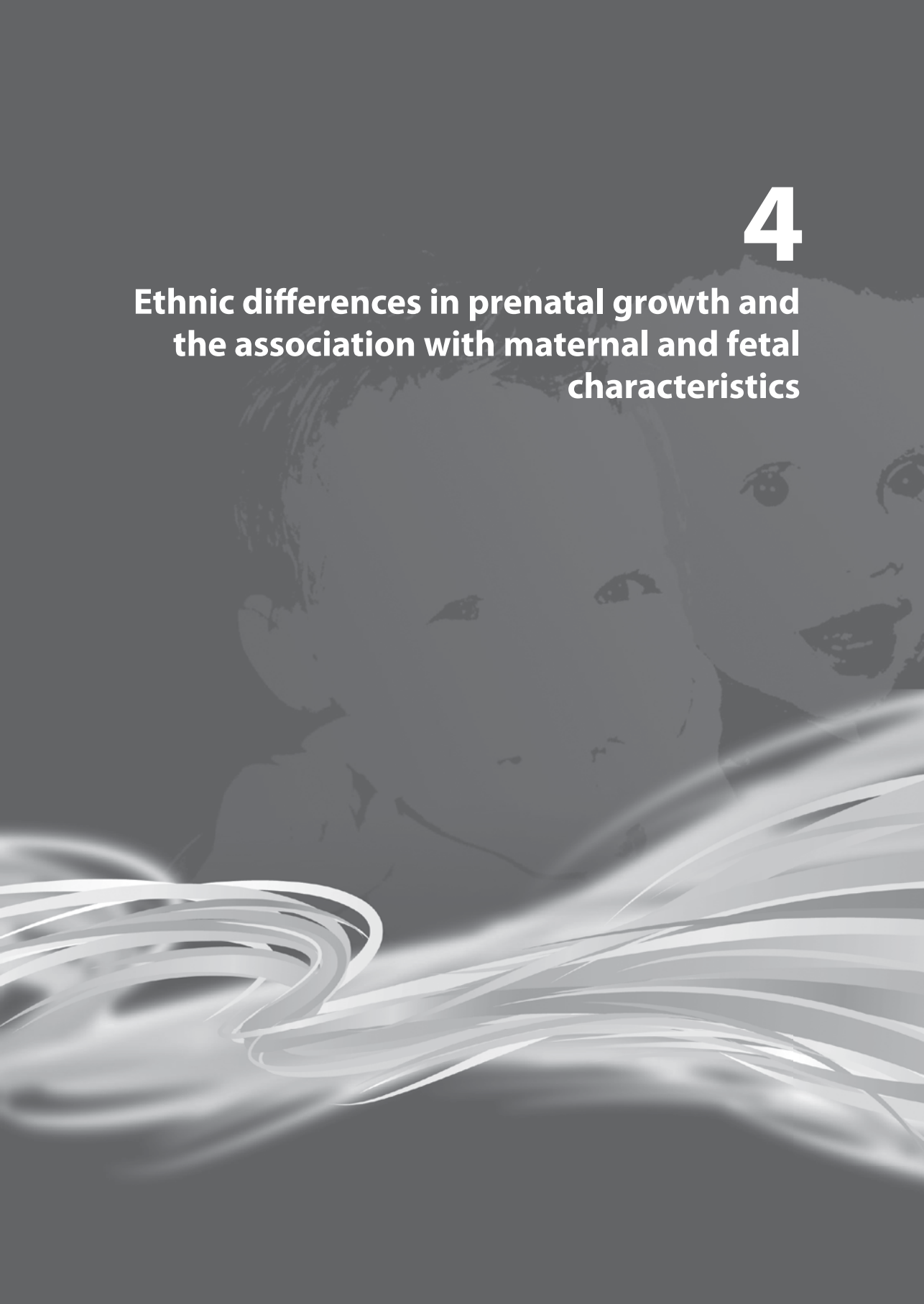
8. Gould JB, Madan A, Qin C, Chavez G. Perinatal outcomes in two dissimilar immigrant populations in the United States: a dual epidemiologic paradox. Pediatrics. 2003 Jun;111(6 Pt 1):e676-82.
9. Acevedo-Garcia D, Soobader MJ, Berkman LF. The differential effect of foreign-born status on low birth weight by race/ethnicity and education. Pediatrics. 2005 Jan;115(1):e20-30.
10. Guendelman S, English PB. Effect of United States residence on birth outcomes among Mexican immigrants: an exploratory study. Am J Epidemiol. 1995 Nov 1;142(9 Suppl):S30-8.
11. Stephen EH, Foote K, Hendershot GE, Schoenborn CA. Health of the foreign-born population: United States, 1989-90. Adv Data. 1994 Feb 14(241):1-12.
12. International Classification of Diseases and Related Health Problems, 1989 Revision. Geneva: World Health Organization; 1992.
13. Cobas JA, Balcazar H, Benin MB, Keith VM, Chong Y. Acculturation and low-birthweight infants among Latino women: a reanalysis of HHANES data with structural equation models. Am J Public Health. 1996 Mar;86(3):394-6.
14. Scribner R, Dwyer JH. Acculturation and low birthweight among Latinos in the Hispanic HANES. Am J Public Health. 1989 Sep;79(9):1263-7.
15. Marin G, Perez-Stable EJ, Marin BV. Cigarette smoking among San Francisco Hispanics: the role of acculturation and gender. Am J Public Health. 1989 Feb;79(2):196-8.
16. Acevedo-Garcia D, Pan J, Jun HJ, Osypuk TL, Emmons KM. The effect of immigrant generation on smoking. Soc Sci Med. 2005 Sep;61(6):1223-42.
17. van Leest LATM, van Dis SJ, Verschuren WMM. Cardiovascular diseases in non-western immigrants in the Netherlands. An exploratory study into lifestyle- and risk factors, morbidity and mortality [In Dutch]. Bilthoven: National Institute for Public Health and the Environment; 2002.
18. Emancipation in relay. The position of women of ethnic minority populations [In Dutch]. Social and cultural planning office of the Netherlands (SCP); 2004.
19. Report of ethnic minorities 2003. Education, work and socio-cultural integration.: Social and cultural planning office of the netherlands (SCP); 2003.
20. van Enk A, Buitendijk SE, van der Pal KM, van Enk WJ, Schulpen TW. Perinatal death in ethnic minorities in The Netherlands. J Epidemiol Community Health. 1998 Nov;52(11):735-9.

# Determinants of fetal growth, birth weight and gestational age



# 4

# Ethnic differences in prenatal growth and the association with maternal and fetal characteristics



## Abstract

*Objectives:* The objectives of this study were to determine ethnic differences in prenatal growth and to examine their association with differences in maternal and fetal characteristics such as maternal height, weight, age, parity and fetal gender.
*Methods:* A total of 1494 women from Rotterdam, The Netherlands, with a low-risk pregnancy who participated in a population-based cohort study, the Generation R Study, were offered three ultrasound examinations during pregnancy. Multilevel modeling was applied to determine ethnic differences in (estimated) fetal weight (including birth weight) and in the separate biometric variables that were used to calculate the estimated fetal weight (abdominal circumference, head circumference and femur length). Additionally the association of ethnic differences with maternal and fetal characteristics (i.e. maternal weight, height, age, parity and fetal gender) was studied.
*Results:* Turkish, Capeverdean, Surinamese-creole and Surinamese-hindustani women had on average smaller fetuses than the native Dutch women. The differences became more pronounced towards term. In the Turkish group the differences were no longer statistically significant when adjusted for maternal weight, height, age, parity and fetal gender. In the Capeverdean, Surinamese-creole and Surinamese-hindustani groups the differences decreased after adjustment (31%, 16% and 39%, respectively).
*Conclusions:* This study shows that there are ethnic differences in fetal growth, which to a large extent may be attributed to differences in maternal weight, height, age and parity. For some ethnic groups, however, additional factors are involved, as differences remain significant after correction for fetal and maternal characteristics.

## Introduction

Compared with the native Dutch population, the three largest ethnic minority groups in the Netherlands (i.e. Turkish, Moroccan and Surinamese) have higher rates of perinatal mortality (1). The main determinant of perinatal mortality is low birth weight. Because low birth weight can be caused by preterm delivery, intrauterine growth restriction or a combination of the two, accurate assessment of fetal growth is a principal aim in antenatal care. A distinction should be made between constitutionally small and growth-restricted fetuses. While a growth-restricted fetus has an increased risk of perinatal mortality and morbidity, a constitutionally small baby does not have this increased risk.

Ethnic differences in the incidence of preterm delivery, low birth weight and fetal growth have been reported for the Netherlands (2, 3). Surinamese women have an increased risk of low birth weight and small-for-gestational-age infants. Turkish women have an increased risk of preterm delivery. No increased risk for preterm birth or low birth weight has been found for Moroccans (2, 3). A crosssectional study in Belgium showed ethnic differences in fetal biometry between Belgian, Turkish and Moroccan people (4). Turkish and Moroccan individuals had a higher birth weight compared to the Belgian participants. Longitudinal studies in the UK showed the same growth pattern in different ethnic groups, while the growth velocity was different (5, 6).

Different approaches have been used to study ethnic differences in fetal growth. Some studies used a crosssectional design (4). Longitudinal studies have mainly looked at growth in the third trimester of pregnancy (5, 6). A problem with this method of analysis is that curves are fitted for each individual's data separately. This results in an over-representation of intra-individual variation and the estimation of a large number of regression coefficients from the data. A better way to handle longitudinal data is with multilevel modeling, which takes into account the fact that there are multiple measurements for each fetus (7, 8).

The factors associated with differences in growth can be divided into maternal and fetal characteristics, and environmental factors (e.g. smoking, socio-economic status and malnutrition (9, 10)). Ethnicity is one of the maternal and fetal characteristics; others are maternal height, weight, age, parity, and fetal gender. Models for growth curves should take these determinants into account to distinguish between constitutionally small and growth-restricted infants. While studies on differences in birth weight in general take these variables into account, only a few studies on prenatal growth have investigated these maternal and fetal characteristics (11-14).

This study had two objectives: (1) to determine whether there are ethnic differences in prenatal growth for lowrisk pregnancies and (2) to examine to what extent these ethnic differences in prenatal growth are attributable to differences in maternal and fetal characteristics such as maternal height, weight, age, parity and fetal gender. The study used longitudinal data obtained with ultrasound fetal biometry measurements.

## Methods

### Study population

This study was part of the Generation R Study. The Generation R Study is a prospective, multi-ethnic cohort study starting early in pregnancy. All pregnant women living in Rotterdam are invited to participate in this study. Rotterdam is a multi-ethnic city and the second largest city in the Netherlands. Data are collected by means of physical examinations, questionnaires, interviews, ultrasound and biological samples. The study population comprising the Generation R Study is described in detail elsewhere (15).

The population of this particular study comprised singleton pregnancies included in the Generation R Study during the starting phase. All relevant prenatal data and data on the birth outcomes were available for a total of 1725 pregnancies. Only low-risk pregnancies were studied. Pregnant women with pre-existing diseases that may affect fetal growth (e.g. diabetes mellitus and hypertension) were excluded. Women with pregnancy complications (e.g. pre-eclampsia, pregnancy-induced hypertension and diabetes gravidarum) were also excluded. If a major fetal malformation was detected then the subject was excluded. Other exclusion criteria were intrauterine death, stillbirth and preterm delivery (before 37 weeks of pregnancy). In total, 231 women were excluded because of these criteria, leaving 1494 cases for analysis.



### Measurements

A questionnaire completed by the mother at 12 weeks of gestation was used to obtain the following information: last menstrual period, menstrual cycle, parity, pre-pregnancy weight, height, countries of birth of (grand)parents and ethnic origin. The delivery notes, which were filled out by the midwife or gynecologist, were used to obtain information on: maternal age, pre-existing maternal diseases, pregnancy complications, major fetal abnormalities, gestational age (GA), birth weight and gender of the child. Pregnant women were assessed at approximately 12, 20 and 30 weeks of gestation to collect information about fetal growth by ultrasound examination. The following ultrasound variables were used: crown–rump length (CRL), biparietal diameter from outer to outer skull (BPD), transverse cerebellar diameter (TCD), head circumference (HC), abdominal circumference (AC) and femur length (FL). All these measurements were made using standardized techniques (16). CRL was measured only in the first trimester, while the other measurements were performed at all three ultrasound examinations.

Estimated fetal weight (EFW) was calculated using the formula of Hadlock: log (EFW) = 1.326 − 0.00326 * AC * FL + 0.0107 * HC + 0.0438 * AC + 0.158 * FL (17). We calculated EFW only after 18 weeks of gestation, because this formula is not reliable early in pregnancy. The weight recorded at birth was also used, leading to a maximum of three weight estimates per fetus (i.e. EFW at 20 and 30 weeks of GA and birth weight).

In a part of our population, pregnancy dating based on the self-reported first day of the last menstrual period was not possible because of missing data or because women reported having an irregular menstrual cycle. Also some of the women had their first ultrasound scan in the second trimester. Therefore, the following method for pregnancy dating was used: GA was calculated on the basis of the first ultrasound measurement. CRL was used if this measurement was smaller than 84 mm (until 14 weeks of gestation, n = 658) (18). TCD was used if this measurement was between 17 and 26 mm (between 18 and 25 weeks of gestation, n = 619). In the remaining cases GA was calculated on the basis of the BPD (n = 217) (19).

Ethnicity of the infant was defined on the basis of the countries of birth of the grandparents as reported by the mother. Only if all four grandparents were born in a certain country did that country define ethnicity. Because for most migrant groups the migration history to the Netherlands is relatively recent, this enabled us to distinguish homogeneous ethnic groups. The Surinamese group was subdivided into Surinamese-hindustani and Surinamese-creole based on the mother's ethnic origin. In this way nine different ethnic groups were defined: Native Dutch, Moroccan, Turkish, Capeverdean, Dutch Antillean/Aruban, Surinamese-hindustani, Surinamese-creole, other origin and mixed origin. Native Dutch was used as the reference group.

The covariates we used were maternal and fetal characteristics known to affect fetal growth: maternal pre-pregnancy weight, maternal height, maternal age at birth of the child, fetal gender and parity. Parity was divided into two groups (nulliparous and parous). Maternal age was divided into three groups (≤25, 25–35 and ≥35 years). Maternal height and weight were used as continuous variables.

**Statistical analysis**

EFW and the separate ultrasound variables, which are used in the fetal weight equation (AC, HC and FL), were modeled as a function of GA. When necessary, GA and the outcome variables (EFW, AC, HC or FL) were transformed to obtain a linear relationship between the outcome variable and GA. Fetal longitudinal data are hierarchical in structure, with two levels: variation between GAs within fetuses and variation between fetuses. Therefore we used a multilevel model (7, 8). At the individual level, a linear model was fitted (EFW = a + b * GA) with the outcome as a function of GA. Parameters (slope and intercept) of this first level were modeled at the second level with ethnicity and the other determinants as predictors. Restricted maximum likelihood was used to estimate the different parameters. A model was fitted with random effects for both intercept and GA. Analyses showed that for the separate ultrasound variables the random effect for GA was not required. So for the separate ultrasound variables a model could be used, with only random effects for the intercept, assuming that there is no interperson difference in slope within ethnic groups. This model was used to explain the ethnic differences in fetal growth.

The intercept and the slope of the curveswere compared between the different ethnic groups. Estimates of least squares means for the outcome variable were also compared at certain GAs (i.e. for EFW at 20, 30 and 40 weeks of gestation and for ultrasound measurements of abdomen, head and femur at 12, 20 and 30 weeks of gestation). These comparisons were done using a twotailed t-test.

The covariates, which all act at the fetal level, were accommodated one by one in the models, and all simultaneously as predictors (fixed effects) at the second level (variation between fetuses) of the model. This was done only for the EFW.

For all analyses, a value of P = 0.05 was taken to indicate statistical significance. Statistical analyses were carried out using SPSS v.11.5 (SPSS Inc., Chicago, IL, USA) and SAS v.8.2 (Stata Corporation, College Station, TX, USA). To estimate the multilevel models the SAS 'proc mixed' procedure was used8.

## Results

The characteristics of the study population are summarized according to ethnicity in table 1. The numbers in the ethnic minority groups are relatively small, ranging from 20 for the Dutch Antillean to 66 for the Turkish population. The Dutch women in our population are taller, older and more often nulliparous compared to those from the other



**Table 1.** Characteristics of the study population according to ethnicity.

| | Native Dutch | Moroccan | Turkish | Capeverdean | Antillean | Surinamese-creole | Surinamese-hindustani | Other | Mixed | Total population |
|---|---|---|---|---|---|---|---|---|---|---|
| Maternal weight (SD) | 67.9 (11.6) | 69.4 (11.3) | 63.5 (10.6) | 62.1 (8.6) | 67.0 (16.2) | 69.0 (15.0) | 57.2 (11.5) | 61.1 (11.9) | 64.3 (13.1) | 66.0 (12.4) |
| Maternal height (SD) | 171.1 (6.4) | 165.2 (4.7) | 163.4 (5.3) | 164.5 (7.4) | 165.5 (6.9) | 167.2 (6.0) | 161.2 (5.6) | 163.4 (6.9) | 167.7 (7.2) | 168.7 (7.1) |
| Maternal BMI (SD) | 23.2 (3.6) | 25.4 (4.1) | 23.8 (3.8) | 23.0 (3.0) | 24.4 (5.2) | 24.7 (5.5) | 22.0 (4.1) | 22.9 (4.2) | 22.8 (4.2) | 23.2 (3.9) |
| Maternal age (%) | | | | | | | | | | |
| *< 25 years* | 6.6 | 30.2 | 40.9 | 43.3 | 40.0 | 33.3 | 23.7 | 19.6 | 17.1 | 14.7 |
| *25-35 years* | 71.1 | 62.3 | 53.0 | 46.7 | 55.0 | 47.6 | 65.8 | 73.2 | 62.3 | 66.1 |
| *> 35 years* | 22.3 | 7.5 | 6.1 | 10.0 | 5.0 | 19.0 | 10.5 | 7.1 | 20.7 | 19.1 |
| Parity (% primiparous) | 58.4 | 39.6 | 51.5 | 56.7 | 35.0 | 61.9 | 55.3 | 51.8 | 56.5 | 56.2 |
| Fetal gender (% male) | 52.4 | 56.6 | 54.6 | 50.0 | 50.0 | 52.4 | 34.2 | 42.9 | 53.9 | 52.2 |
| 3 ultrasounds (%) | 81.5 | 71.7 | 75.8 | 80.0 | 60.0 | 66.7 | 76.3 | 73.2 | 76.1 | 78.2 |

BMI = body mass index

Weight in kg, height in cm, BMI in $kg/m^2$

ethnic groups. In the native Dutch group more women underwent all three ultrasound examinations.

First a statistical model was constructed, to describe prenatal growth using our data. It was necessary to transform both GA and EFW to the logarithmic scale to obtain a linear relationship between these two variables. Because growth slows down somewhat in

**Table 2.** Coefficients, standard errors and P-values for the different determinants in the full model for (estimated) fetal weight

| | Coefficient | Standard Error | P-value |
|---|---|---|---|
| Intercept | 0.7056 | 0.1092 | <0.0001 |
| Native Dutch (reference) | 0 | - | - |
| Moroccan | 0.005849 | 0.02352 | 0.8036 |
| Turkish | 0.02336 | 0.02106 | 0.2674 |
| Capeverdian | 0.05112 | 0.03061 | 0.0951 |
| Dutch Antilean/Aruban | 0.1269 | 0.03820 | 0.0009 |
| Surinamese-creole | 0.01397 | 0.03886 | 0.7193 |
| Surinamese-hindustani | -0.02510 | 0.02800 | 0.3702 |
| Other ethnicity | 0.02347 | 0.02220 | 0.2905 |
| Mixed ethnicity | -0.01134 | 0.009640 | 0.2398 |
| Maternal heigt | -0.00084 | 0.000678 | 0.2173 |
| Maternal weight | -0.00005 | 0.000371 | 0.8823 |
| Maternal age ≤ 25 years | 0.01765 | 0.01557 | 0.2572 |
| Maternal age 25-35 years | 0.008677 | 0.01094 | 0.4279 |
| Nulliparous | 0.04541 | 0.000290 | <0.0001 |
| Male sex | -0.02725 | 0.008176 | 0.0009 |
| G.A. (= transformed gestational age) | 1.7921 | 0.08535 | <0.0001 |
| G.A. * Native Dutch (reference) | 0 | - | - |
| G.A. * Moroccan | -0.00897 | 0.01829 | 0.6237 |
| G.A. * Turkish | -0.01982 | 0.01648 | 0.2293 |
| G.A. * Capeverdian | -0.05371 | 0.2388 | 0.0246 |
| G.A. * Dutch Antilean/Aruban | -0.09766 | 0.02974 | 0.0010 |
| G.A. * Surinamese-creole | -0.02923 | 0.03007 | 0.3312 |
| G.A * Surinamese-hindustani | -0.00389 | 0.02184 | 0.8588 |
| G.A. * Other ethnicity | -0.02155 | 0.01738 | 0.2154 |
| G.A. * Mixed ethnicity | 0.006825 | 0.007532 | 0.3650 |
| G.A. * Maternal heigt | 0.001262 | 0.000530 | 0.0173 |
| G.A. * Maternal weight | 0.000505 | 0.000290 | 0.0819 |
| G.A. * Maternal age ≤ 25 years | -0.01332 | 0.01214 | 0.2728 |
| G.A. * Maternal age 25-35 years | -0.00290 | 0.008528 | 0.7340 |
| G.A. * Nulliparous | -0.04286 | 0.006785 | <0.0001 |
| G.A. * Male sex | 0.02893 | 0.006388 | <0.0001 |

**Table 3.** Average differences in EFW between the ethnic groups in grams at 20, 30 and 40 weeks of gestation. For the native Dutch population (reference group) the estimates are given.

| | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|
| **Gestational age (weeks)** | **20** | **30** | **40** | **20** | **30** | **40** |
| Native Dutch, estimate | 327 | 1492 | 3519 | 325 | 1477 | 3479 |
| Moroccan | - 4 | -26 | -72 | -2 | -19 | -58 |
| Turkish | 0 | -35 | -130* | +3 | -6 | -45 |
| Capeverdian | -3 | -90* | -309* | 0 | - 58* | -213* |
| Dutch Antillean/Aruban | +23* | -6 | -155 | +26* | +7 | -125 |
| Surinamese-creole | -11 | -91* | -264* | -10 | -77* | -223* |
| Surinamese-hindustani | -26* | -49* | -391* | -21* | -99* | -238* |
| Other | -2 | -48* | -165* | +2 | -14 | -64 |
| Mixed | -6* | -25* | -59* | -4 | -9 | -10 |

* $p \leq 0.05$

the final weeks before delivery, 11 weeks of GA were subtracted before the logarithmic transformation to obtain a better fit. This transformation was derived by trial and error and showed the best visual fit and the highest overall value for R2 (0.998).

Ethnicity was always included in the models. When the other determinants were entered one by one into the model, significant effects were found for all determinants. Male infants had a higher weight than female infants. Firstborn infants weighed less than subsequent infants. There was a consistent increase in fetal weight with greater maternal height and with greater maternal weight. Fetal weight was highest in the 25–35 years age group. Because each separate determinant had a significant effect on EFW when entered into the model with ethnicity, we decided to include all determinants in the full model. Table 2 shows the coefficients, standard errors and P-values for the different determinants in the full model. Main effects (intercepts) and interactions (slopes) are shown. With these parameters predicted values can be calculated. The overall effects of ethnicity and of the interaction between ethnicity and transformed GA were significant (P = 0.0102 and 0.0076, respectively), demonstrating ethnic differences in mean intercept and mean slope of the transformed growth curves.

The average differences in EFW between the different ethnic groups and the native Dutch group at 20, 30 and 40 weeks of gestation are shown in table 3. In the unadjusted model Turkish, Capeverdean, Dutch Antillean/Aruban, Surinamese-creole, Surinamese-hindustani women and women with other or mixed ethnicity had significantly smaller fetuses than the native Dutch group. These differences became more pronounced towards term. After adjusting for the covariates, weight in the Turkish, other and mixed origin groups did not differ significantly from that in the Dutch group. For Capeverdean, Surinamese-creole and Surinamese-hindustani infants the corrected weight remained significantly lower than that in the native Dutch group. In the Dutch Antillean/Aruban group the weight was

**Figure 1.** EFW plotted against gestational age for the different ethnic groups, unadjusted model.

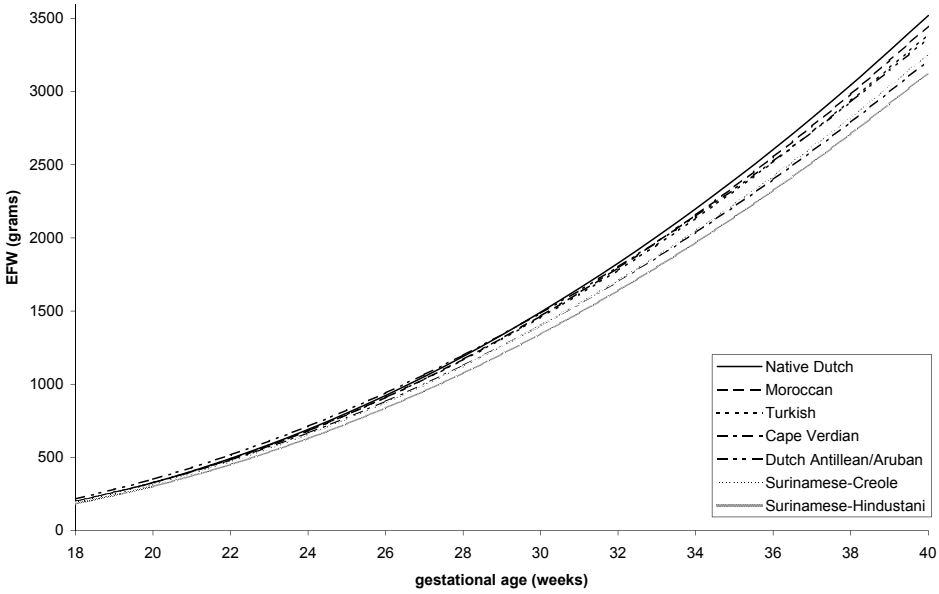



**Figure 2.** EFW plotted against gestational age for the different ethnic groups; predicted values calculated for primiparous women with a mean weight, height and age, for a male fetus.

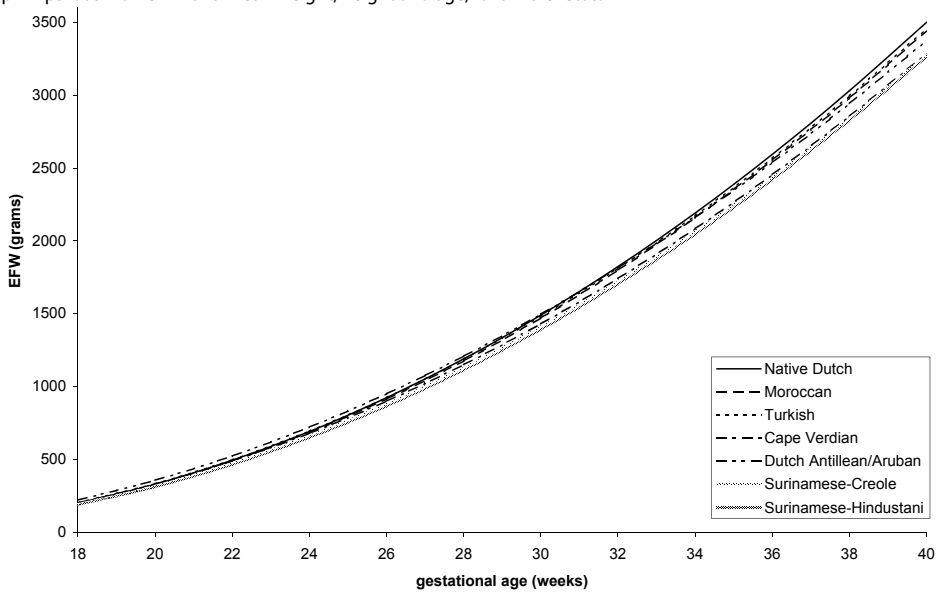


**Table 4.** Average differences in abdominal circumference (AC), head circumference (HC) and femur length (FL) in millimeters with the native Dutch population. For the native Dutch population (reference group) the estimates are given.

| | AC | | HC | | FL | |
|---|---|---|---|---|---|---|
| **Gestational age (weeks)** | **20** | **30** | **20** | **30** | **20** | **30** |
| Native Dutch, estimate | 149 | 261 | 168 | 282 | 30 | 57 |
| Moroccan | -1 | -3* | 0 | -2 | 0 | 0 |
| Turkish | 0 | -1 | 0 | -1 | 0 | 0 |
| Capeverdian | -3 | -8* | -1 | -6* | +1 | 0 |
| Dutch Antillean/Aruban | +1 | -3 | +1 | -4* | +2* | +3* |
| Surinamese-creole | -4* | -8* | -1 | -5* | 0 | 0 |
| Surinamese-hindustani | -6* | -12* | -4* | -8* | 0 | 0 |
| Other | -1 | -5* | -1 | -3* | 0 | -1 |
| Mixed | -1* | -3* | -1 | -2* | 0 | 0 |

* $p \leq 0.05$

relatively high at 20 weeks whilst there was a tendency towards low birth weight at term. The predicted EFW values for the different groups (unadjusted and adjusted for the maternal and fetal characteristics) are plotted against GA in figures 1 and 2.

For the separate ultrasound variables (AC, HC and FL) it was not necessary to make any transformations. The overall R2 values were 0.998, 0.997 and 0.994, respectively. The separate variables were compared at three points in pregnancy (at 12, 20 and 30 gestational weeks). The significant differences are displayed in table 4. At 12 weeks no significant differences were found. Moroccan, Capeverdean, Surinamese-creole, Surinamese-hindustani fetuses and fetuses with other or mixed ethnicity all had significantly smaller AC measurements at 30 weeks. A significantly smaller HC measurement was found in Capeverdean, Dutch Antillean/ Aruban, Surinamese-creole, Surinamese-hindustani women and in women with other or mixed ethnicity at 30 weeks. A significantly greater FL was found for Dutch Antillean/Aruban fetuses at 20 and 30 weeks of gestation.





## Discussion

Differences in fetal size (i.e. EFW) in the third trimester of pregnancy were found for Turkish, Capeverdean, Surinamese-creole and Surinamese-hindustani women and for groups with mixed or other ethnic origin as compared to the Dutch population. For the Turkish group and for the groups with mixed or other origin, the differences in EFW could be totally explained by differences in the maternal and fetal characteristics. For Surinamese-creole, Surinamese-hindustani and Capeverdean women up to one-third of the differences was explained by the maternal and fetal characteristics. A signifi-

cantly smaller AC measurement was found at 30 weeks for the Moroccan, Capeverdean, Surinamese-creole and Surinamese-hindustani groups. A significantly smaller HC measurement was found in Capeverdean, Dutch Antillean/Aruban, Surinamese-creole and Surinamese-hindustani women at 30 weeks.

The estimates for both the separate biometric variables and the EFW are in line with existing reference curves (20-23). Our results confirm the results of Van der Wal et al. (2) who showed for the Netherlands that Surinamese and Turkish women have a significantly lower birth weight compared to the Dutch population. The difference for the Surinamese group persisted when correcting for rank number and gender of the child and maternal height and age. Van der Wal et al. did not find significant differences in birth weight for Moroccans compared to the native Dutch population (2). Our findings also show that these differences are not only present in birth weight but also during the whole prenatal period. A significantly higher weight was found at 20 weeks and a significantly greater FL at 20 and 30 weeks in Dutch Antilleans and Arubans compared to the Dutch population. Since the number of cases was small, and since there are no clinical implications, there is no need to take this into account in clinical practice.

When adjusting for the most important maternal and fetal characteristics (i.e. maternal weight, height, age, parity and fetal gender) the differences with most groups became smaller but still remained statistically significant. For Capeverdean, Surinamese-hindustani and Surinamese-creole women two-thirds of the differences could not be explained by the maternal and fetal characteristics. There are many explanations possible for the residual differences. Environmental variables such as smoking, nutrition, nutritional deficiencies and social class may play a role (9, 24, 25). Taking these variables into account can lead to smaller or larger ethnic differences. Low socio-economic class, for example, might be more prevalent in the non-Dutch population and could explain part of the ethnic differences. However, smoking is more prevalent among the Dutch and Turkish population compared to the Surinamese, Moroccan and Antillean population. So it might be possible that taking smoking into account will enlarge the ethnic differences. The dataset we used did not have enough power to take all these different environmental factors into account.

In a recent study Graafmans et al. compared birth weights in seven Western European countries and found substantial differences in birth weight distributions between these countries (26). They concluded that to improve the identification of growth-restricted infants, population-specific standards for birth weight should be developed. Results from the present study indicate that there are substantial differences in prenatal growth and birth weight distributions between subgroups within a population. Several maternal and fetal factors contribute to these differences. Instead of developing subgroup-specific standards for birth weight within countries, it seems more useful to develop individual growth curves, which take into account different variables influencing prenatal growth.

In previously published models it has been proposed that ethnicity and maternal and fetal characteristics should be taken into account to derive individualized growth curves (11, 12, 14). With a similar approach to that used by Gardosi et al. (11, 12), individual growth curves may be derived taking into account prenatal ultrasound growth data. This may lead to a more accurate diagnosis of intrauterine growth restriction and the prevention of unnecessary obstetric interventions. It can be questioned whether it is useful to include ethnicity as a separate variable in the individualized growth curves. Models that include ethnicity might be limited in use to the population in which they are developed, while a model that includes fetal and maternal characteristics might be useful in different populations.

Several factors should be taken into account when interpreting the results of the present study. The numbers in the ethnic minority groups are relatively small, though comparable to the numbers presented in previous studies on ethnic differences in fetal growth (4-6). The small numbers are partly due to our stringent definition of ethnicity. By taking into account the countries of birth of the grandparents, homogeneous ethnic groups could be distinguished. It is important to also take the ethnicity of the father into account because it is known that fathers have an effect on birth weight (27). Due to the lack of data on ethnic origin, in many other Dutch studies the Surinamese-creole and Surinamese-hindustani people are pooled in the analysis. Also Dutch Antillean, Aruban and Surinamese-creole people are often pooled together because they are all Caribbean. However, since the Hindustani people have their origins in India and Pakistan, the Creole group is of African origin and the Antilleans/Arubans are partly from European and partly from African origin, it is preferable to distinguish these groups in research on ethnic differences. The differences between these groups are also reflected in the maternal characteristics (Table 1). A relatively large group with mixed ethnicity was studied. In most cases one of the parents was native Dutch while the other was not. The results of this group fitted in between those of the native Dutch and the other ethnic groups. The group of 'others' is a very heterogeneous group, consisting mainly of people of non-Western origin. The enrolment of migrants is difficult because of cultural and language barriers. It is likely that migrants with a high socio-economic status were over-represented in our study population. Since higher socio-economic status is associated with higher fetal growth and birth weight, it is possible that our findings somewhat underestimate the ethnic differences in fetal growth.

The present study excluded women with maternal diseases and pregnancy complications. It is important to note that small- or large-for-gestational-age fetuses were not excluded. In some other studies on fetal growth, fetuses with abnormal neonatal outcome, such as low Apgar score, were also excluded (6, 28). We chose to include these fetuses in the present study since abnormal neonatal outcome is not generally related to growth disturbances when there is no other condition present that affects growth. Our

population thus reflects an urban, low-risk population. In additional analyses in which women with maternal diseases and pregnancy complications were included (data not shown) comparable outcomes were found.

GA was based on CRL, BPD or TCD measurements. This is a valid method for pregnancy dating. The distribution of these three different ultrasound methods of pregnancy dating was different between the ethnic groups. We do not think this introduces a bias, because all three methods have a good correlation with pregnancy dating based on a reliable last menstrual period (18, 19). For the calculation of EFW there are several formulae available. Most of these formulae have been developed for Caucasians. We chose to use the formula of Hadlock that uses AC, HC and FL. Many of the other available formulae also use the BPD, which was not appropriate in the present study because the BPD was used for pregnancy dating. The same analyses were done with EFW derived from the formula of Campbell that only takes the AC into account (29). These analyses generated similar results.

In conclusion, this study shows that there are ethnic differences in fetal growth, which to a large extent are associated with maternal weight, height, age and parity. For some ethnic groups, however, additional factors are involved in the explanation of these ethnic differences. Further research should focus on these environmental factors since some of them can be changed by prevention and education, which is important from a public health point of view. A lower rate of fetal growth restriction in the ethnic minority groups will probably decrease the ethnic differences in adverse pregnancy outcomes. A better definition of fetal growth restriction will probably decrease the number of unnecessary obstetric interventions. Consequently, it is important to develop individualized growth curves that take different maternal and fetal characteristics into account.

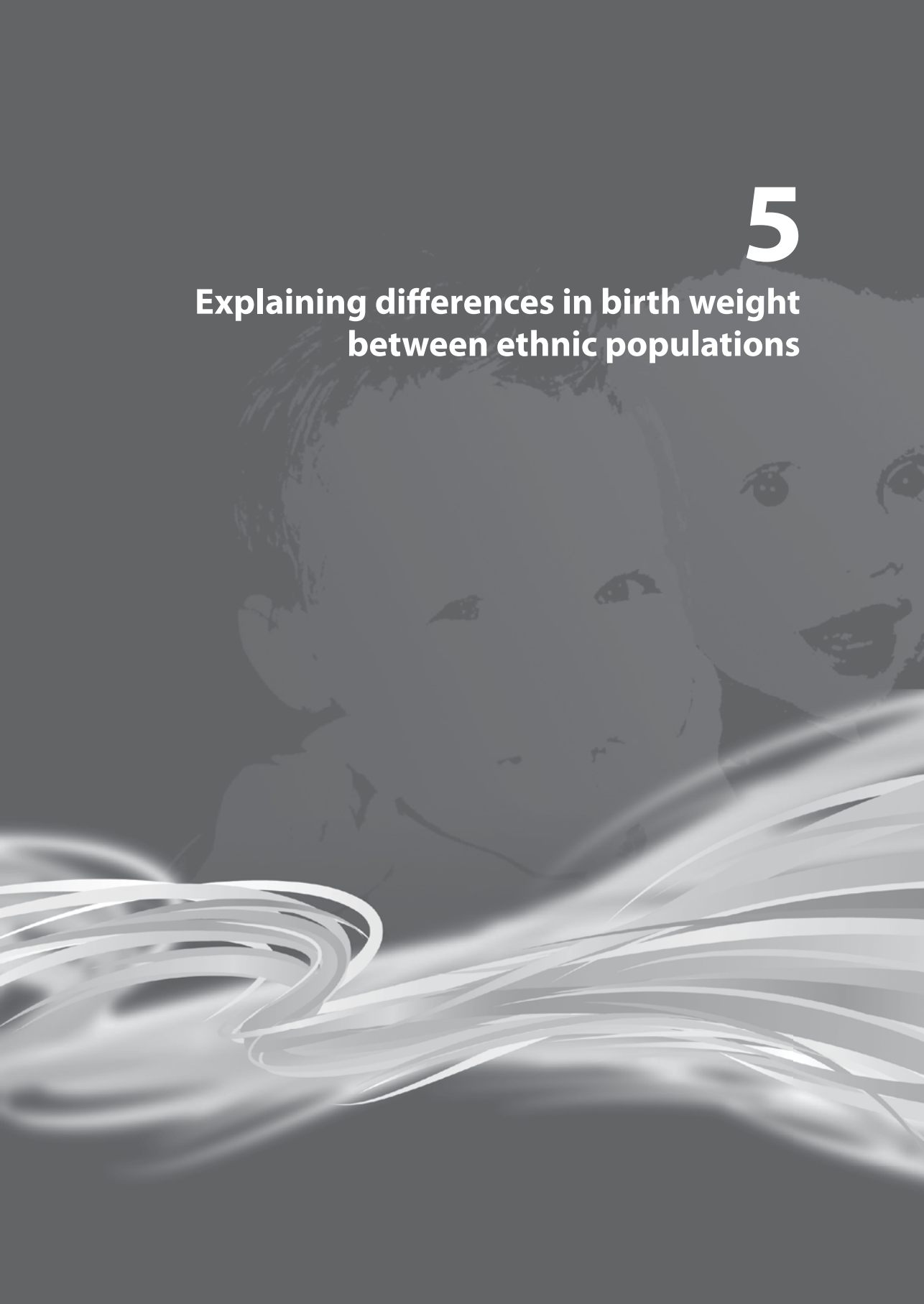
## References

1. Schulpen TWJ, van Steenbergen JE, van Driel HF. Influences of ethnicity on perinatal and child mortality in the Netherlands. Arch Dis Child 2001; 84: 222–226.
2. Van der Wal MF, Uitenbroek DG, van Buuren S. Birth weight of Amsterdam infants according to ethnic background [In Dutch]. Tijdschrift Sociale Gezondheidszorg 2000; 78: 15–20.
3. Van Enk A, Buitendijk SE, van der Pal KM, van Enk WJJ, Schulpen TWJ. Perinatal death in ethnic minorities in the Netherlands. J Epidemiol Community Health 1998; 52: 735–739.
4. Jacquemyn Y, Sys SU, Verdonk P. Fetal biometry in different ethnic groups. Early Hum Dev 2000; 57: 1–13.
5. Spencer JAD, Chang TC, Robson SC, Gallivan S. Fetal size and growth in Bangladeshi pregnancies. Ultrasound Obstet Gynecol 1995; 5: 313–317.
6. Mongelli M, Gardosi J. Longitudinal study of fetal growth in subgroups of a low-risk population. Ultrasound Obstet Gynecol 1995; 6: 340–344.
7. Royston P, Altman DG. Design and analysis of longitudinal studies of fetal size (Opinion). Ultrasound Obstet Gynecol 1995; 6: 307–312.

8. Verbeke G, Molenberghs G (eds). Linear Mixed Models in Practice: A SAS-Oriented Approach. Springer-Verlag: New York, NY, 1997.
9. Gardosi J. Ethnic differences in fetal growth (Editorial). Ultrasound Obstet Gynecol 1995; 6: 773–774.
10. Cogswell ME, Yip R. The influence of fetal and maternal factors on the distribution of birthweight. Semin Perinatol 1995; 19: 222–240.
11. Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. Lancet 1992; 339: 283–287.
12. Gardosi J, Mongelli M, Wilcox M, Chang A. An adjustable fetal weight standard. Ultrasound Obstet Gynecol 1995; 6: 169–174.
13. Bromley B, Frigoletto D Jr, Harlow BL, Evans JK, Benacerraf BR. Biometric measurements in fetuses of different race and gender. Ultrasound Obstet Gynecol 1993; 3: 395–402.
14. Pang MW, Leung TN, Sahota DS, Lau TK, Chang AMZ. Customizing fetal biometric charts. Ultrasound Obstet Gynecol 2003; 22: 271–276.
15. Hofman A, Jaddoe VWV, Mackenbach JP, Moll HA, Snijders RFM, Steegers EAP, Verhulst FC, Witteman JCM, Buller HA. Growth, development and health from early fetal life until young adulthood: the Generation R Study. Paediatr Perinat Epidemiol 2004; 18: 61–72.
16. Routine Ultrasound Screening in Pregnancy: Protocol, Standards and Training (Supplement to Ultrasound Screening for Fetal Abnormalities). Report of a Royal College of Obstetricians and Gynaecologists (RCOG) Working Party. RCOG Press: London, UK, 2000.
17. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements – a prospective study. Am J Obstet Gynecol 1985; 151: 333–337.
18. Robinson HP, Sweet EM. The accuracy of radiological estimates of gestational age using early crown rump measurements by ultrasound. Br J Obstet Gynaecol 1979; 86: 525–528.
19. Altman DG, Chitty LS. New charts for ultrasound dating of pregnancy. Ultrasound Obstet Gynecol 1997; 10: 174–191.
20. Gallivan S, Robson SC, Chang TC, Vaughan J, Spencer JAD. An investigation of fetal growth using serial ultrasound data. Ultrasound Obstet Gynecol 1993; 3: 109–114.
21. Chitty LS, Altman DG, Henderson AH, Campbell S. Charts of fetal size: 2 Head measurements. Br J Obstet Gynaecol 1994; 101: 35–43.
22. Chitty LS, Altman DG, Henderson AH, Campbell S. Charts of fetal size: 3 Abdominal measurements. Br J Obstet Gynaecol 1994; 101: 125–131.
23. Chitty LS, Altman DG, Henderson AH, Campbell S. Charts of fetal size: 4 Femur length. Br J Obstet Gynaecol 1994; 101: 132–135.
24. Shiono PH, Rauh VA, Park M, Lederman SA, Zuskar D. Ethnic differences in birth weight: the role of lifestyle and other factors. Am J Public Health 1997; 87: 787–793.
25. Verkerk PH, Zaadstra BM, Reerink JD, Herngreen WD, Verloove-Vanhorick SP. Social class, ethnicity and other risk factors for small for gestational age and preterm delivery in the Netherlands. Eur J Obstet Gynecol Reprod Biol 1994; 53: 129–134.
26. Graafmans WC, Richardus JH, Borsboom GJJM, Bakketeig L, Langhoff-Roos J, Bergsjo P,Macfarlane A,Verloove-Vanhorick SPV, Mackenbach JP, EuroNatal Working Group. Birth weight and perinatal mortality: a comparison of "optimal" birth weight in seven Western European countries. Epidemiology 2002; 13: 569–574.
27. Klebanoff MA, Mednick BR, Schulsinger C, Secher NJ, Shiono PH. Father's effect on infant birth weight. Am J Obstet Gynecol 1998; 178: 1022–1026.
28. Altman DG, Chitty LS. Charts of fetal size: 1. Methodology. Br J Obstet Gynaecol 1994; 101: 29–34.
29. Campbell S, Wilkin D. Ultrasonic measurement of fetal abdomen circumference in the estimation of fetal weight. Br J Obstet Gynaecol 1975; 82: 689–697.

# 5

# Explaining differences in birth weight between ethnic populations



## Abstract

*Objective:* To examine whether differences in birth weight of various ethnic groups residing in the Netherlands can be explained by determinants of birth weight.
*Design:* Population-based birth cohort study.
*Setting:* Data of pregnant women and their partners in Rotterdam, the Netherlands.
*Population:* We examined data of 6044 pregnant women with a Dutch, Moroccan, Turkish, Capeverdean, Antillean, Surinamese-creole, Surinamese-hindustani and Surinamese-other ethnic background.
*Methods:* Regression analyses were used to assess the impact of biomedical, socio-demographic and lifestyle related determinants on birth weight differences were studied.
*Main outcome measure:* Birth weight was established immediately after delivery in grams.
*Results:* Compared to mean birth weight of offspring of Dutch women (3485 grams, standard deviation (SD) 555), mean birth weight was lower in all non-Dutch populations, except in Moroccans. Differences ranged from an 88 grams lower birth weight in offspring of the Turkish women to a 424 grams lower birth weight in offspring of Surinamese-hindustani women. Differences in gestational age, maternal and paternal height largely explained the lower birth weight in the Turkish, Antillean, Surinamese-creole and Surinamese-other populations. Differences in birth weight between the Dutch and the Capeverdean and Surinamese-hindustani populations could only partly be explained by the studied determinants.
*Conclusions:* These results confirm significant differences in birth weight between ethnic populations that can only partly be understood from established determinants of birth weight. The part that is understood points to the importance of determinants that cannot easily be modified, such as parental height. Further study is necessary in order to obtain a fuller understanding.

## Introduction

Differences in birth weight between populations of different races or ethnic groups are well documented (1-3). In the United States several studies have shown that the proportion of low birth weight (< 2500 grams) is elevated in Black population (4-7). Similar findings are seen in the United Kingdom (UK) in infants of South-Asian, Black-Caribbean and Black-African descent compared to UK-born white mothers (8). Also in the Netherlands studies have shown differences in birth weight and the proportion of low birth weight between the non-Dutch and Dutch populations (9, 10). Birth weight is strongly related to perinatal and infant mortality (11, 12). The risk of adverse outcomes is seen not only in those with a low birth weight, but in the broad spectrum of birth weight. Additionally, birth weight is also associated with morbidity and mortality in later life; for example, associations of low birth weight with diseases during adulthood, like diabetes mellitus and cardiovascular disease, have been observed (13, 14).

The lower mean birth weight and higher proportion of low birth weight among minority populations could be the result of various determinants (15, 16). Several determinants have been identified that are associated with birth weight, like gestational age (17), parity (18), socio-economic status (19), marital status (20), maternal age (21, 22), maternal height, body mass index, pre-pregnancy weight (23, 24), smoking (25), and alcohol use (26).

These determinants of birth weight vary across ethnic populations. It is still unclear to what extent the lower birth weight of ethnic minority populations can be explained by these determinants. It might be that a lower birth weight in ethnic populations for a large part is related to unchangeable genetic determinants. By the study of determinants of birth weight in a variety of ethnic groups we aim to help to understand which genetic, physiological, socio-demographic and lifestyle determinants explain ethnic differences in birth weight.

The Generation R study is multi-ethnic, population-based birth cohort study, with a large sample size, in which detailed information about a large number of potential determinants is available. Within the Generation R Study we studied if biomedical, socio-demographic and lifestyle related determinants explain differences in birth weight between the Dutch and the non-Dutch populations.

## Methods

### Design

This study is embedded in the Generation R Study, a prospective population-based cohort study from fetal life until young adulthood. The Generation R study is designed

to identify early environmental and genetic determinants of growth, development and health in fetal life, childhood and adulthood and has been described previously in detail (27, 28). Briefly, all pregnant women and their partners in a previously defined area in Rotterdam, the Netherlands, were approached at their first antenatal visit. Most women spoke Dutch; if not, the study was explained and questionnaires were available in their own language (28). In total, 8,880 pregnant women with a delivery date between April 2002 and January 2006 enrolled in the prenatal part of the study. Data in pregnancy were collected from physical examinations, fetal ultrasounds and questionnaires. The partner of pregnant women had one physical examination at enrolment and received one questionnaire. Pregnant women were usually seen for the first time before the 18th week of the pregnancy and in total three times during pregnancy, in early (gestational age < 18 weeks), mid (gestational age 18 - 25 weeks) and late pregnancy (gestational age ≥ 25 weeks) in a research setting. The individual time scheme of these assessments depended on the specific gestational age at enrolment. The children form a prenatal recruited birth cohort, thus the overall response of the study can be calculated at birth. Of all eligible children in the study area, 61% participated at birth in the study (28). The Medical Ethics Committee of the Erasmus Medical Center approved the Generation R Study. Written informed consent was obtained from all participants.



**Ethnic background**

Ethnic background of the pregnant woman was assessed by country of birth of herself and her parents. Information about countries of birth was obtained by questionnaire. The participating pregnant woman was of non-Dutch ethnic origin if one of her parents was born abroad (definition Statistics Netherlands (29)) If both parents were born abroad, the country of birth of the participant's mother decided on the ethnic background. Besides women of Dutch ethnic background, a distinction was made among the non-Dutch minority populations in this study: Moroccan, Turkish, Capeverdean, Antillean and Surinamese. Women with an ethnic background other than these were grouped as 'other-western' for European, North American, Oceanean, Japanese and Indonesian, and as 'other non-western' for African, Asian (except Japanese and Indonesian) and South- and Central American. Women with a Surinamese background are of mixed ethnic origin, mainly consisting of Hindustanis originating from India and Creoles from Africa. These women were asked about their ethnic origin and further classified as: Surinamese-hindustani, Surinamese-creole or Surinamese-other.

**Outcome**

Birth weight of the infant was obtained from community midwifery and hospital registries. Birth weight was established directly postpartum and expressed in grams.

**Determinants**

*Biomedical determinants*. Gestational age was established by fetal ultrasound examination during the first ultrasound visit (30). Maternal height and paternal height were measured at time of enrolment.

*Socio-demographic determinants*. Information about maternal age, marital status, educational level and parity was obtained by questionnaires. Maternal age was assessed as at enrolment in the study and was a continuous variable. Marital status of the pregnant woman was classified into three categories: 1) married; 2) cohabiting; and 3) single parent. Educational level of the pregnant woman was assessed by the highest completed education and reclassified into three categories: 1) primary school; 2) secondary school; and 3) higher education. Parity was classified in two categories: 1) nulliparous; 2) multiparous.

*Lifestyle related determinants*. Maternal weight was measured without shoes and heavy clothing at time of enrolment. Body mass index at early gestation was calculated from maternal weight and maternal height (weight/height$^2$ (kg/m$^2$)) and adjusted for gestational age at intake. Maternal smoking and alcohol use were assessed by questionnaires by asking pregnant women whether they smoked / consumed alcohol during pregnancy (yes/no).

**Population for analysis**

For the present analyses data of all prenatal enrolled women were available (n=8880). Women with missing data on their ethnic background (n=1102) were excluded from analyses. Women with twin pregnancies (n=94), abortion or intra-uterine death (n=95) and perinatal death (n=39) were excluded from analyses. Also excluded were women that withdraw from the study (n=2) and were lost to follow-up (n=109). Of the remaining 7439 pregnant women maternal height and maternal weight were missing in 66 subjects, which were excluded from analyses. Analyses were carried out in pregnant women with a Dutch, Turkish, Moroccan, Surinamese-creole, Surinamese-hindustani, Surinamese-other, Antillean and Capeverdean ethnic background (n = 6044). The results of women with an 'other-western' and 'other non-western' ethnic background are not presented, because of the mixed composition of these populations (n=1329). The analyses with paternal height were restricted to the population of pregnant women from whom the partner participated in the study (n = 4471).

**Data analyses**

The non-Dutch populations under consideration were compared with the Dutch population (reference). Differences in baseline characteristics of the non-Dutch populations were compared with the Dutch population using the Chi-square statistic for categorical variables and analysis of variance (ANOVA) for continuous variables. Univariate linear

regression analysis was used to study the associations of ethnic background with birth weight. Gender of the infant was controlled for in all analyses as potential confounder. To study the individual effect of each potential determinant, each determinant was separately tested. We used separate categories for missing information on the determinants, which were added to the model. A bootstrap analysis was used to calculate a confidence interval around the change of the inequality when adjusting for the separate determinants (31).

In the multivariate analyses we examined the relationship between ethnic background and birth weight with different models. The different variables were gradually entered into the models by taking into account the hierarchical causal position of the variables (32). Gestational age was considered as confounding determinant and first entered into the model. Next the other biomedical variables, maternal and paternal height, were added to the model. To this new model educational level was added, and a similar procedure was repeated for the demographic and lifestyle related variables. Differences in birth weight with the 95% confidence intervals (95% CI) presented are the differences in mean birth weight in grams of the offspring of non-Dutch women compared to the offspring of Dutch women. All statistical analyses were performed using Statistical Package of Social Sciences version 11.0 for Windows (SPSS Inc, Chicago, IL, USA) and Splus 6.0 Professional Release 1.



## Results

Characteristics of the pregnant women according to ethnic background are shown in table 1. Gestational age was lower in the Capeverdean, Antillean and all Surinamese populations compared to the Dutch population. Compared to Dutch women, women of the non-Dutch minority populations and their partners were of lower height and of lower maternal age. Women of the non-Dutch populations were more frequently low educated compared to women of the Dutch population. Turkish and Moroccan pregnant women were more frequent married and multiparous than Dutch women. Maternal body mass index at early gestation was higher in all non-Dutch populations compared to the Dutch population, except in the Surinamese-hindustani population. Turkish women most frequently smoked during pregnancy, while Moroccan women hardly smoked during pregnancy. Compared to the Dutch women, women of the non-Dutch minority populations less frequently consumed alcohol during pregnancy.

Table 2 shows the mean birth weight of the offspring per ethnic population. The mean birth weight of offspring of Dutch women was 3485 grams (standard deviation (SD) 556). Offspring of Moroccan women had the highest mean birth weight (3517 grams, SD 493)), while offspring of Surinamese-hindustani women had the lowest mean

**Table 1.** Subject characteristics.

| | Dutch | Moroccan | Turkish | Cape-verdean | Antillean | Surinamese-creole | Surinamese-hindustani | Surinamese-other | P-value |
|---|---|---|---|---|---|---|---|---|---|
| N | 3659 | 490 | 670 | 297 | 256 | 225 | 237 | 210 | |
| infant sex (%) | | | | | | | | | P = 0.82 |
| *boy* | 50.4 | 52.2 | 51.6 | 47.1 | 49.2 | 55.6 | 49.8 | 52.4 | |
| gestational age (weeks) | 39.8 (1.7) | 40.1 (1.6) | 39.8 (1.7) | 39.6 (1.8) | 39.4 (1.9) | 39.3 (2.3) | 39.2 (1.7) | 39.5 (1.7) | P < 0.001 |
| maternal height (cm) | 170.8 (6.4) | 162.8 (5.6) | 161.6 (5.8) | 164.9 (6.5) | 164.8 (6.1) | 166.2 (6.6) | 160.0 (5.4) | 164.8 (7.0) | P < 0.001 |
| paternal height (cm) [a] | 183.9 (7.2) | 175.9 (6.5) | 175.4 (6.7) | 178.4 (6.2) | 178.2 (7.3) | 180.0 (7.5) | 175.5 (7.2) | 178.7 (8.6) | P < 0.001 |
| educational level (%) | | | | | | | | | P < 0.001 |
| *higher education* | 56.7 | 12.2 | 13.0 | 10.1 | 14.1 | 15.1 | 13.9 | 15.7 | |
| *secondary school* | 37.2 | 52.0 | 49.1 | 61.3 | 62.5 | 68.0 | 67.1 | 68.6 | |
| *primary school* | 5.2 | 26.1 | 31.6 | 23.9 | 19.5 | 14.2 | 16.9 | 15.2 | |
| *missing* | 0.8 | 9.6 | 6.3 | 4.7 | 3.9 | 2.7 | 2.1 | 0.5 | |
| age (years) | 31.2 (4.5) | 27.9 (5.1) | 27.1 (4.9) | 27.1 (6.0) | 26.1 (5.4) | 28.1 (6.5) | 27.6 (4.8) | 26.7 (5.7) | P < 0.001 |
| marital status (%) | | | | | | | | | P < 0.001 |
| *married* | 44.5 | 90.4 | 86.1 | 13.5 | 14.8 | 15.1 | 39.7 | 18.6 | |
| *cohabiting* | 46.8 | 3.7 | 5.7 | 32.7 | 31.6 | 31.1 | 34.2 | 37.1 | |
| *single mother* | 7.8 | 3.3 | 5.4 | 50.8 | 49.2 | 52.9 | 21.9 | 43.3 | |
| *missing* | 1.0 | 2.7 | 2.8 | 3.0 | 4.3 | 0.9 | 4.2 | 1.0 | |
| parity (%) | | | | | | | | | P < 0.001 |
| *0* | 58.6 | 38.0 | 44.8 | 53.9 | 54.3 | 53.3 | 52.7 | 57.1 | |
| *>= 1* | 39.4 | 58.6 | 52.5 | 40.1 | 40.2 | 45.3 | 41.8 | 39.0 | |
| *missing* | 1.9 | 3.5 | 2.7 | 6.1 | 5.5 | 1.3 | 5.5 | 3.8 | |
| body mass index (kg/m$^2$) | 24.3 (4.2) | 26.6 (4.8) | 26.3 (5.1) | 24.8 (4.4) | 26.5 (5.6) | 26.2 (5.7) | 24.2 (5.0) | 25.6 (5.4) | P < 0.001 |
| smoking (%) | | | | | | | | | P < 0.001 |
| *non-smoker* | 81.0 | 92.4 | 66.3 | 75.1 | 77.0 | 79.1 | 83.5 | 71.4 | |
| *smoker during pregnancy* | 17.0 | 4.9 | 30.1 | 20.2 | 19.1 | 18.7 | 14.3 | 25.7 | |
| *missing* | 1.9 | 2.7 | 3.6 | 4.7 | 3.9 | 2.2 | 2.1 | 2.9 | |
| alcohol consumption (%) | | | | | | | | | P < 0.001 |
| *no* | 47.2 | 94.7 | 90.1 | 64.3 | 61.7 | 53.8 | 76.4 | 63.8 | |
| *yes* | 49.0 | 3.1 | 7.2 | 29.6 | 29.7 | 36.4 | 15.2 | 28.1 | |
| *missing* | 3.8 | 2.2 | 2.7 | 6.1 | 8.6 | 9.8 | 8.4 | 8.1 | |

Values are means (standard deviation) or percentages.

P-values are result of $\chi^2$ test for categorical variables or analysis of variance (ANOVA) for continuous variables, Dutch is reference.

[a] n = 4471 (Dutch: 3194; Moroccan: 219; Turkish: 396; Capeverdean: 145; Antillean: 126; Surinamese-creole: 101; Surinamese-hindustani: 167; Surinamese-other: 123).

birth weight (3061 grams, SD 541). All the studied ethnic populations, except the Moroccan population, had a significant lower mean birth weight than the Dutch population.

In additional analyses we tested the effect of the individual determinants on the observed differences in birth weight between the Dutch and non-Dutch populations.

**Table 2.** Mean birthweight per ethnic population and difference in birthweight compared to the Dutch population.

| | Dutch | Moroccan | Turkish | Cape-verdean | Antillean | Surinamese-creole | Surinamese-hindustani | Surinamese-other |
|---|---|---|---|---|---|---|---|---|
| **Mean birth weight (grams)** | 3485 (555) | 3517 (493) | 3397 (503) | 3227 (543) | 3210 (570) | 3192 (629) | 3061 (541) | 3282 (559) |
| **Difference in birth weight (grams)** | Reference | + 32 (-19, 84) | - 88 (-133, -43) | - 258 (-323, -192) | -274 (-344, -204) | -292 (-366, -218) | -424 (-496, -352) | -203 (-279, -126) |

Values are means (standard deviation) or differences (95% confidence interval).

Maternal and parental height were the most important determinants of the lower birth weight in the non-Dutch populations. The lower gestational age was another important determinant, specifically in the Antillean, Surinamese-creole, Surinamese-hindustani and Surinamese-other populations. Educational level, maternal age and marital status had a smaller, but still significant contribution to the observed differences in birth weight between the Dutch and non-Dutch populations (detailed information available in Appendix).

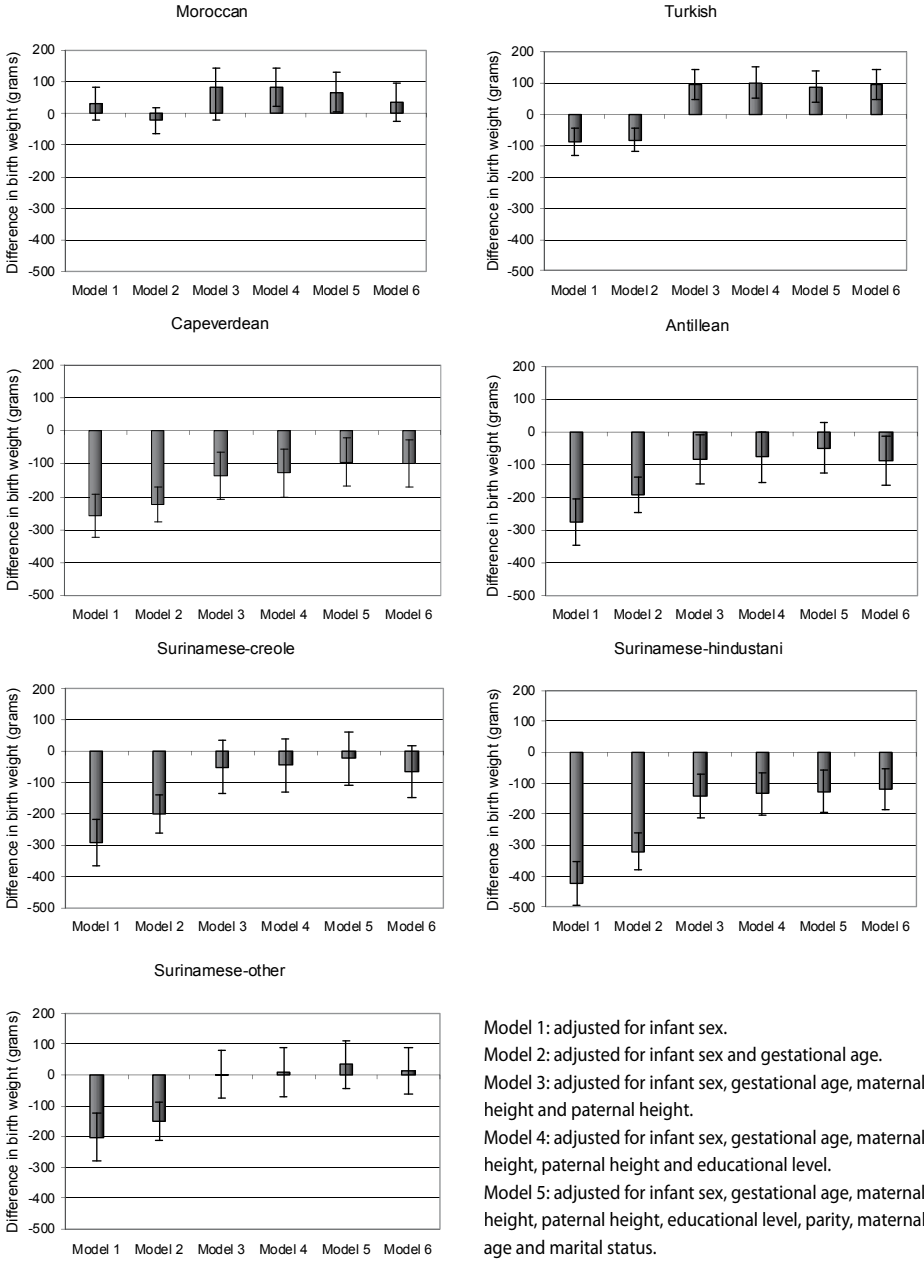
In Figures 1 to 7 the results of the multivariate analyses are shown. The differences in birth weight of the Turkish, Surinamese-creole and Surinamese-other populations compared to the Dutch population became non-significant after adjustment for gestational age, maternal and paternal height (model 3, Figure 2, 5 and 7). After additional adjustment for educational level the difference in birth weight between the Antillean and Dutch population was not significant any more (model 4, Figure 4). When the demographic determinants were added to the model (model 5) a further decrease in birth weight differences was observed in the Capeverdean, Antillean and all Surinamese populations. In the last step, lifestyle related determinants were added to the model (model 6). Differences in birth weight with the Dutch population could only partly be explained in the Capeverdean and Surinamese-hindustani populations (Figure 3 and 6).



## Discussion

Our main finding is that the lower mean birth weight in the non-Dutch populations compared to the Dutch population to a large extent is determined by the shorter gestational age and lower maternal and paternal height in these populations. Educational level, maternal age and marital status had a smaller, but significant, contribution to the differences in birth weight between the Dutch and non-Dutch populations. Differences in birth weight between the Dutch and the Turkish, Antillean, Surinamese-creole and Surinamese-other populations could largely be explained by the observed determinants. However, the differences in birth weight between the Dutch and the Capeverdean and Surinamese-hindustani populations could only be partly understood by the established determinants.

**Figure 1** to 7. Difference in birth weight (grams) of infants of non-Dutch populations compared to infants of Dutch mothers.




Model 1: adjusted for infant sex.
Model 2: adjusted for infant sex and gestational age.
Model 3: adjusted for infant sex, gestational age, maternal height and paternal height.
Model 4: adjusted for infant sex, gestational age, maternal height, paternal height and educational level.
Model 5: adjusted for infant sex, gestational age, maternal height, paternal height, educational level, parity, maternal age and marital status.
Model 6: adjusted for infant sex, gestational age, educational level, maternal height, paternal height, parity, maternal age, marital status, maternal body mass index, maternal smoking and maternal alcohol use.

**Methodological considerations**

The strength of this study is the population-based cohort with a large number of subjects in the studied non-Dutch populations studied from early pregnancy. Questionnaires in different languages were available to allow non-Dutch pregnant women that do not understand the Dutch language well enough, to participate in the Generation R Study (28). Detailed information about a large number of potential determinants was available in this study.

There are some limitations we might have to consider regarding this study. Information on ethnic background of the pregnant woman was missing for 1102 subjects, due to missing data on country of birth of the pregnant woman and her parents. Compared to the offspring of Dutch pregnant women, birth weight in this population was 109 (95% CI: -146, -72) grams lower. The response in the Generation R study is 61%. Selective participation of pregnant women could have influenced the observed mean birth weight of different ethnic populations. We compared birth weights in our study with the Netherlands Perinatal Registry. Although a different definition of ethnic background limited an accurate comparison, we observed no differences in mean birth weight for the Surinamese-creole and Surinamese-hindustani populations (Generation R: 3192 and 3061 grams; Netherlands Perinatal Registry: 3128 and 3043 grams respectively). In contrast, birth weight in offspring of Dutch women differed between the Generation R study and the Netherlands Perinatal Registry (Generation R: 3485 grams; Netherlands Perinatal Registry: 3353 grams respectively). Thus selective participation might have influenced the magnitude of birth weight differences between ethnic populations. However, it is unlikely that this results in a different association between the studied determinants and birth weight in those women in the study and those who are not studied.

We classified the ethnic background of the pregnant women by country of birth of the participating women and their parents. Classification by country of birth has been proposed by Statistics Netherlands as method of choice to classify common ethnic groups in the Netherlands. It is widely applied in national registries and health policy applications. Advantages of this classification are that it is objective and stable over time. However, limitations are that it does not distinguish third generation migrants, does not take into account the heterogeneity of ethnic groups and therefore does not differentiate between ethnic subgroups (like hindustani and creoles). Several other approaches to classify ethnic groups have been proposed in the international literature, including self-classification of ethnicity or race, and classification of the nationality of a subject (33). However, accurate classification of race, ethnicity and nationality is limited because of the subjective nature and can change over time. In additional analyses of our data we compared the magnitude of birth weight differences between ethnic groups based on self-classification with ethnic groups based on the classification by country

of birth. Despite these theoretical differences between both classifications, in our data birth weight differences between ethnic groups were virtually identical.

The associations between ethnic background and birth weight could be affected in the non-Dutch populations because of selection effects. Over 60% of the non-Dutch pregnant women were of first generation. These first generation women will have had relatively good health and their health potential may have contributed to a higher birth weight of their children. Therefore, the healthy migrant effect might have influenced our findings.

We observed only a small effect of lifestyle determinants on ethnic differences in birth weight. This small effect could be because our study did not optimally capture the lifestyle characteristics. The small effect of smoking and alcohol consumption could be due to the use of binary variables for smoking and alcohol consumption. Possibly, residual effects of smoking and alcohol consumption are present and the impact of smoking and alcohol consumption might be more expressive if a more refined classification was available. It could also be that unmeasured lifestyle determinants, such as illicit drug use, physical activity and food habits, can contribute to ethnic differences in birth weight.

We were unable to study several determinants that might be of importance in explaining the differences in birth weight. Data on gestational weight gain and energy intake during pregnancy, two important variables to predict birth weight (34, 35), were not available for present analysis. Also data on blood pressure during pregnancy, pregnancy-interval and pregnancy-related diseases were not available for present analysis.

**Ethnic differences in birth weight**

Our results demonstrated that, compared to the Dutch population, the mean birth weight is lower in all studied non-Dutch populations, except in the Moroccan population. These results are in line with a previous study in the Netherlands (10). Although the mechanisms of these disparities are not well understood, our results suggest that gestational age and parental height most strongly determined the lower birth weight in the non-Dutch populations.

In our study shorter gestational age was of particular importance in the Antillean and all Surinamese populations, which is in line with previous studies in the Netherlands indicating that preterm birth is more frequently seen in the black (mainly Surinamese-creole) and Hindustani populations (36, 37). Also in our study a higher proportion of births were preterm (<37 weeks) in these populations compared to the Dutch population (preterm birth: Antillean 7.8%, Surinamese-creoles 7.6%, Surinamese-hindustani 7.6% and Surinamese-other 6.7% compared to Dutch 5.0%, results not shown). Prevention of preterm births in these populations might therefore reduce birth weight differences. Single motherhood might be associated with several factors that may increase the risk

of preterm births. Single mothers might be exposed to more stress during pregnancy than mothers who have a partner. Maternal stress during pregnancy seems to be associated with preterm birth (38). Besides, single mothers might engage in more risky sexual behaviour, which may lead to a higher prevalence of urogenital infections. Several studies have found associations between urogenital infections and preterm birth (39, 40). These hypotheses need to be elucidated in future studies in order to develop prevention strategies in these populations. Another factor that might influence gestational age at birth and/or the proportion of preterm births in the non-Dutch populations is the use of prenatal care. Several studies have suggested that prenatal care use and gestational age at first visit are associated with gestational age at birth and preterm birth (41, 42). However, complete data about prenatal care use were available only in a small sample of our study population. In this sub-sample we examined whether ethnic differences in gestational age and preterm birth could be explained by differences in prenatal care use. These separate analyses showed that, although ethnic differences in prenatal care use were found, these differences did not affect the ethnic differences in gestational age and preterm birth.

This study showed that maternal and paternal height are important determinants for the lower birth weight in all non-Dutch populations. Several studies have reported an effect of maternal height on birth weight (23, 43). Maternal and paternal height represents a complex conjuncture of genetic and environmental influences, especially long-term dietary intake and nutritional status. The observed shorter height in the non-Dutch populations might reflect the long-term poorer nutritional and living conditions they were exposed to. In a separate analysis, maternal height of second-generation women in our study showed to be significantly taller compared to their first generation counterparts (results not shown). These results indicate that, although height is partly genetically determined, environmental influences might affect the mean height of populations. Reducing the socio-economic and environmental inequalities between ethnic populations could in long-term decrease differences in birth weight. Except for the large effect of maternal height on birth weight, short maternal height is also associated with other unfavourable pregnancy outcomes. Previous studies have reported an increased risk for idiopathic preterm labour, prolonged labour and caesarean delivery in women with short height (44-46).

The socio-demographic determinants maternal age, educational level and marital status had a smaller, but significant contribution in explaining differences in birth weight between ethnic populations. Especially the extremes of these determinants, i.e. teenage motherhood, low educated women and single motherhood, could result in an increased risk of lower birth weight (20, 22, 47). The exact pathways of teenage and single motherhood and low education leading to lower birth weight are unclear. Possible pathways to low birth weight might be less optimal use of prenatal care, more unhealthy behaviours

(drug use, risk full sexual behaviour), more stress and unfavourable material conditions. Further study of these determinants could help to obtain a fuller understanding of the causal pathways.

In our study lifestyle related determinants only had a marginal role in explaining ethnic differences in birth weight. Maternal body mass index at early gestation, which was higher in women with a non-Dutch ethnic background compared to Dutch women, lead to a higher birth weight. However, obesity is also associated with an increased risk of gestational diabetes, pre-eclampsia, caesarean section and neonatal hypoglycaemia (48). Attention to the high body mass index at early gestation in the non-Dutch populations is wanted because of these possible harmful complications. Since maternal smoking during pregnancy is quite equally distributed among the ethnic populations, it does not contribute much to the observed differences in birth weight. Prevention of maternal smoking however remains needed across all populations because of the detrimental prenatal and postnatal effects (49).

**Conclusions**

Our findings suggest that differences in birth weight between ethnic populations can only partly be understood from established determinants of birth weight, and that further study is necessary in order to obtain a fuller understanding. The part that is understood points to the importance of differences in parental height and gestational age. These risk factors are partly determined by genetic factors and cannot easily be modified. In short run only small reductions of differences in birth weight between ethnic populations seem feasible.

## References

1. David RJ, Collins JW, Jr. Differing birth weight among infants of U.S.-born blacks, African-born blacks, and U.S.-born whites. N Engl J Med. 1997 Oct 23;337(17):1209-14.
2. Guendelman S, Buekens P, Blondel B, Kaminski M, Notzon FC, Masuy-Stroobant G. Birth outcomes of immigrant women in the United States, France, and Belgium. Matern Child Health J. 1999 Dec;3(4):177-87.
3. Migone A, Emanuel I, Mueller B, Daling J, Little RE. Gestational duration and birthweight in white, black and mixed-race babies. Paediatr Perinat Epidemiol. 1991 Oct;5(4):378-91.
4. Hessol NA, Fuentes-Afflick E, Bacchetti P. Risk of low birth weight infants among black and white parents. Obstet Gynecol. 1998 Nov;92(5):814-22.
5. MacDorman MF, Minino AM, Strobino DM, Guyer B. Annual summary of vital statistics--2001. Pediatrics. 2002 Dec;110(6):1037-52.
6. Buekens P, Notzon F, Kotelchuck M, Wilcox A. Why do Mexican Americans give birth to few low-birthweight infants? Am J Epidemiol. 2000 Aug 15;152(4):347-51.
7. Fuentes-Afflick E, Lurie P. Low birth weight and Latino ethnicity. Examining the epidemiologic paradox. Arch Pediatr Adolesc Med. 1997 Jul;151(7):665-74.

8. Harding S, Rosato M, Cruickshank J. Lack of change in birthweights of infants by generational status among Indian, Pakistani, Bangladeshi, Black Caribbean, and Black African mothers in a British cohort study. Int J Epidemiol. 2004 December 1, 2004;33(6):1279-85.
9. Doornbos JP, Nordbeck HJ, Van Enk AE, Muller AS, Treffers PE. Differential birthweights and the clinical relevance of birthweight standards in a multiethnic society. Int J Gynaecol Obstet. 1991 Apr; 34(4):319-24.
10. van der Wal MF, Uitenbroek DG, van Buuren S. Birth weight of infants in Amsterdam according to ethnic origin [In Dutch]. Tijdschrift voor Gezondheidswetenschappen. 2000;78:15-20.
11. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J. US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, hispanics, and blacks. Pediatrics. 2003 Jan; 111(1):e61-6.
12. Wilcox AJ, Russell IT. Birthweight and perinatal mortality: II. On weight-specific mortality. Int J Epidemiol. 1983 Sep;12(3):319-25.
13. Barker DJP. Fetal origins of coronary heart disease. BMJ. 1995 July 15, 1995;311(6998):171-4.
14. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ. Birth Weight and Adult Hypertension, Diabetes Mellitus, and Obesity in US Men. Circulation. 1996 December 15, 1996; 94(12):3246-50.
15. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ. 1987;65(5):663-737.
16. Valero De Bernabe J, Soriano T, Albaladejo R, Juarranz M, Calle ME, Martinez D, et al. Risk factors for low birth weight: a review. Eur J Obstet Gynecol Reprod Biol. 2004 Sep 10;116(1):3-15.
17. Wilcox AJ, Skjaerven R. Birth weight and perinatal mortality: the effect of gestational age. Am J Public Health. 1992 Mar;82(3):378-82.
18. Bai J, Wong FW, Bauman A, Mohsin M. Parity and pregnancy outcomes. Am J Obstet Gynecol. 2002 Feb;186(2):274-8.
19. Kramer MS, Seguin L, Lydon J, Goulet L. Socio-economic disparities in pregnancy outcome: why do the poor fare so poorly? Paediatr Perinat Epidemiol. 2000 Jul;14(3):194-210.
20. Raatikainen K, Heiskanen N, Heinonen S. Marriage still protects pregnancy. BJOG. 2005 Oct;112(10): 1411-6.
21. Lee KS, Corpuz M. Teenage pregnancy: trend and impact on rates of low birth weight and fetal, maternal, and neonatal mortality in the United States. Clin Perinatol. 1988 Dec;15(4):929-42.
22. Fraser AM, Brockert JE, Ward RH. Association of young maternal age with adverse reproductive outcomes. N Engl J Med. 1995 Apr 27;332(17):1113-7.
23. Mohanty C, Prasad R, Srikanth Reddy A, Ghosh JK, Singh TB, Das BK. Maternal anthropometry as predictors of low birth weight. J Trop Pediatr. 2006 Feb;52(1):24-9.
24. Cnattingius S, Bergstrom R, Lipworth L, Kramer MS. Prepregnancy weight and the risk of adverse pregnancy outcomes. N Engl J Med. 1998 Jan 15;338(3):147-52.
25. Cliver SP, Goldenberg RL, Cutter GR, Hoffman HJ, Davis RO, Nelson KG. The effect of cigarette smoking on neonatal anthropometric measurements. Obstet Gynecol. 1995 Apr;85(4):625-30.
26. Abel EL, Hannigan JH. 'J-shaped' relationship between drinking during pregnancy and birth weight: reanalysis of prospective epidemiological data. Alcohol Alcohol. 1995 May;30(3):345-55.
27. Hofman A, Jaddoe VW, Mackenbach JP, Moll HA, Snijders RF, Steegers EA, et al. Growth, development and health from early fetal life until young adulthood: the Generation R Study. Paediatr Perinat Epidemiol. 2004 Jan;18(1):61-72.
28. Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, et al. The Generation R Study: Design and cohort profile. Eur J Epidemiol. 2006;21(6):475-84.
29. Statistics Netherlands. Migrants in the Netherlands, 2003. 2003.
30. Tunon K, Eik-Nes SH, Grottum P. A comparison between ultrasound and a reliable last menstrual period as predictors of the day of delivery in 15,000 examinations. Ultrasound Obstet Gynecol. 1996 Sep;8(3):178-85.

31. Sobel ME. Asympotic confidence intervals for indirect effects in structural equation models. Sociological Methodology. 1982;12:290-312.
32. Victora CG, Huttly SR, Fuchs SC, Olinto MT. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. Int J Epidemiol. 1997 Feb;26(1):224-7.
33. Senior PA, Bhopal R. Ethnicity as a variable in epidemiological research. Bmj. 1994 Jul 30;309(6950): 327-30.
34. Rode L, Hegaard HK, Kjaergaard H, Moller LF, Tabor A, Ottesen B. Association between maternal weight gain and birth weight. Obstet Gynecol. 2007 Jun;109(6):1309-15.
35. Shapiro C, Sutija VG, Bush J. Effect of maternal weight gain on infant birth weight. J Perinat Med. 2000;28(6):428-31.
36. Schulpen TW, van Steenbergen JE, van Driel HF. Influences of ethnicity on perinatal and child mortality in the Netherlands. Arch Dis Child. 2001 Mar;84(3):222-6.
37. van Enk A, Buitendijk SE, van der Pal KM, van Enk WJ, Schulpen TW. Perinatal death in ethnic minorities in The Netherlands. J Epidemiol Community Health. 1998 Nov;52(11):735-9.
38. Dole N, Savitz DA, Hertz-Picciotto I, Siega-Riz AM, McMahon MJ, Buekens P. Maternal stress and preterm birth. Am J Epidemiol. 2003 Jan 1;157(1):14-24.
39. Andrews WW, Klebanoff MA, Thom EA, Hauth JC, Carey JC, Meis PJ, et al. Midpregnancy genitourinary tract infection with Chlamydia trachomatis: association with subsequent preterm delivery in women with bacterial vaginosis and Trichomonas vaginalis. Am J Obstet Gynecol. 2006 Feb;194(2): 493-500.
40. Hillier SL, Nugent RP, Eschenbach DA, Krohn MA, Gibbs RS, Martin DH, et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group. N Engl J Med. 1995 Dec 28;333(26):1737-42.
41. Miranda JA, Herruzo AJ, Mozas J, Calderon MA, Aguera J, Biel E, et al. Influence of obstetric and perinatal care on perinatal mortality. Eur J Obstet Gynecol Reprod Biol. 1996 Aug;67(2):103-7.
42. Vintzileos AM, Ananth CV, Smulian JC, Scorza WE, Knuppel RA. The impact of prenatal care in the United States on preterm births in the presence and absence of antenatal high-risk conditions. Am J Obstet Gynecol. 2002 Nov;187(5):1254-7.
43. Abrams B, Newman V. Small-for-gestational-age birth: maternal predictors and comparison with risk factors of spontaneous preterm delivery in the same cohort. Am J Obstet Gynecol. 1991 Mar; 164(3):785-90.
44. Maternal anthropometry for prediction of pregnancy outcomes: memorandum from a USAID/WHO/ PAHO/MotherCare meeting. Bull World Health Organ. 1991;69(5):523-32.
45. Kramer MS, Coates AL, Michoud MC, Dagenais S, Hamilton EF, Papageorgiou A. Maternal anthropometry and idiopathic preterm labor. Obstet Gynecol. 1995 Nov;86(5):744-8.
46. Witter FR, Caulfield LE, Stoltzfus RJ. Influence of maternal anthropometric status and birth weight on the risk of cesarean delivery. Obstet Gynecol. 1995 Jun;85(6):947-51.
47. Millar WJ, Chen J. Maternal education and risk factors for small-for-gestational-age births. Health Rep. 1998 Autumn;10(2):43-51 (Eng); 47-56 (Fre).
48. Baeten JM, Bukusi EA, Lambe M. Pregnancy complications and outcomes among overweight and obese nulliparous women. Am J Public Health. 2001 Mar;91(3):436-40.
49. Hofhuis W, de Jongste JC, Merkus PJFM. Adverse health effects of prenatal and postnatal tobacco smoke exposure on children. Arch Dis Child. 2003 December 1, 2003;88(12):1086-90.

***Appendix. Difference and change in difference of birth weight (grams) of infants of ethnic minority populations compared to infants of Dutch mothers after adjustment for separate determinants.***

| | Moroccan | Turkish | Capeverdean | Antillean | Surinamese-creoles | Surinamese-hindustani | Surinamese-other |
|---|---|---|---|---|---|---|---|
| Basic model (BM) | 30 (-21, 82) | -89 (-134, -44) | -254 (-318, -189) | -273 (-342, -203) | -298 (-372, -225) | -423 (-495, -351) | -205 (-281, -129) |
| BM + gestational age | -22 (-64, 20) | -82 (-118, -45) | -223 (-276, -171) | -192 (-248, -136) | -200 (-259, -140) | -321 (-379, -262) | -150 (-212, -89) |
| change in birth weight | -52 | +7 | +31 | *+81 ** | *+98 ** | *+102 ** | *+55 ** |
| BM + maternal height | 166 (114, 219) | 68 (21, 115) | -153 (-218, -89) | -169 (-238, -101) | -220 (-292, -147) | -238 (-311, -147) | -103 (-178, -27) |
| change in birth weight | *+136 ** | *+157 ** | *+100 ** | *+104 ** | *+78 ** | *+185 ** | *+102 ** |
| BM + paternal height [a] | 78 (4, 152) | -2 (-59, 56) | -215 (-303, -126) | -187 (-282, -92) | -182 (-288, -77) | -330 (-414, -246) | -123 (-220, -27) |
| change in birth weight | +48 | *+87 ** | +39 | *+86 ** | *+116 ** | *+93 ** | *+82 ** |
| BM + educational level | 73 (20, 127) | -45 (-92, 2) | -208 (-274, -142) | -231 (-302, -161) | -259 (-333, -185) | -382 (-455, -309) | -166 (-242, -89) |
| change in birth weight | *+43 ** | *+44 ** | *+46 ** | *+42 ** | *+39 ** | *+41 ** | *+39 ** |
| BM + maternal age | 60 (8, 112) | -57 (-103, -11) | -214 (-279, -149) | -228 (-298, -158) | -264 (-337, -190) | -394 (-466, -322) | -163 (-240, -87) |
| change in birth weight | *+30 ** | *+32 ** | *+40 ** | *+45 ** | *+34 ** | *+29 ** | *+42 ** |
| BM + marital status | -3 (-56, 50) | -117 (-163, -70) | -178 (-245, -112) | -200 (-271, -129) | -222 (-297, -146) | -402 (-473, -330) | -143 (-220, -66) |
| change in birth weight | *-33 ** | *-28 ** | *+75 ** | *+73 ** | *+77 ** | *+21 ** | *+62 ** |
| BM + parity | -7 (-58, 44) | -115 (-159, -70) | -256 (-320, -193) | -275 (-344, -207) | -309 (-382, -237) | -429 (-500, -358) | -205 (-280, -130) |
| change in birth weight | *-37 ** | *-26 ** | -2 | -2 | -11 | -6 | 0 |
| BM + maternal BMI | -11 (-62, 41) | -124 (-169, -79) | -262 (-326, -198) | -312 (-381, -243) | -333 (-405, -260) | -421 (-492, -350) | -227 (-303, -152) |
| change in birth weight | *-41 ** | *-35 ** | -8 | *-40 ** | *-35 ** | +2 | *-22 ** |
| BM + maternal smoking | 6 (-46, 57) | -61 (-105, -16) | -244 (-308, -180) | -266 (-335, -198) | -295 (-368, -222) | -429 (-500, -357) | -186 (-262, -111) |
| change in birth weight | *-24 ** | *+28 ** | +10 | +7 | +3 | -6 | *+19 ** |
| BM + maternal alcohol consumption | 52 (-1, 105) | -70 (-116, -23) | -243 (-307, -178) | -260 (-329, -191) | -289 (-362, -215) | -404 (-476, -331) | -192 (-268, -116) |
| change in birth weight | +22 * | +19 * | *+10 ** | *+13 ** | +9 * | *+19 ** | *+13 ** |

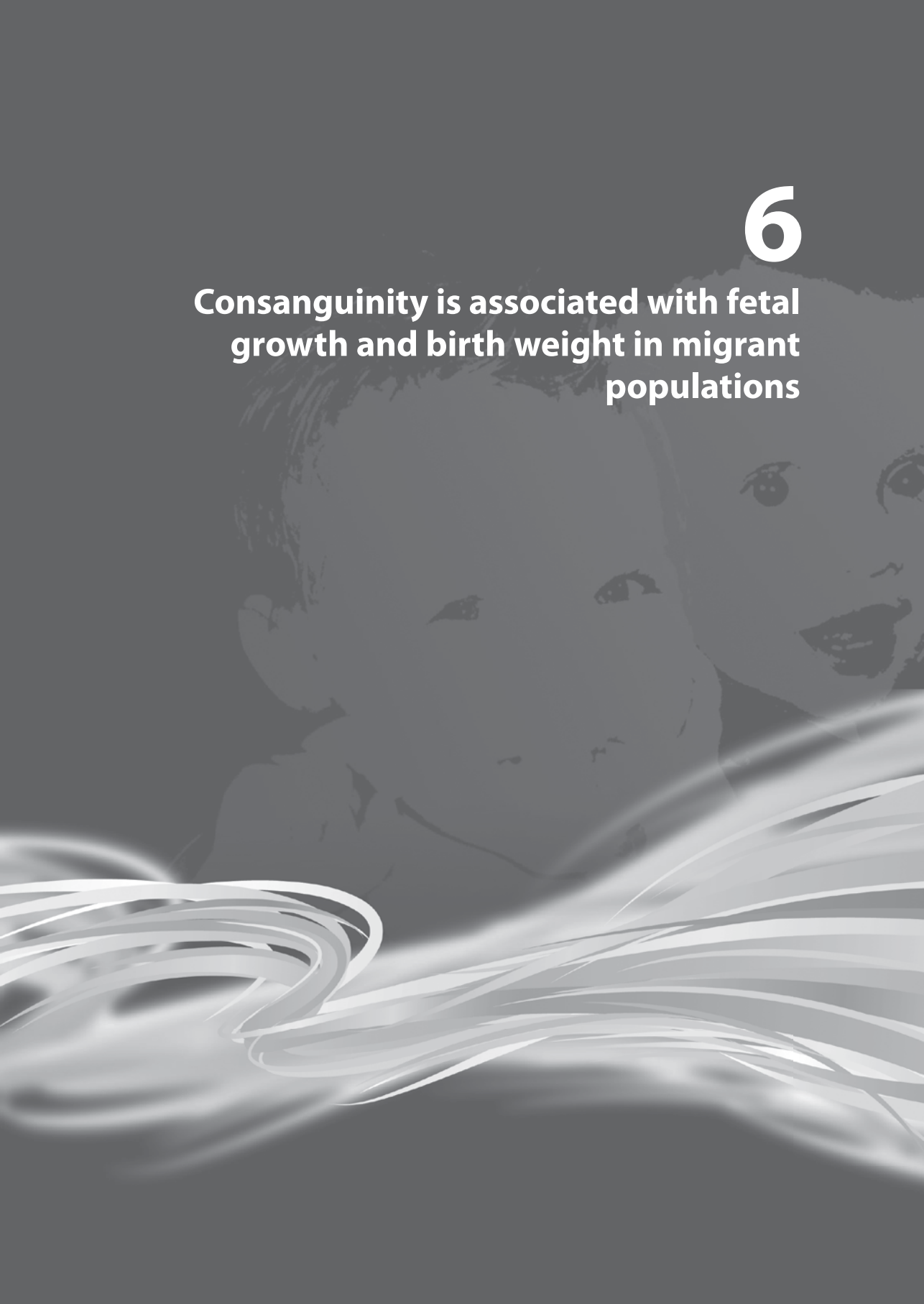
Basic model: adjusted for infant sex

[a] n = 4471

* $p < 0.05$, significant change in the difference in birth weight.

# 6

# Consanguinity is associated with fetal growth and birth weight in migrant populations



## Abstract

*Objective:* We examined the effects of consanguinity on fetal growth and birth weight in Turkish and Moroccan populations.

*Methods:* This study is embedded in the Generation R study, a population-based prospective cohort study. Analyses were performed among subjects with a Turkish and Moroccan ethnic background. We examined the associations of consanguinity with birth outcomes (birth weight, low birth weight, macrosomia) and with repeatedly measured growth characteristics (head circumference, abdominal circumference, femur length and fetal growth).

*Results:* Consanguinity of the pregnant women was associated with a higher mean birth weight in their offspring compared to the mean birth weight in offspring of non-consanguineous women (72 grams, 95% CI: 12, 132). The risk of macrosomia, defined as birth weight above the 95th percentile, was non-significantly higher in the offspring of consanguineous women compared to non-consanguineous women (OR 1.6, 95% CI: 0.8, 3.2). Consanguinity was associated with an accelerated fetal growth in weight (difference 3.7 grams/week, 95% CI: 0.6, 6.7) and with an accelerated growth in fetal abdominal circumference (difference 0.21 mm/week, 95% CI: 0.03, 0.39). Consanguinity was not statistically significant associated with growth differences in fetal head circumference and femur length.

*Conclusions:* Our findings suggest that in our population consanguinity is associated with an increase in mean birth weight and an accelerated fetal abdominal circumference growth. This may be related to specific selection factors, or to genetic, immunological and social factors linked to consanguinity. The over-all health consequences of these findings remain to be elucidated in future studies.

## Introduction

Previous research has shown that Moroccan and Turkish populations in the Netherlands have a higher perinatal and infant mortality rate and a higher incidence of (inherited) congenital disorders (1-4). These observations may be partly related to the lower socio-economic status in these populations, and to the higher frequency of teenage pregnancies and grande multiparity (1, 3). It has also been suggested that consanguinity, the marriage between relatives, may be one additional risk factor that could be of importance. Consanguinity is relatively common in Turkish and Moroccan populations in the Netherlands, although exact figures are lacking.

Consanguinity has been shown to be a risk factor for perinatal and infant mortality and is also associated with congenital abnormalities and other birth defects (5-12). Since birth weight is a strong determinant of perinatal and infant mortality, the increased risk of perinatal and infant mortality in offspring of consanguineous couples might be mediated by a change in the birth weight distribution. There are indications that birth weight might be affected by consanguinity, although results of previous studies are non-conclusive. Some studies found no association between consanguinity and birth weight (13-17), while other studies found a significant reduction in birth weight (18-20). Since the primary reason for consanguineous marriage is social, consanguineous pregnant women might receive more social support and have less stress during pregnancy than non-consanguineous pregnant women. Therefore, there could also be positive effects of consanguinity on birth weight, as it has been suggested that these factors affect pregnancy outcomes (21, 22).

Previous studies on the association of consanguinity with birth weight were unable to take into account several potential confounders. There are important confounders, like socio-economic status, gestational age, maternal age and parity that might explain differences in birth weight in the offspring between consanguineous and non-consanguineous parents. Additionally, these previous studied did not assess the effects of consanguinity on fetal growth during pregnancy. Birth weight is only a proxy for fetal growth and an inappropriate measure for assessing adverse effects of consanguinity on fetal growth and development. This may be relevant for identifying specific fetal growth patterns.

The Generation R Study is a multi-ethnic, population-based cohort study, in which detailed information about fetal growth and a large amount of potential confounders is available. Within the Generation R Study we examined the effect of consanguinity on fetal growth and birth weight in Turkish and Moroccan populations, in which consanguinity is most frequent.

## Methods

### Design

This study is embedded in the Generation R study, a population-based prospective cohort study from fetal life until young adulthood. The Generation R Study is designed to identify early environmental and genetic determinants of growth, development and health in fetal life, childhood and adulthood and has been described previously in detail (23, 24). Briefly, all pregnant women and their partners in a previously defined area in Rotterdam, the Netherlands, were approached, either by community midwife or hospital based Generation R staff, at their first antenatal visit. Most women spoke Dutch and if otherwise, the study was explained and questionnaires were available in their own language. In total, 9,778 women participated, of which 8,880 enrolled during pregnancy and 898 at birth of their child. All participating women had a delivery date between April 2002 and January 2006. Data in pregnancy were collected from physical examinations, fetal ultrasounds and questionnaires. Women were usually seen for the first time before the 18th week of the pregnancy and in total three times during pregnancy, in early- (gestational age < 18 weeks), mid- (gestational age 18 - 25 weeks) and late pregnancy (gestational age ≥ 25 weeks) in a research setting. The individual time scheme of these assessments depended on the specific gestational age at enrolment. Of all eligible children in the study area, 61% participated at birth (24). The Medical Ethics Committee of the Erasmus Medical Center approved the Generation R Study. Written informed consent was obtained from all participants.



### Consanguinity

Information on consanguinity was obtained from pregnant women by questionnaire. The response rate for this questionnaire was 91%. Consanguinity was assessed by asking whether the biological father of the baby was a blood relative of the pregnant woman (no; yes, first cousin; yes, second cousin; other, namely). Answers from the category 'other, namely' were reclassified as 'no', 'yes, first cousin' or 'yes, second cousin' depending on the answer. If the answer did not make clear the blood relationship between parents, the pregnant woman was classified in the category 'no'. Finally, these answer categories were combined and consanguinity was classified into two categories: consanguineous for first or second-cousin relations, and non-consanguineous.

### Fetal growth and birth weight

Fetal ultrasound examinations were carried out at the visits at one of the research centers in early-, mid- and late pregnancy. These fetal ultrasound examinations were used for both establishing gestational age and assessing fetal growth characteristics (25). Gestational age was established by ultrasound examination until the 24th week of

gestational age (95 % of the pregnant women). After 24 weeks the last menstrual period was used for pregnancy dating. Fetal growth measurements used for the present study included head circumference, abdominal circumference and femur length measured in mid and late pregnancy. Early pregnancy was not included since these fetal ultrasound examinations were primarily used to establish gestational age. Fetal growth was established by the use of information on estimated fetal weight in mid and late pregnancy and birth weight. Estimated fetal weight was calculated by Hadlock's formula using head circumference, abdominal circumference and femur length, all measured to the nearest millimetre (26).

Information on birth weight was obtained from community midwifery and hospital registries. Birth weight was established directly postpartum and expressed in grams. Low birth weight was defined as birth weight below the 5th percentile of the birth weight distribution of the population for analysis (below 2670 grams). Macrosomia was defined as birth weight above the 95th percentile of the birth weight distribution of the population for analysis (above 4270 grams).

**Covariates**

Information about maternal age, marital status, educational level, and parity was obtained by questionnaires. Information on pre-eclampsia, gestational hypertension and gestational diabetes was retrieved from the medical records of the participating women. Ethnic background of the participating pregnant woman was assessed by the country of birth of the woman herself and her parents. Information about countries of birth was obtained by questionnaire. The participating pregnant woman was of non-Dutch ethnic origin if one of her parents was born abroad (27). If both parents were born abroad, the country of birth of the participant's mother decided on the ethnic background. Generational status of the non-Dutch pregnant women was classified as: 1) first generation, for non-Dutch women who were born outside the Netherlands; 2) second-generation, for non-Dutch women who were born in the Netherlands. Maternal height and weight were measured without shoes and heavy clothing at time of enrolment. Maternal body mass index was calculated from maternal weight and maternal height (weight/height$^2$ (kg/m$^2$)).

**Population for analysis**

For the present analyses, we selected all prenatal enrolled women with a Turkish or Moroccan ethnic background (n=1220). Women with missing data on consanguinity (n=94) were excluded from analyses. Analyses focusing on birth weight were carried out in 1103 women due to missing data on birth weight (n=13) and exclusion of intrauterine deaths (n=9) and induced abortion (n=1).

**Data analyses**

The differences in baseline characteristics between consanguineous and non-consanguineous population were determined by the chi-square statistic for categorical variables and analysis of variants for continuous variables. Linear regression analyses were used to examine the associations of consanguinity with continuously measured birth weight. To assess the significance of consanguinity in high-risk pregnancy outcomes, we studied with multivariable logistic regression analyses the association of consanguinity with low birth weight and macrosomia. These linear and logistic regressions were adjusted for socio-demographic, anthropometrical, lifestyle and obstetric related variables (gestational age at birth, educational level, marital status, maternal age, parity, maternal height, maternal smoking, body mass index, pre-eclampsia, gestational hypertension, gestational diabetes). Although the number of infants with low birth weight and macrosomia is not optimal for adjusting for all covariates in the regression analyses, we choose to use the same models (models A, B and C) for linear and logistic regression analyses. When we selected variables for adjustment in the logistic regression analyses the results were virtually identical to the models used in analyses.

The associations between consanguinity and repeatedly measured parameters of fetal growth (estimated fetal weight, head circumference, biparietal diameter, abdominal circumference) were analyzed using longitudinal multilevel analysis to account for the dependency between measurements in the same subject. Royston has shown to apply a particular type of statistical model to longitudinal data to produce growth centiles. (28) The best fitting model as with the outcome as a function of gestational age was constructed using fractional polynomials (29). This approach of multilevel modeling was used in the Generation R Study and is described by Verburg et al. (25). Consanguinity as main determinant was brought into the model. The final curve was fitted with random effects for both intercept and gestational age. The interaction term of consanguinity with gestational age was included to compare the slope of the curves between the non-consanguineous and consanguineous subjects. When this interaction term did not result in a significant improvement of the model (evaluated by comparing –2 log likelihood of the model with the interaction term to the –2 log likelihood of the model without the interaction term), the term was left out in further analyses.

The best-fitting following models were the following:

Head circumference = $\beta 0 + \beta 1$*consanguinity + $\beta 2$*gestational age$^2$ + $\beta 3$*gestational age$^2$*ln(gestational age) + $\beta 4$*consanguinity*gestational age.

Femur length = $\beta 0 + \beta 1$*consanguinity + $\beta 2$*gestational age + $\beta 3$*gestational age$^3$ + $\beta 4$*consanguinity*gestational age

Estimated fetal growth = β0 + β1*consanguinity + β2*gestational age + β3*gestational age$^2$*ln(gestational age) + β4*consanguinity*gestational age.

The model structure for abdominal circumference was similar as the model for head circumference. In these models, 'β0 + β1*consanguinity' reflects the intercept and the terms including 'β2' and 'β3' reflect the slope of growth per week. Terms including 'β4' reflect the differences in growth between non-consanguineous and consanguineous subjects. All models were additionally controlled for socio-demographic, anthropometrical, lifestyle and obstetrical determinants of fetal growth.

All measures of association are presented with their 95 % confidence intervals (CI). The statistical analyses were performed using Statistical Package of Social Sciences version 11.0 for Windows (SPSS Inc, Chicago, IL, USA) and the Statistical Analysis System version 8.2 (SAS, Stata Corporation, College station, TX, USA).

## Results

Characteristics of the non-consanguineous and consanguineous pregnant women are presented in table 1. Of the 1126 pregnant women available for analyses, 237 women (21.0%) were classified as consanguineous. Compared to non-consanguineous women, consanguineous pregnant women were on average shorter of height (p-value 0.01), had an higher mean body mass index above 25 kg/m2 (p-value = 0.05), were lower educated (p-value < 0.001), more likely to be married (p-value < 0.001), more frequent of first generation (p-value < 0.001) and more frequent multiparous (p-value < 0.001).

The associations between consanguinity and birth weight are shown in table 2. Consanguinity of the pregnant women was associated with a higher mean birth weight in their offspring compared to the mean birth weight in offspring of non-consanguineous women (119 grams (95% CI: 58, 180)). This difference remained significantly after controlling for potential confounders (72 (95% CI: 12, 132)). The odds ratio of low birth weight (birth weight < 5th percentile) did not differ between offspring of consanguineous and those of non-consanguineous women (OR 1.1 (95% CI: 0.4, 2.9)). The odds ratio of macrosomia (birth weight > 95th percentile) was non-significantly higher in the offspring of consanguineous women compared to non-consanguineous women (OR 1.6 (95% CI: 0.8, 3.2)).

The associations between consanguinity and longitudinally measured fetal growth characteristics are presented in table 3. Compared to non-consanguineous women, consanguinity was associated with accelerated estimated fetal growth in weight in offspring (difference 3.7 grams/week (95% CI: 0.6, 6.7). Consanguinity was associated with a significant difference in abdominal circumference growth (0.21 mm/week, 95% CI: 0.03,

**Table 1.** Characteristics in consanguineous and non-consanguineous pregnant women with Turkish or Moroccan ethnic background.

| | Non-consanguineous | Consanguineous | p-value |
|---|---|---|---|
| | N = 889 | N = 237 | |
| Ethnicity (%) | | | p = 0.33 |
| *Turkish* | 57.3 | 60.8 | |
| *Moroccan* | 42.7 | 39.2 | |
| Age (years) | 27.4 (5.1) | 27.5 (5.1) | p = 0.81 |
| Height (cm) | 162.5 (5.7) | 161.2 (5.7) | p = 0.01 |
| Body mass index (kg/m$^2$) | 26.1 (4.8) | 27.4 (5.3) | p = 0.01 |
| Education (%) | | | p < 0.001 |
| *Primary* | 27.3 | 34.2 | |
| *Secondary* | 53.7 | 44.3 | |
| *High education* | 13.8 | 8.0 | |
| *Missing* | 5.2 | 13.5 | |
| Marital status (%) | | | p < 0.001 |
| *Married* | 86.2 | 94.5 | |
| *Unmarried* | 11.1 | 2.1 | |
| *Missing* | 2.7 | 3.4 | |
| Generation (%) | | | p < 0.001 |
| *First* | 67.4 | 80.2 | |
| *Second* | 31.3 | 15.6 | |
| *Unknown* | 1.3 | 4.2 | |
| Parity | | | p < 0.001 |
| *0* | 46.2 | 33.3 | |
| *>= 1* | 53.8 | 66.7 | |
| Smoking in pregnancy (%) | | | p = 0.10 |
| *Non-smoker* | 75.7 | 81.9 | |
| *Smoker* | 20.9 | 16.5 | |
| *Missing* | 3.4 | 1.7 | |
| Pre-eclampsia (%) | | | p = 0.12 |
| *No* | 96.6 | 95.8 | |
| *Yes* | 1.8 | 0.8 | |
| *Missing* | 1.6 | 3.4 | |
| Gestational hypertension (%) | | | p = 0.12 |
| *No* | 97.2 | 94.5 | |
| *Yes* | 1.2 | 2.1 | |
| *Missing* | 1.6 | 3.4 | |
| Gestational diabetes (%) | | | p = 0.25 |
| *No* | 95.1 | 93.2 | |
| *Yes* | 1.1 | 2.5 | |
| *Missing* | 3.8 | 4.2 | |
| Birth weight (grams) | 3427 (871) | 3545 (543) | p = 0.002 |
| Low birth weight (%) | 4.9 | 4.3 | p = 0.69 |
| Macrosomia (%) | 4.2 | 7.3 | p = 0.05 |

Values are means (standard deviation) or percentages.

P-value is result of Chi-square test.

**Table 2.** Associations between consanguinity and birth weight in the Turkish and Moroccan populations.

| | Difference in birth weight (grams) and 95 % CI | | |
|---|---|---|---|
| **Birth weight** | Model A | Model B | Model C |
| Non-consanguineous | *Reference* | *Reference* | *Reference* |
| Consanguineous | 119 (58, 180)** | 89 (28, 150)* | 72 (12, 132)* |
| | **Odds ratio (95% CI)** | | |
| **Low birth weight (< 5th percentile)** | Model A | Model B | Model C |
| Non-consanguineous | *Reference* | *Reference* | *Reference* |
| Consanguineous | 0.8 (0.3, 2.1) | 1.0 (0.4, 2.5) | 1.1 (0.4, 2.9) |
| | **Odds ratio (95% CI)** | | |
| **Macrosomia (> 95th percentile)** | Model A | Model B | Model C |
| Non-consanguineous | *Reference* | *Reference* | *Reference* |
| Consanguineous | 1.8 (1.0, 3.4)* | 1.8 (1.0, 3.5) | 1.6 (0.8, 3.2) |

Model A: adjusted for gestational age at birth;
Model B: adjusted for gestational age at birth, educational level, marital status, maternal age, parity and maternal height.
Model C: adjusted for gestational age at birth, educational level, marital status, maternal age, parity, maternal height, maternal smoking, body mass index, pre-eclampsia, gestational hypertension and gestational diabetes.
* p-value < 0.05, ** p-value < 0.01
CI = confidence interval

0.39), but was not associated with statistically significant growth differences in head circumference and femur length.

## Discussion

In our study we found a positive association between consanguinity and birth weight. Consanguinity was associated with a higher mean birth weight in their offspring. We observed a non-significant increased rate of macrosomic infants born to consanguineous women. The accelerated fetal growth in the offspring of consanguineous couples was mainly explained by an accelerated growth of the abdominal circumference. No associations were observed between consanguinity and other fetal growth characteristics.

### Methodological considerations

The strengths of this study are the prospective population-based design and the repeated measurements of fetal growth parameters during pregnancy. Therefore we were able to examine the associations of consanguinity with fetal growth characteristics. More important, in the present study we had information on numerous variables

**Table 3.** Associations between consanguinity and fetal growth parameters in the Turkish and Moroccan populations.

| | **Difference in estimated fetal growth (grams/week)** | | |
|---|---|---|---|
| | Model A | Model B | Model C |
| Non-consanguineous | *Reference* | *Reference* | *Reference* |
| Consanguineous | 5.6 (2.4, 8.7)** | 4.1 (1.0, 7.2)* | 3.7 (0.6, 6.7)* |
| | **Difference in head circumference growth (mm/week)** | | |
| | Model A | Model B | Model C |
| Non-consanguineous | *Reference* | *Reference* | *Reference* |
| Consanguineous | 0.11 (-0.02, 0.23) | 0.08 (-0.05, 0.20) | 0.07 (-0.06, 0.20) |
| | **Difference in abdominal circumference growth (mm/week)** | | |
| | Model A | Model B | Model C |
| Non-consanguineous | *Reference* | *Reference* | *Reference* |
| Consanguineous | 0.29 (0.11, 0.47)* | 0.22 (0.04, 0.40)* | 0.21 (0.03, 0.39)* |
| | **Difference in femur length growth (mm/week)** | | |
| | Model A | Model B | Model C |
| Non-consanguineous | *Reference* | *Reference* | *Reference* |
| Consanguineous | 0.02 (-0.01, 0.05) | 0.02 (-0.01, 0.05) | 0.02 (-0.01, 0.05) |

Model A: adjusted for gestational age at birth;
Model B: adjusted for gestational age at birth, educational level, marital status, maternal age, parity and maternal height.
Model C: adjusted for gestational age at birth, educational level, marital status, maternal age, parity, maternal height, maternal smoking, body mass index, pre-eclampsia, gestational hypertension and gestational diabetes.
* p-value < 0.05, ** p-value < 0.01



that may confound the association between consanguinity and fetal growth or birth weight.

However, some methodological issues need to be considered. Most previous studies on consanguinity and birth weight were carried out in consanguineous populations in their country of origin. We did not found studies that examined the association of consanguinity with birth weight in migrant populations. There are only a few studies that have examined the associations between consanguinity and birth defects and infant mortality in migrant populations (9, 30, 31). The associations between consanguinity and birth weight could be different in migrant populations because of selection effects or changes in health behavior. In our data, we observed that consanguineous pregnant women are more likely to be of first generation compared to non-consanguineous pregnant women. These women will have had relatively good health and their health potential may have contributed to the higher birth weight of their children. Therefore, selective migration of Turkish and Moroccan women to the Netherlands might have influenced our findings. To examine the possibility of selection effects, we examined the self-reported health of the consanguineous and non-consanguineous women. We did

not observe consistent differences in self-reported health that could indicate that selective migration is involved in our study population. However, selective migration could not be ruled out and should be considered by interpreting the results.

Our study was lacking information on congenital disorders that might have influenced our findings. A previous study by Schulpen et al. showed that the proportion of hereditary causes of death, especially autosomal recessive disorders, is four to five times higher in the Turkish and Moroccan populations (2). There is no information of a single gene disorder that might segregate in these populations. However, it is well known that consanguinity is associated with autosomal recessive disorders and therefore we cannot exclude that a higher proportion of congenital disorders in the consanguineous population have influenced our findings.

Underreporting or misclassification of consanguinity could be present. Information of consanguinity was missing in 94 cases (7.7 %). Birth weight in the offspring of these women was 15 (95% CI: -124, 94) grams lower than in the offspring of non-consanguineous women. The percentage of consanguineous women may be higher among those with missing information on consanguinity than among the women included in the present analysis. This may have lead to some overestimation of the estimated effects of consanguinity on fetal growth and birth weight.

In the analyses, consanguineous relation of first and second cousins were combined into one category. This was done to increase the number of consanguineous couples and to increase the power of the analyses. As a consequence, information on the associations of first cousin or second cousin relationship with birth weight is lost. Compared to offspring of non-consanguineous couples, birth weight was higher both in offspring of consanguineous relations of first cousins (86 grams, 95% CI: -7, 179) and in offspring of second-cousins (165 grams 95% CI: 58, 272). This indicates that the positive association with birth weight was observed in all consanguineous relations.

Finally, we did not distinguish the Turkish and Moroccan population in the analyses. The Turkish and Moroccan populations have some migration, social and cultural characteristics in common, which in our opinion makes the clustering of the two populations acceptable. Both the Turkish and Moroccan populations came to the Netherlands as migrant laborers in the 1970s, mainly live in deprived areas, have a low socio-economic status, healthy diet and experience language problems. Besides, in the analyses we tested for the interaction of ethnic background with consanguinity to examine if the association of consanguinity with birth weight differed according to ethnic background. Since the interaction-term was not significant (p-value 0.25) we did not perform stratified analyses on fetal growth and birth weight.

**Birth weight and fetal growth**

In our study we found a higher mean birth weight in the offspring of consanguineous couples compared to non-consanguineous couples. In the literature, there is no agreement on the effect of consanguinity on birth weight. Some previous studies reported that consanguinity was associated with a significant reduction in birth weight (13-17), while other studies did not detect any relation between consanguinity and birth weight (18-20). Our study found a positive association between consanguinity and birth weight. In order to clarify this unexpected finding, possible hypotheses to explain the higher birth weight might be situated in genetic, immunological and/or socio-cultural factors.

Since an important determinant of fetal growth is genetic constitution, variations in genotypes between consanguineous and non-consanguineous populations may account for the observed higher birth weight in the offspring of consanguineous couples. It is well known that the offspring of consanguineous couples is at increased risk for genetic disorders because of the expression of autosomal recessive gene mutations (32). It could be possible that the close biological relationship between parents leads to the probability that their offspring inherit copies of recessive genes responsible for a favorable fetal growth. Since insulin is the most important fetal growth hormone, genetic variance of the insulin gene and its receptor may account for the higher birth weight. Genetic variance of the insulin gene and its receptor has been observed (33). In our data we found a non-significant higher rate of gestational diabetes among consanguineous pregnant women compared to non-consanguineous pregnant women (2.5% versus 1.1%, respectively, p-value=0.24). Possibly, there is increased maternal insulin resistance due to pooling of specific genotypes among consanguineous couples. Further studies are necessary to elucidate this hypothesis.

Secondly, we presumed about an immunological explanation for the higher birth weight in the offspring of consanguineous couples. During pregnancy a women is exposed to paternal antigens, which could lead to adverse immune responses, as observed in pre-eclampsia. It might be that in consanguineous couples, fetal/maternal incompatibility by the expression of paternal antigens is less frequent. In our data we observed a non-significant lower frequency of pre-eclampsia among consanguineous pregnant women compared to non-consanguineous pregnant women (0.8% versus 1.8%, respectively, p-value = 0.12). This might indicate that a more optimal intrauterine environment is present in consanguineous couples, which enhances the growth potential of the fetus.

Finally, consanguineous marriages serve important social, cultural and economic functions, which may have positive consequences for health outcomes in their offspring. The actual reasons given for the preference for consanguineous marriage are primarily social. It is believed that family ties will be strengthened, and health or financial uncertainties that may arise through marriage with a partner from a distant family or com-

munity are simultaneously avoided (34). A stronger social coherence of consanguineous couples might result in less emotional stress and more social support. It has been suggested that these factors affect pregnancy outcomes and consanguineous pregnant women might benefit from this (21, 22). This might contribute to the higher mean birth weight in the offspring of consanguineous women.

Besides the higher mean birth weight in the offspring of consanguineous couples, we observed a non-significant positive association of consanguinity with macrosomia. However, it is not clear whether the higher mean birth weight and the higher rate of macrosomia among the offspring of consanguineous couples may have health consequences, like an increased risk of perinatal and infant mortality. To get some notion of the effect of the higher mean birth weight and the increased odds of macrosomia on infant mortality, we estimated the neonatal mortality rates among the offspring of consanguineous and non-consanguineous couples. In these separate analyses we calculated the neonatal mortality rate for the offspring of consanguineous couples and non-consanguineous couples by using birth weight specific neonatal mortality rates from literature (35, 36). With these data we estimated neonatal mortality rates for the offspring of consanguineous population (total neonatal mortality rates 1.0/1000 live births (35)) that were lower compared to rates in the non-consanguineous population (total neonatal mortality rates 1.4/1000 live births (35)). These findings suggest that the higher average birth weight, including the higher prevalence of macrosomia, among the offspring of consanguineous couples may have a net beneficial effect on their risk of neonatal mortality. However, macrosomia is a significant risk factor for shoulder dystocia, brachial palsy and maternal and perinatal complications (37-40). Moreover, macrosomia could also have long-term consequences. The newborn with macrosomia is more likely to become an overweight adolescent (41). There are indications that increasing birth weight is associated with childhood cancers and blood pressure (42, 43). Therefore, the net effects of the higher mean birth weight and increased rate of macrosomia on health outcomes in these populations remain to be elucidated.

We demonstrated that consanguinity was associated with an increase in growth of abdominal circumference. This finding is in line with the observed higher birth weight and increased odds ratio for macrosomia in the consanguineous population. The abdominal circumference is the most useful dimension to evaluate fetal growth and is a sensitive indicator of accelerated growth (44). The finding of an abdominal circumference above the 90$^{th}$ percentile during the second or third trimester is positively associated with fetal macrosomia (45). We did not observe significant differences in growth for head circumference and femur length. This phenomenon of an increased growth in abdominal circumference, but not in head circumference is also observed in macrosomic diabetic fetuses (46). Further studies examining the differences in fetal growth among consanguineous couples and possible health effects are needed.

### Study implications

Our findings suggest that in our population consanguinity is associated with an increase in mean birth weight and an accelerated fetal abdominal circumference growth. This may be related to specific selection factors, or to genetic, immunological and social factors linked to consanguinity. The over-all health consequences of the higher birth weight and accelerated fetal abdominal circumference growth in the offspring of consanguineous couple remain to be elucidated in future studies.

## References

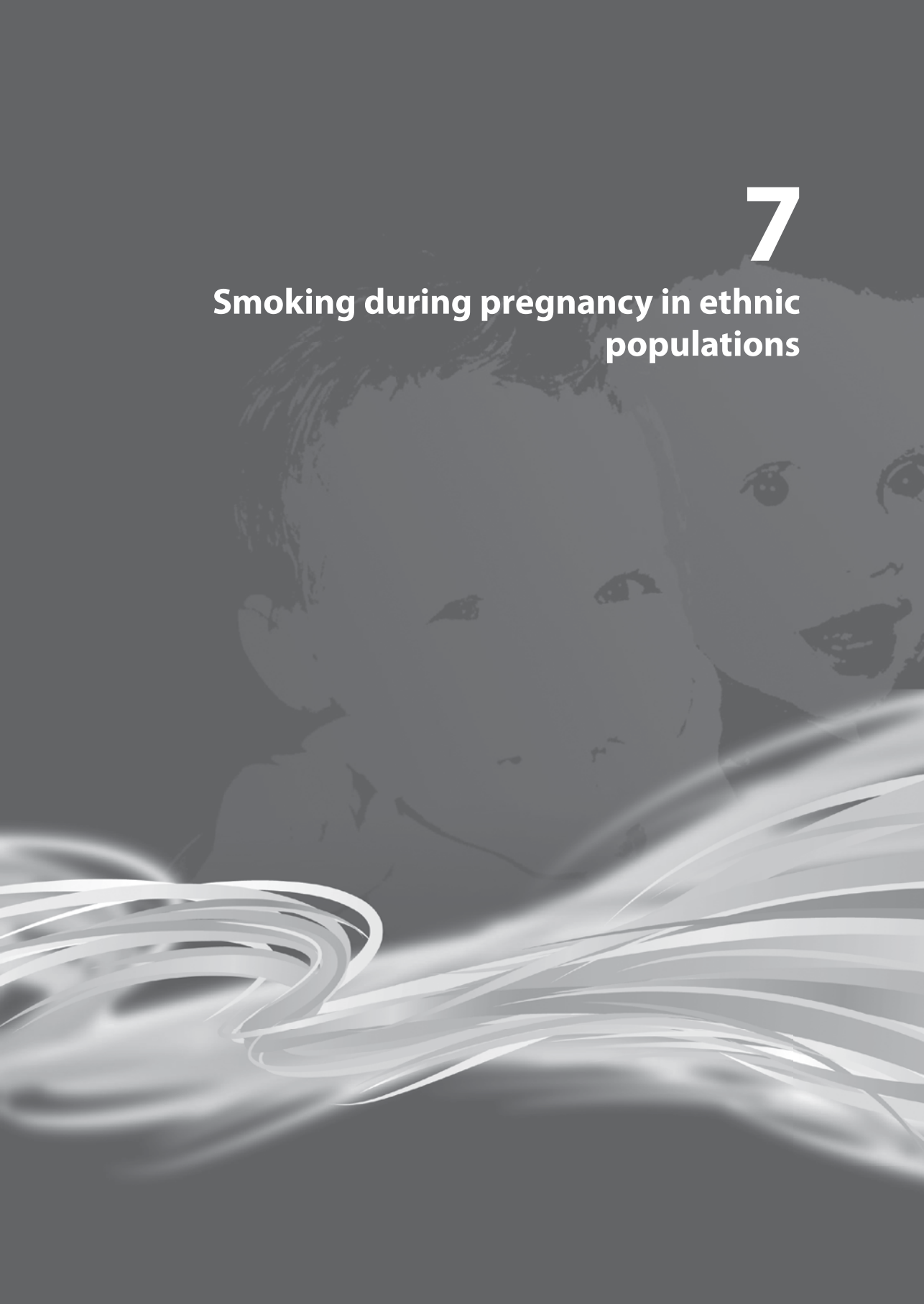

1. Schulpen TW, van Steenbergen JE, van Driel HF. Influences of ethnicity on perinatal and child mortality in the Netherlands. Arch Dis Child. 2001 Mar;84(3):222-6.
2. Schulpen TW, van Wieringen JC, van Brummen PJ, van Riel JM, Beemer FA, Westers P, et al. Infant mortality, ethnicity, and genetically determined disorders in The Netherlands. Eur J Public Health. 2006 Jun;16(3):291-4.
3. Troe EJWM, Bos V, Deerenberg IM, Mackenbach JP, Joung IM. Ethnic differences in total and cause-specific infant mortality in The Netherlands. Paediatr Perinat Epidemiol. 2006 Mar;20(2):140-7.
4. van Enk A, Buitendijk SE, van der Pal KM, van Enk WJ, Schulpen TW. Perinatal death in ethnic minorities in The Netherlands. J Epidemiol Community Health. 1998 Nov;52(11):735-9.
5. Bittles AH, Grant JC, Shami SA. Consanguinity as a determinant of reproductive behaviour and mortality in Pakistan. Int J Epidemiol. 1993 Jun;22(3):463-7.
6. Hussain R, Bittles AH, Sullivan S. Consanguinity and early mortality in the Muslim populations of India and Pakistan. Am J Hum Biol. 2001 Nov-Dec;13(6):777-87.
7. Grant JC, Bittles AH. The comparative role of consanguinity in infant and childhood mortality in Pakistan. Ann Hum Genet. 1997 Mar;61(Pt 2):143-9.
8. Tuncbilek E, Koc I. Consanguineous marriage in Turkey and its impact on fertility and mortality. Ann Hum Genet. 1994 Oct;58(Pt 4):321-9.
9. Stoltenberg C, Magnus P, Lie RT, Daltveit AK, Irgens LM. Birth defects and parental consanguinity in Norway. Am J Epidemiol. 1997 Mar 1;145(5):439-48.
10. Stoltenberg C, Magnus P, Lie RT, Daltveit AK, Irgens LM. Influence of consanguinity and maternal education on risk of stillbirth and infant death in Norway, 1967-1993. Am J Epidemiol. 1998 Sep 1; 148(5):452-9.
11. Zlotogora J. What is the birth defect risk associated with consanguineous marriages? Am J Med Genet. 2002 Apr 15;109(1):70-1.
12. Bromiker R, Glam-Baruch M, Gofin R, Hammerman C, Amitai Y. Association of parental consanguinity with congenital malformations among Arab newborns in Jerusalem. Clin Genet. 2004 Jul;66(1): 63-6.
13. al-Abdulkareem AA, Ballal SG. Consanguineous marriage in an urban area of Saudi Arabia: rates and adverse health effects on the offspring. J Community Health. 1998 Feb;23(1):75-83.
14. Asha Bai PV, John TJ. The effect of consanguinity on the gestation period and anthropometric traits of the new-born in Southern India. Trop Geogr Med. 1982;34(3):225-9.
15. Basaran N, Artan S, Yazicioglu S, Sayli BS. Effects of consanguinity on anthropometric measurements of newborn infants. Clin Genet. 1994 Apr;45(4):208-11.
16. Honeyman MM, Bahl L, Marshall T, Wharton BA. Consanguinity and fetal growth in Pakistani Moslems. Arch Dis Child. 1987 Mar;62(3):231-5.

17. Khlat M. Inbreeding effects on fetal growth in Beirut, Lebanon. Am J Phys Anthropol. 1989 Dec;80(4): 481-4.
18. Jaber L, Merlob P, Gabriel R, Shohat M. Effects of consanguineous marriage on reproductive outcome in an Arab community in Israel. J Med Genet. 1997 Dec;34(12):1000-2.
19. Fried K, Davies AM. Some effects on the offspring of uncle-niece marriage in the Moroccan Jewish community in Jerusalem. Am J Hum Genet. 1974 Jan;26(1):65-72.
20. Sibert JR, Jadhav M, Inbaraj SG. Fetal growth and parental consanguinity. Arch Dis Child. 1979 Apr; 54(4):317-9.
21. Copper RL, Goldenberg RL, Das A, Elder N, Swain M, Norman G, et al. The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1996 Nov;175(5):1286-92.
22. Hoffman S, Hatch MC. Stress, social support and pregnancy outcome: a reassessment based on recent research. Paediatr Perinat Epidemiol. 1996 Oct;10(4):380-405.
23. Hofman A, Jaddoe VW, Mackenbach JP, Moll HA, Snijders RF, Steegers EA, et al. Growth, development and health from early fetal life until young adulthood: the Generation R Study. Paediatr Perinat Epidemiol. 2004 Jan;18(1):61-72.
24. Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, et al. The Generation R Study: Design and cohort profile. Eur J Epidemiol. 2006;21(6):475-84.
25. Verburg BO, Steegers EAP, de Ridder MA, Snijders RJM, Hofman A, Moll HA, et al. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. Ultrasound in obstetrics and gynecology. 2007;In press.
26. Hadlock FP, Harrist RB, Carpenter RJ, Deter RL, Park SK. Sonographic estimation of fetal weight. The value of femur length in addition to head and abdomen measurements. Radiology. 1984 Feb;150(2): 535-40.
27. Statistics Netherlands. Migrants in the Netherlands, 2003; 2003.
28. Royston P, Altman DG. Design and analysis of longitudinal studies of fetal size. Ultrasound Obstet Gynecol. 1995 Nov;6(5):307-12.
29. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol. 1999 Oct;28(5):964-74.
30. Bundey S, Alam H. A five-year prospective study of the health of children in different ethnic groups, with particular reference to the effect of inbreeding. Eur J Hum Genet. 1993;1(3):206-19.
31. Stoltenberg C, Magnus P, Skrondal A, Lie RT. Consanguinity and recurrence risk of birth defects: a population-based study. Am J Med Genet. 1999 Feb 19;82(5):423-8.
32. Bennett RL, Motulsky AG, Bittles A, Hudgins L, Uhrich S, Doyle DL, et al. Genetic counseling and screening of consanguineous cuoples and their offspring: recommendations of the national society of genetic counselors. J Genetic Couns. 2002 April;11(2):97-119.
33. Dunger DB, Ong KK, Huxtable SJ, Sherriff A, Woods KA, Ahmed ML, et al. Association of the INS VNTR with size at birth. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. Nat Genet. 1998 May;19(1):98-100.
34. Bittles A. Consanguinity and its relevance to clinical genetics. Clin Genet. 2001 Aug;60(2):89-98.
35. Mathews TJ, MacDorman MF, Menacker F. Infant mortality statistics from the 1999 period linked birth/infant death data set. 2002 Jan 30;50(4):1-28.
36. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J. US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, hispanics, and blacks. Pediatrics. 2003 Jan; 111(1):e61-6.
37. Berard J, Dufour P, Vinatier D, Subtil D, Vanderstichele S, Monnier JC, et al. Fetal macrosomia: risk factors and outcome. A study of the outcome concerning 100 cases >4500 g. Eur J Obstet Gynecol Reprod Biol. 1998 Mar;77(1):51-9.

38. Raio L, Ghezzi F, Di Naro E, Buttarelli M, Franchi M, Durig P, et al. Perinatal outcome of fetuses with a birth weight greater than 4500 g: an analysis of 3356 cases. Eur J Obstet Gynecol Reprod Biol. 2003 Aug 15;109(2):160-5.
39. Pollack RN, Buchman AS, Yaffe H, Divon MY. Obstetrical brachial palsy: pathogenesis, risk factors, and prevention. Clin Obstet Gynecol. 2000 Jun;43(2):236-46.
40. Ferber A. Maternal complications of fetal macrosomia. Clin Obstet Gynecol. 2000 Jun;43(2):335-9.
41. Pettitt DJ, Knowler WC. Long-term effects of the intrauterine environment, birth weight, and breast-feeding in Pima Indians. Diabetes Care. 1998 Aug;21 Suppl 2:B138-41.
42. Yeazel MW, Ross JA, Buckley JD, Woods WG, Ruccione K, Robison LL. High birth weight and risk of specific childhood cancers: a report from the Children's Cancer Group. J Pediatr. 1997 Nov;131(5): 671-7.
43. Yiu V, Buka S, Zurakowski D, McCormick M, Brenner B, Jabs K. Relationship between birthweight and blood pressure in childhood. Am J Kidney Dis. 1999 Feb;33(2):253-60.
44. Degani S. Fetal biometry: clinical, pathological, and technical considerations. Obstet Gynecol Surv. 2001 Mar;56(3):159-67.
45. Keller JD, Metzger BE, Dooley SL, Tamura RK, Sabbagha RE, Freinkel N. Infants of diabetic mothers with accelerated fetal growth by ultrasonography: are they all alike? Am J Obstet Gynecol. 1990 Sep; 163(3):893-7.
46. Driscoll SG, Benirschke K, Curtis GW. Neonatal deaths among infants of diabetic mothers. Postmortem findings in ninety-five infants. Am J Dis Child. 1960 Dec;100:818-35.

# 7

# Smoking during pregnancy in ethnic populations



## Abstract

*Objectives:* Patterns and correlates of maternal smoking could differ according to ethnic background and these differences might have consequences for intervention strategies.

*Methods:* In the Generation R study, we examined patterns of smoking during pregnancy and the associations of socio-economic (educational level), demographic (maternal age, marital status, generational status, parity) and lifestyle (alcohol consumption, partner smoking) correlates with smoking during pregnancy in 5748 women of Dutch, Turkish, Moroccan, Surinamese-hindustani, Surinamese-creole, Capeverdean and Antillean ethnic background.

*Results:* Smoking rates before pregnancy were highest in the Turkish group (43.7%) and lowest in the Moroccan group (7.0%). Compared to Dutch women (24.1%), Turkish and Moroccan women were less likely to quit smoking before pregnancy (17.0% and 5.9%, respectively; $p < 0.001$). Turkish and Moroccan women (72.0% and 70.6%, respectively) were more likely to continue smoking during pregnancy compared to Dutch women (58.6%; $p < 0.001$). Lower education was associated with smoking during pregnancy only in the Dutch group. No significant association of education with smoking was seen in the non-Dutch groups. Second-generation (i.e. foreign-born) Turkish and Capeverdean women were more likely to smoke during pregnancy compared to first generation women. Partner smoking was associated with smoking during pregnancy in all ethnic groups, except for the Surinamese-creole and Antillean groups. Maternal alcohol consumption was associated with smoking during pregnancy in all ethnic groups, except for the Capeverdean group.

*Conclusions:* Smoking rates and correlates of smoking during pregnancy varied by ethnic background of the pregnant women. These observations should be considered when designing maternal smoking prevention and intervention strategies.

## Introduction

Maternal smoking during pregnancy is an important modifiable risk factor for unfavourable pregnancy outcomes and childhood morbidity and mortality. Smoking of pregnant women is associated with increased risks of spontaneous abortion, low birth weight and preterm birth (1-4). There is also evidence that smoking during pregnancy increases the risk of infant mortality, childhood asthma and psychopathology (5-8). Previous research suggests that 20-40% of pregnant smokers spontaneously quit smoking (9-11). Because pregnant women might be motivated to quit smoking, pregnancy offers a window of opportunity to modify smoking behaviour of women. Smoking cessation programs in pregnancy have shown to reduce the rates of low birth weight and preterm birth (12).

Several correlates of smoking before and during pregnancy have been identified. For example, low education is associated with high smoking prevalence before and during pregnancy in white and black women (13-16). Another strong predictor of maternal smoking is partner smoking. Pregnant women with smoking partners are less likely to quit smoking during pregnancy and more likely to relapse to smoking postpartum (17, 18). Besides partner smoking, the neighbourhood context could influence smoking behaviour during pregnancy (19). For example, living in a neighbourhood where smoking is common, and smoking during pregnancy is acceptable, may increase the risk of a woman continuing smoking during pregnancy. Additional risk factors in white and black women associated with higher rates of smoking before and during pregnancy are being unmarried (13, 20), low maternal age (13, 15) and maternal alcohol use (15). However, Shankar et al. observed no association between indicators of socio-economic status, including education, and smoking in a study among Salvadorean immigrants (21). Ethnic differences in smoking behaviours have been found in the United States. In the United States lower rates of smoking have been demonstrated in blacks and Hispanics compared to Non-Hispanic whites (22-26). In Canada, high rates of maternal smoking are seen among Aboriginal women compared to non-Aboriginal women (27). A study by Acevedo-Garcia et al. suggests that rates of smoking might even differ by immigrant generation (28). However, only a few studies offer details on the possible variation of the known correlates of smoking during pregnancy in ethnic populations (27). A better understanding of these variations could improve prevention and intervention strategies for pregnant women from different ethnic populations.

The Generation R study is multi-ethnic, population-based cohort study, with a large sample size. Within the Generation R Study we examined smoking behaviour before and during pregnancy in several large, not previously studied, ethnic groupss. Additionally, we investigated associations of socio-economic, demographic and lifestyle correlates with maternal smoking during pregnancy in each ethnic group.

## Methods

### Design

This study is embedded in the Generation R study, a population-based prospective cohort, and has been described previously in detail (29, 30). Briefly, all pregnant women and their partners in a previously defined area in Rotterdam, the Netherlands, were approached, either by community midwife or Generation R staff, at their first antenatal visit. Most women spoke Dutch; if not, the study was explained and questionnaires were available in their own language. In total, 9,778 women participated, of which 8,880 enrolled during pregnancy and 888 at birth of their child. The pregnant women who enrolled during pregnancy had a delivery date between April 2002 and January 2006. Data during pregnancy were collected from physical examinations, foetal ultrasounds and questionnaires. Women were usually seen for the first time before the 18th week of the pregnancy and in total three times during pregnancy, in early (gestational age < 18 weeks), mid (gestational age 18 - 25 weeks) and late pregnancy (gestational age ≥ 25 weeks). Of all pregnant women that were eligible for study inclusion within the study area, 61% participated at birth (30). The Medical Ethics Committee of the Erasmus Medical Center approved the Generation R Study. Written informed consent was obtained from all participants.



### Ethnic background

Ethnic background of the participating pregnant woman was assessed by the country of birth of the woman herself and her parents. Information about countries of birth was obtained by questionnaire. The participating pregnant woman was of non-Dutch ethnic origin if one of her parents was born abroad (31) (Table 1). If both parents were born abroad, the country of birth of the participant's mother determined the ethnic background.

**Table 1.** Classification of the ethnic background of pregnant woman based on the country of birth of the participating woman and her parents.

| Ethnic background | Country of birth pregnant women | Country of birth participant's mother | Country of birth participant's father |
|---|---|---|---|
| **Dutch** | Netherlands | Netherlands | Netherlands |
| | Abroad | Netherlands | Netherlands |
| **Non-Dutch** | Netherlands | Netherlands | Abroad |
| | Netherlands | Abroad | Netherlands / Abroad |
| | Netherlands | Abroad | Abroad |
| | Abroad | Abroad | Netherlands |
| | Abroad | Netherlands | Abroad |
| | Abroad | Abroad | Abroad |

Besides women of Dutch ethnic background, a distinction was made among the non-Dutch groups included in this study: Moroccan, Turkish, Capeverdean, Antillean and Surinamese. Women with an ethnic background other than these were grouped as 'other-western' for European, Northamerican, Oceanean, Japanese and Indonesian, and as 'other non-western' for African, Asian (except Japanese and Indonesian) and South- and Central American. Women with a Surinamese background are of mixed ethnic origin, mainly consisting of Hindustanis originating from India, and Creoles from Africa. These women were asked about their ethnic origin and further classified as: Surinamese-hindustani, Surinamese-creole or Surinamese-other.

**Sample for analysis**

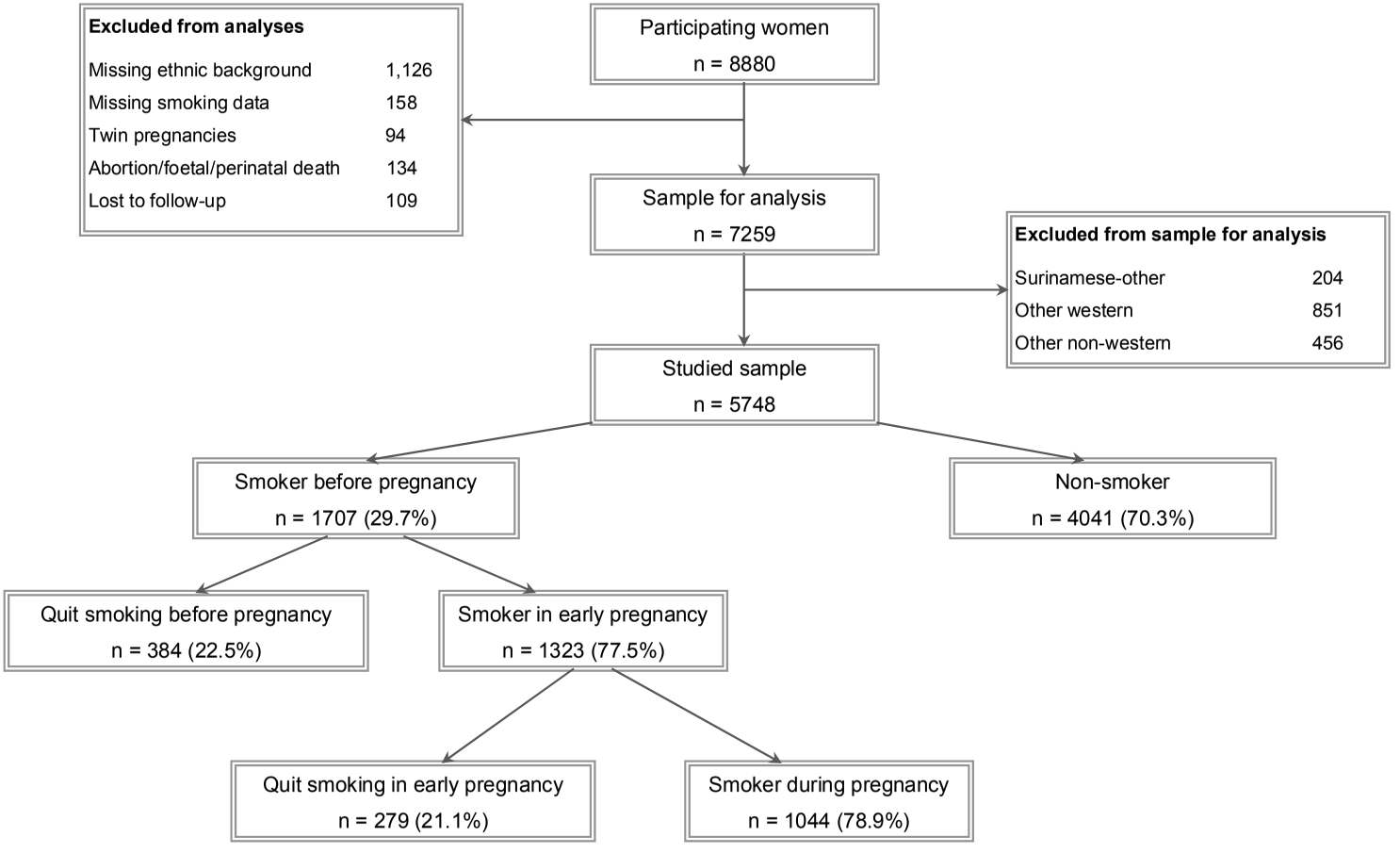
For the present analyses data for all prenatal recruited women were available (n=8,880). Women with missing information on their ethnic background (n=1,126) were excluded from analysis. Additionally, information on maternal smoking behaviour was missing in 158 subjects (2%). Women with twin pregnancies (n=94), abortion or early foetal death (n=95) and perinatal death (n=39) were excluded since our main interest was in low-risk pregnancies. Also excluded were women who were lost to follow-up (n=109). Of the remaining 7,259 pregnant women, women with a Surinamese-other (n = 204), other western (n = 851) and other non-western (n = 456) ethnic background were excluded from analysis, because of the mixed composition of these groups, which would complicate the interpretation and generalizability of the results in these groups. Analyses focusing on correlates of smoking during pregnancy were not carried out in Moroccan women, because no accurate analysis could be performed due to the low prevalence of smoking in this group (n = 34).

**Maternal smoking**

Information about maternal smoking before and during pregnancy was obtained by postal questionnaires in early, mid and late pregnancy. In the first questionnaire pregnant women were asked whether they smoked at 6 months prior to the pregnancy, whether they had stopped smoking before pregnancy, and whether they had smoked in early pregnancy. In the second and third questionnaires, the pregnant women were asked whether they had smoked in mid and late pregnancy, respectively.

On the basis of these questions smoking behaviour before and during pregnancy was defined as: 1) 'Non-smoker', for women who had never smoked or stopped smoking more than 6 months before pregnancy; 2) 'Quit smoking before pregnancy', for smokers who stopped smoking less 6 months before pregnancy; 3) 'Quit smoking in early pregnancy', for smokers who smoked until pregnancy was established; 4) 'Smoker during pregnancy', for smokers who continued to smoke after pregnancy was known or smoked in mid or late pregnancy (Figure 1). Women who reported in the first question-

**Figure 1.** Smoking patterns before and during pregnancy.



naire to have quit smoking before pregnancy (n = 669) or smoked until pregnancy was known (n = 872) but still reported to smoke in the second or third questionnaire (n = 159 and 157, respectively), were allocated to the 'Smokers during pregnancy' category. The same strategy was used for women who reported not to smoke in the first questionnaire (n = 5147) but reported smoking in the second or third questionnaire (n = 45).

Among the women who smoked before pregnancy, the number of cigarettes was initially assessed in the following six categories: less than one per day; 1-2 per day; 3-4 per day; 5-9 per day; 10-19 per day; and 20 or more per day. To increase the number of subjects per group, these categories were later combined and reclassified into the following three categories: 1) less than 5 cigarettes per day; 2) 5-9 cigarettes per day; and 3) 10 or more cigarettes per day.

**Correlates**

Information about maternal age, marital status, educational level, parity, smoking of the father, maternal alcohol use, and generational status of the pregnant woman was obtained by questionnaire.

*Socio-economic status.* Educational level was assessed by the highest completed education. These educational levels were combined and classified into three categories: 1) primary school; 2) secondary school; and 3) higher education.

*Demographic correlates*. Maternal age was assessed as continuous variable at enrolment in the study and classified into three categories: 1) < 20 years; 2) 20-30 years; 3) ≥ 30 years. Marital status was classified into three categories: 1) married; 2) cohabiting; and 3) single motherhood. Generational status of non-Dutch groups was classified as: 1) first generation, for migrant women who were born outside the Netherlands; 2) second-generation, for women who were born in the Netherlands. Parity was classified in two categories: 1) nulliparous; 2) primiparous and multiparous.

*Lifestyle correlates.* Pregnant women were asked about smoking of their partner (yes/no) and about their own alcohol use during pregnancy (yes/no).

**Data analyses**

We estimated the smoking behaviour and the amount of smoking of the women by ethnic group. Differences in prevalence rates compared to the Dutch group were determined by the Chi-square statistic and associated p-value. Multivariate logistic regression analyses were used to examine the associations of the correlates with smoking during pregnancy stratified for the specific ethnic groups. We used separate categories for missing information on the correlates, which were added to the logistic model. We tested for interaction between ethnic background and the correlates to check the equivalence of the effect of correlates on smoking across ethnicities. Odds ratios (OR) are presented with their 95% confidence intervals (CI). All statistical analyses were performed using

Statistical Package of Social Sciences version 11.0 for Windows (SPSS Inc, Chicago, IL, USA).

## Results

### Subject characteristics

Characteristics of the pregnant women are presented in Table 2. The mean maternal age was lower in all non-Dutch groups (26.2-28.1 years, SD 5.5-6.5) compared to the Dutch group (31.2 years, SD 4.5; $p < 0.001$). Compared to the Dutch group (5.2%), the percentage of primary educated women was higher in the non-Dutch groups (12.1%-31.5%; $p < 0.001$). More Turkish and Moroccan women were married (86.2% and 90.6%, respectively) compared to Dutch women (44.5%; $p < 0.001$), while single motherhood was more common in the Surinamese-hindustani, Surinamese-creole, Capeverdean and Antillean women (22.0%-52.9%) than in Dutch women (7.8 %; $p <0.001$). Significantly more Turkish women smoked during pregnancy (31.5%) compared to the Dutch women (17.4%; $p < 0.001$), while less Moroccan women smoked during pregnancy (4.9%; $p < 0.001$). Compared to Dutch women (65.2%), the proportion of women that consumed alcohol during pregnancy was lower in the non-Dutch groups (3.7%-52.0%; $p < 0.001$). Partner smoking was more frequent in the Turkish, Surinamese-hindustani and Surinamese-creole groups (50.7%- 62.5%) compared to the Dutch group (42.2%; $p < 0.001$).



### Maternal smoking before and during pregnancy

In Figures 2 to 4 the smoking behaviour of the women before and during pregnancy are presented. Of the Dutch women 29.7% smoked before pregnancy. Compared to the Dutch group, smoking before pregnancy was more frequently observed in the Turkish group (43.7%; $p < 0.001$) and less frequently in the Moroccan group (7.0%; $p < 0.001$). Also, a higher proportion of the women of Surinamese-creole background were smoking before pregnancy compared to Dutch women (37.3%; $p < 0.05$, Figure 2).

Of the women who smoked before pregnancy, Surinamese-hindustani and Surinamese-creole women were more likely to smoke < 5 cigarettes per day (46.9% and 42.6%, respectively) compared to Dutch women (30.2%; $p <0.05$). All non-Dutch groups, except the Moroccan group, were more likely to smoke 5-9 cigarettes per day (28.9%-34.4%) compared to the Dutch group (18.5%; $p < 0.05$). Compared to the Dutch women (51.3%), Turkish, Surinamese-hindustani, Surinamese-creole and Antillean women were less likely to smoke ≥ 10 cigarettes per day (38.6%, 18.8%, 23.4% and 32.5%, respectively; $p < 0.05$, Figure 3).

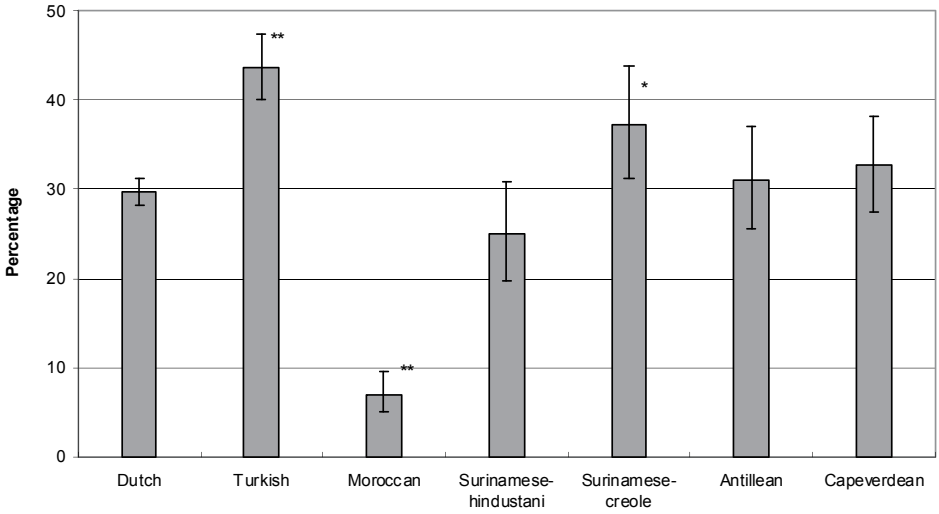
Of the women who smoked before pregnancy, the lowest rates of women that stopped smoking before pregnancy were observed in the Turkish and Moroccan groups

**Table 2.** Characteristics of the studied population (n = 5748).

| | Dutch | Turkish | Moroccan | Surinamese-hindustani | Surinamese-creole | Capeverdean | Antillean |
|---|---|---|---|---|---|---|---|
| | n = 3598 | n = 661 | n = 487 | n = 232 | n = 225 | n = 291 | n = 254 |
| Maternal age (years) | | | | | | | |
| *Mean age* | 31.2 (4.5) | 27.0 (4.9) | 27.9 (5.2) | 27.6 (4.9) | 28.1 (6.5) | 27.0 (6.0) | 26.2 (5.5) |
| *< 20* | 1.7 | 4.4 | 4.1 | 6.0 | 10.7 | 14.1 | 12.2 |
| *20-29* | 32.1 | 68.4 | 64.1 | 59.1 | 52.4 | 52.6 | 62.2 |
| *>= 30* | 66.2 | 27.2 | 31.8 | 34.9 | 36.9 | 33.3 | 25.2 |
| | *Reference* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p < 0.001* |
| Marital status (%) | | | | | | | |
| *Married* | 44.5 | 86.2 | 90.6 | 39.7 | 14.7 | 13.7 | 15.4 |
| *Cohabiting* | 46.7 | 5.7 | 3.5 | 34.1 | 31.6 | 33.0 | 31.1 |
| *single motherhood* | 7.8 | 5.4 | 3.1 | 22.0 | 52.9 | 50.5 | 50.0 |
| *missing* | 0.9 | 2.6 | 2.9 | 4.3 | 0.9 | 2.7 | 3.5 |
| | *Reference* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p < 0.001* |
| Education (%) | | | | | | | |
| *high* | 56.8 | 12.9 | 25.3 | 13.8 | 14.7 | 10.0 | 13.8 |
| *secondary* | 37.2 | 49.8 | 52.6 | 66.8 | 68.4 | 61.5 | 63.0 |
| *primary* | 5.2 | 31.5 | 12.1 | 17.2 | 13.8 | 24.1 | 19.3 |
| *missing* | 0.8 | 5.9 | 10.1 | 2.2 | 3.1 | 4.5 | 3.9 |
| | *Reference* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p < 0.001* |
| Parity (%) | | | | | | | |
| *0* | 58.5 | 45.2 | 38.0 | 51.7 | 53.8 | 54.6 | 55.1 |
| *>= 1* | 39.6 | 52.3 | 58.5 | 42.7 | 44.4 | 39.5 | 39.8 |
| *Missing* | 1.8 | 2.4 | 3.5 | 5.6 | 1.8 | 5.8 | 5.1 |
| | *Reference* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *P = 0.36* | *p < 0.001* | *p < 0.05* |
| Generation (%) | | | | | | | |
| *First* | | 64.8 | 79.1 | 76.3 | 70.2 | 62.2 | 83.1 |
| *Second* | | 33.3 | 18.9 | 23.3 | 28.4 | 36.8 | 16.1 |
| *missing* | | 2.0 | 2.1 | 0.4 | 1.3 | 1.0 | 0.8 |
| | | NA | NA | NA | NA | NA | NA |
| Maternal smoking behaviour (%) | | | | | | | |
| *Non-smoker* | 70.3 | 56.3 | 93.0 | 75.0 | 62.7 | 67.4 | 68.9 |
| *Smoker, quit before pregnancy* | 7.1 | 7.4 | 0.4 | 5.6 | 11.6 | 6.5 | 7.1 |
| *Smoker, quit in early pregnancy* | 5.1 | 4.8 | 1.6 | 4.7 | 7.1 | 5.5 | 4.3 |
| *Smoker during pregnancy* | 17.4 | 31.5 | 4.9 | 14.7 | 18.7 | 20.6 | 19.7 |
| | *Reference* | *p < 0.001* | *p < 0.001* | *p = 0.49* | *p = 0.03* | *p = 0.55* | *p = 0.78* |
| Alcohol consumption of pregnant woman (%) | | | | | | | |
| *non-drinking* | 34.4 | 89.7 | 96.1 | 70.3 | 47.1 | 51.9 | 54.7 |
| *drinking* | 65.2 | 9.7 | 3.7 | 29.7 | 52.0 | 47.1 | 43.3 |
| *missing* | 0.4 | 0.6 | 0.2 | | 0.9 | 1.0 | 2.0 |
| | *Reference* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p < 0.001* |
| Smoking of partner (%) | | | | | | | |
| *no* | 56.7 | 35.6 | 61.0 | 43.1 | 44.9 | 58.4 | 52.8 |
| *yes* | 42.2 | 62.5 | 38.2 | 55.2 | 50.7 | 36.8 | 45.3 |
| *missing* | 1.1 | 2.0 | 0.8 | 1.8 | 4.4 | 4.8 | 2.0 |
| | *Reference* | *p < 0.001* | *p = 0.23* | *p < 0.001* | *p < 0.001* | *p < 0.001* | *p = 0.14* |

Values are percentages or means (standard deviation). P-values are based on Chi-square test, Dutch is reference group. NA = not applicable.

**Figure 2.** Proportion of women that smoked before pregnancy per ethnic population.




Values are percentages and 95% confidence intervals.
Proportions are based on total number of women. Women that smoked before pregnancy are: women that quit smoking before pregnancy + women that quit smoking in early pregnancy + women that smoke during pregnancy.
* $p < 0.05$, ** $p < 0.001$, result of Chi-square test, Dutch is reference group.

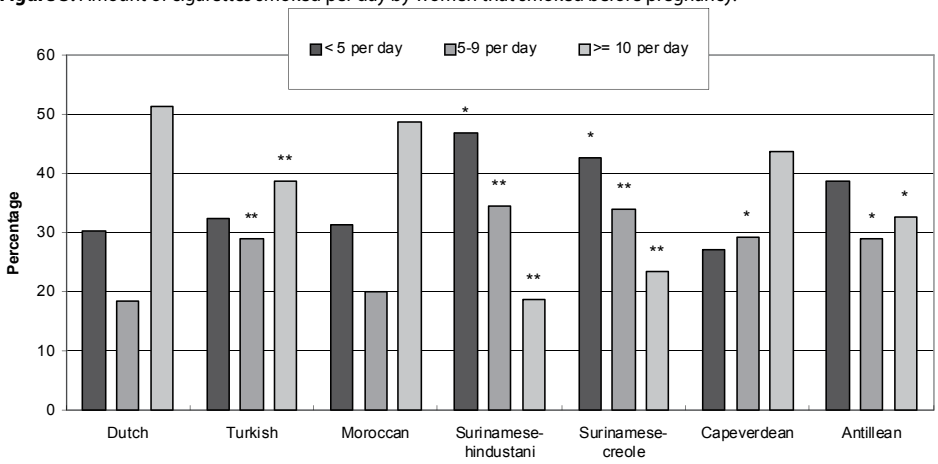


(17.0% and 5.9%, respectively). These rates were significantly lower than the quitting rates before pregnancy in the Dutch women (24.1%; $p < 0.05$). Compared to the Dutch women, Turkish women were also less likely to quit smoking in early pregnancy (11.1%; $p < 0.001$). Of the Dutch women who smoked before pregnancy, almost 60% continued to smoke during pregnancy. Compared to the Dutch women, Turkish and Moroccan women were more likely to continue smoking during pregnancy (72.0% and 70.6%, respectively, $p < 0.001$, Figure 4).

**Correlates of maternal smoking during pregnancy**

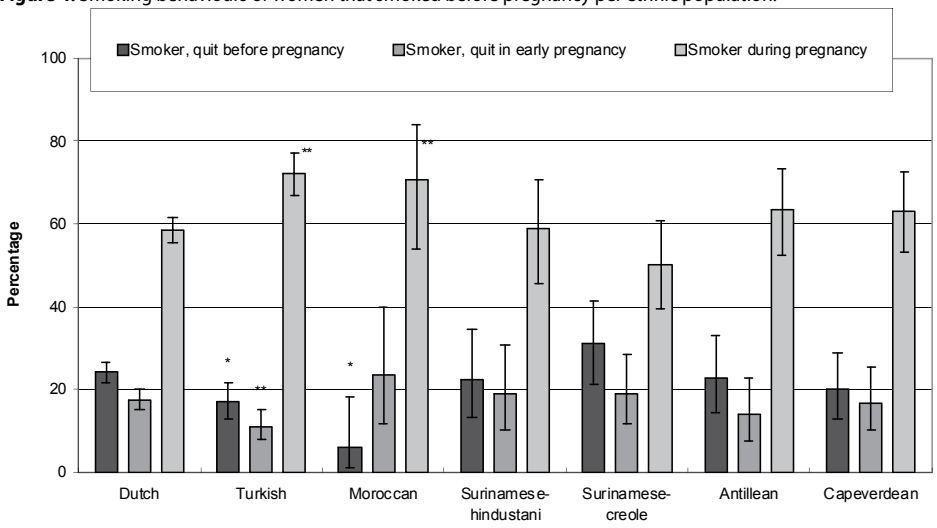
Single motherhood was significantly associated with smoking during pregnancy in Dutch and Surinamese-hindustani women (Dutch: OR 3.5, 95% CI 2.5-5.0; Surinamese-hindustani: OR 3.5, 95% CI 1.3-9.9). Within the Dutch group, women with primary school were more likely to smoke during pregnancy (OR 12.1 95% CI 8.1-18.0, Table 3). No significant association was found between educational level and smoking during pregnancy in the non-Dutch groups. Strong predictors of smoking during pregnancy were alcohol use of the pregnant women and smoking of the partner. In all non-Dutch groups, except the Capeverdean group, women that consumed alcohol during pregnancy were more likely to smoke during pregnancy compared to women that did not consume alcohol during pregnancy. Partner smoking was associated with smoking during pregnancy

**Figure 3.** Amount of cigarettes smoked per day by women that smoked before pregnancy.




Values are percentages.
Proportions are based on total number of women that smoked before pregnancy. Women that smoked before pregnancy are: women that quit smoking before pregnancy + women that quit smoking in early pregnancy + women that smoke during pregnancy.
* $p < 0.05$, ** $p < 0.001$, result of Chi-square test, Dutch is reference group.

**Figure 4.** Smoking behaviours of women that smoked before pregnancy per ethnic population.




Values are percentages and 95% confidence intervals.
Proportions are based on total number of mothers that smoked before pregnancy. Mothers that smoked before pregnancy are: mothers that quit smoking before pregnancy + mothers that quit smoking in early pregnancy + mothers that smoke during pregnancy.
* $p < 0.05$, ** $p < 0.001$, result of Chi-square test, Dutch is reference group.

of the pregnant women in all groups, except in the Surinamese-creole and Antillean groups. Second-generation Turkish and Capeverdean women were more likely to smoke

during pregnancy compared to first generation women (Turkish: OR 1.7, 95% CI 1.1-2.5; Capeverdean: OR 3.0, 95% CI 1.4-6.2). The association of maternal age, educational level, parity, partner smoking and maternal alcohol consumption with maternal smoking during pregnancy differed significantly across the ethnic groups.

## Discussion

In our study sample smoking before pregnancy was frequent among Turkish and Surinamese-creole women and was rarely observed among Moroccan women. The highest proportions of continual smoking during pregnancy were observed in the Turkish and Moroccan groups. Educational level was strongly associated with smoking during pregnancy only in the Dutch group and no significant association was seen in the non-Dutch groups. Partner smoking and alcohol consumption of the pregnant woman were associated in almost all studied groups with smoking during pregnancy. Second-generation Turkish and Capeverdean pregnant women were more likely to smoke during pregnancy compared to first generation women.



The diffusion of smoking through populations can be described as going through four stages known as the 'tobacco epidemic' (32) and is characterized by changes in prevalence, consumption and mortality. In the tobacco epidemic smoking prevalence increases rapidly from less than 15% in the first stage, in which smoking-attributable mortality is low, to a peak of 50-80% in the second stage. By the end of the second stage smoking-attributable mortality is already about 10%. From the third stage onwards, smoking prevalence declines to 35-40%. The last stage is characterised by a slow decline in smoking prevalence. However, the smoking-attributable mortality further increases to 20-30% in the last two stages. Earlier studies suggest that the non-Dutch populations are in the first or early second stage of the tobacco epidemic (33, 34), which seems to be confirmed by our results. In the present study, smoking prevalence is low among Moroccan women, which is in line with previous findings (33). The low prevalence might be due to the low degree of acculturation and the traditional lifestyle in Moroccan women. However, the low quitting rates are noteworthy. Over 70% of the Moroccan women who smoke before pregnancy continue to smoke during pregnancy. As prevalence rates of smoking might increase among Moroccan women, this emphasizes that continuing attention to smoking prevention strategies is also needed in this population with low rates of smoking.

Remarkably, educational level of the pregnant women was associated with smoking during pregnancy only in the Dutch group and no significant effect of maternal educational level was found in the non-Dutch groups. Other studies found associations

**Table 3.** Correlates of smoking during pregnancy in the studied populations.

| | | Dutch | | Turkish | | Surinamese-hindustani | | Surinamese-creole | | Capeverdean | | Antillean | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Significant Ethnic Difference #** | **aOR** | **95% CI** | **aOR** | **95% CI** | **aOR** | **95% CI** | **aOR** | **95% CI** | **aOR** | **95% CI** | **aOR** | **95% CI** |
| **Maternal age** | Yes | | | | | | | | | | | | |
| < 20 years | | 0.8 | 0.4, 1.4 | 1.8 | 0.8, 4.1 | 0.7 | 0.1, 3.7 | 1.5 | 0.5, 5.3 | 1.9 | 0.8, 4.7 | 0.9 | 0.3, 2.7 |
| 20-30 years | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| >= 30 years | | 0.8 | 0.7, 1.1 | 1.0 | 0.7, 1.6 | 0.7 | 0.2, 2.0 | 1.3 | 0.6, 3.2 | 0.8 | 0.3, 1.9 | 0.2 | 0.1, 0.6* |
| **Marital status** | No | | | | | | | | | | | | |
| married | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| cohabiting | | 1.8 | 1.5, 2.3** | 1.4 | 0.7, 2.8 | 0.5 | 0.1, 1.6 | 4.4 | 0.9, 21.6 | 2.6 | 0.6, 10.6 | 1.0 | 0.3, 3.8 |
| single motherhood | | 3.5 | 2.5, 5.0** | 2.0 | 0.9, 4.1 | 3.5 | 1.3, 9.9* | 3.3 | 0.7, 15.8 | 3.2 | 0.8, 12.9 | 2.2 | 0.7, 7.6 |
| **Education** | Yes | | | | | | | | | | | | |
| high | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| secondary | | 4.0 | 3.1, 5.0** | 1.7 | 0.9, 3.2 | 2.2 | 0.4, 12.0 | 1.1 | 0.4, 3.3 | 1.3 | 0.3, 5.0 | 1.3 | 0.4, 4.3 |
| primary | | 12.1 | 8.1, 18.0** | 1.5 | 0.7, 2.9 | 4.1 | 0.6, 27.5 | 1.1 | 0.3, 4.4 | 3.2 | 0.8, 14.0 | 1.6 | 0.4, 6.8 |
| **Parity** | Yes | | | | | | | | | | | | |
| 0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| >= 1 | | 1.5 | 1.2, 1.9** | 1.6 | 1.0, 2.4* | 0.8 | 0.3, 2.0 | 1.7 | 0.8, 3.9 | 1.6 | 0.7, 3.8 | 1.5 | 0.7, 3.2 |
| **Generation** | No | | | | | | | | | | | | |
| first | | | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| second | | | | 1.7 | 1.1, 2.5* | 1.4 | 0.5, 4.1 | 2.0 | 0.9, 4.6 | 3.0 | 1.4, 6.2* | 2.0 | 0.8, 4.9 |
| **Alcohol consumption** | Yes | | | | | | | | | | | | |
| non-drinking | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| drinking | | 1.5 | 1.2, 1.9** | 4.1 | 2.2, 7.3** | 4.8 | 2.0, 11.8* | 2.7 | 1.2, 5.9* | 1.5 | 0.8, 3.0 | 3.0 | 1.4, 6.1* |
| **Smoking of partner** | Yes | | | | | | | | | | | | |
| no | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| yes | | 4.9 | 4.0, 6.1** | 3.2 | 2.1, 4.8** | 4.3 | 1.5, 12.2* | 1.6 | 0.7, 3.4 | 3.8 | 1.9, 7.6** | 1.9 | 0.9, 3.8 |

aOR = Odds Ratio adjusted for all variables listed

95% CI = 95% confidence interval

* $p < 0.05$, ** $p < 0.001$, # = Yes indicates that the interaction term (ethnic background x correlate) was significant at $p < 0.05$

between educational level and smoking before and during pregnancy (13, 15), but did not distinguish between different ethnic populations. The lack of socio-economic gradients in smoking among the non-Dutch groups might reflect the more recent uptake of smoking among non-Dutch groups. The uptake of smoking starts in high socio-economic groups, who adopt innovations and new behaviour quickly; as the behaviour diffuses throughout the population this socio-economic gradient diminishes. The absence

of an association between socio-economic status and smoking was also observed in Salvadorean immigrants in the US, and might be present in more migrant populations (21). The lack of a socio-economic gradient in non-Dutch groups might also be due to contextual influences, like cultural and neighbourhood factors. Non-Dutch groups in the Netherlands are more likely to live collectively in deprived areas. Living in a neighbourhood where smoking is common and smoking during pregnancy is acceptable, could increase the risk of continual smoking during pregnancy independent of a woman educational level (19, 35).

Our study showed that the strong relationship between partner smoking and smoking of the women during pregnancy is also observed in the non-Dutch groups. The effect of partner smoking on smoking behaviour of the pregnant women has been documented in other studies (15, 17). Also, the postpartum relapse rate of women who quitted smoking during pregnancy is higher in women whose partner is smoking (18, 36, 37). Partner smoking not only influences the smoking behaviour of the pregnant woman but also adversely affects the health of the infant during and after pregnancy. Passive exposure to tobacco smoke during pregnancy could lead to birth weight reduction of the infant (38). Postpartum exposure to tobacco smoke is associated with infant diseases and infant mortality (39). The high prevalence of partner smoking in specific ethnic groups and the possible harmful health effects for their infants emphasizes the need for interventions directed not only at pregnant woman, but also their partners.



In our study, maternal alcohol consumption during pregnancy was associated with maternal smoking in almost all studied groups. Other studies have also documented the association of maternal alcohol use and smoking during pregnancy (15, 40). It is well known that a person's smoking behaviour and the consumption of alcohol are closely related. Moreover, alcohol consumption might be associated with the co-occurrence of other health risk behaviours during pregnancy, such as drug use and heavy caffeine use (1, 41, 42). Alcohol consumption during pregnancy itself might have harmful effects on the unborn child, e.g. leading to low birth weight, intrauterine growth retardation and preterm delivery (43, 44).

Generational status showed to predict smoking behaviour before and during pregnancy of Turkish and Capeverdean women. A tendency to increased ORs for smoking in second-generation women was observed in the other non-Dutch groups. Other studies have also shown that smoking behaviour of migrant populations might differ by generational status (28, 45). Second-generation women, who are likely to be more acculturated in the host country, might adopt unhealthy behaviours, which could explain the increased ORs for smoking of second-generation pregnant women in our study. Other studies have shown that more acculturated women are more likely to adopt life-style behaviours of the host country (46, 47). The second-generation non-Dutch population is a relatively young population and the proportion of women reaching fertile ages will

increase over time. This emphasizes the need for intervention strategies to prevent a deterioration of lifestyle behaviours in the second-generation migrant population.

**Methodological considerations**

The strength of this study is the population-based cohort with a large number of subjects in the non-Dutch groups that were studied from early pregnancy onwards. Detailed information about ethnic background and smoking before and during pregnancy was available in this study.

Some limitations, however, need to be addressed. Of all pregnant women that were eligible for study inclusion within the study area, 61% participated at birth in the Generation R Study (30). Selective participation of women and missing data on ethnic background might have led to biased results. Therefore, we compared data from the Generation R Study with data from the Center of Research and Statistics, Rotterdam. In general, we observed that women with a higher socio-economic status, a first pregnancy and lower age were over represented in the Generation R cohort compared to population figures in Rotterdam. However, this picture was generally seen in both the Dutch and non-Dutch groups, suggesting that selection mechanisms were the same across the ethnic groups. Nonetheless, this could have led to biased estimates of the prevalence of smoking in different groups. However, in our study the prevalence of smoking before pregnancy corresponds with previous studies in the Netherlands, suggesting that selective participation did not strongly affect our estimates (33, 34). Selective non-response could also have biased the associations of the correlates with smoking during pregnancy. Selective non-response could introduce selection bias if the association of correlates with smoking during pregnancy differs between non-responders and those women in the study.

Information about maternal smoking was collected by anonymous questionnaires during pregnancy. Although assessing smoking habits during pregnancy by questionnaire seems to be a valid method, misclassification may occur (48). Also underreporting of smoking may be present. To overcome these latter limitations other studies have used biomarkers of tobacco exposure including cotinine levels in maternal urine samples (49-51), to which we did not have access. However, previous studies demonstrated that use of cotinine levels is not superior to self-report in questionnaires in studying the effect of maternal smoking during pregnancy (52, 53). Underreporting of smoking could also differ between ethnic populations and therefore lead to biased estimates. Previous studies reported conflicting results regarding ethnic differences in self-report (54, 55). However, Wagenknecht et al. showed that the misclassification rate of smoking between ethnic populations is low by means of interview-collected data (56). Furthermore, because we did not have information to assess the amount of smoking during pregnancy, light and heavy smokers during pregnancy are clustered. Information on the

amount of smoking during pregnancy might have benefited our study. However, other studies have shown that a detrimental effect on birth outcomes is already observed at low levels of maternal smoking (49, 57). Therefore, a high proportion of smokers during pregnancy in certain populations still imply that the aim should be to prevent smoking during pregnancy, independent of their amount of smoking.

**Study implications**

Our findings suggest that partner smoking, maternal alcohol use and single motherhood are important predictors of smoking during pregnancies across ethnic groups. An educational gradient in smoking behaviour could be lacking in migrant populations, and therefore smoking intervention strategies in migrants should be aimed at women at all educational levels. An increased risk of smoking during pregnancy of second-generation women is of concern because this could result in increasing inequalities in health outcomes of mother and infant.

## References

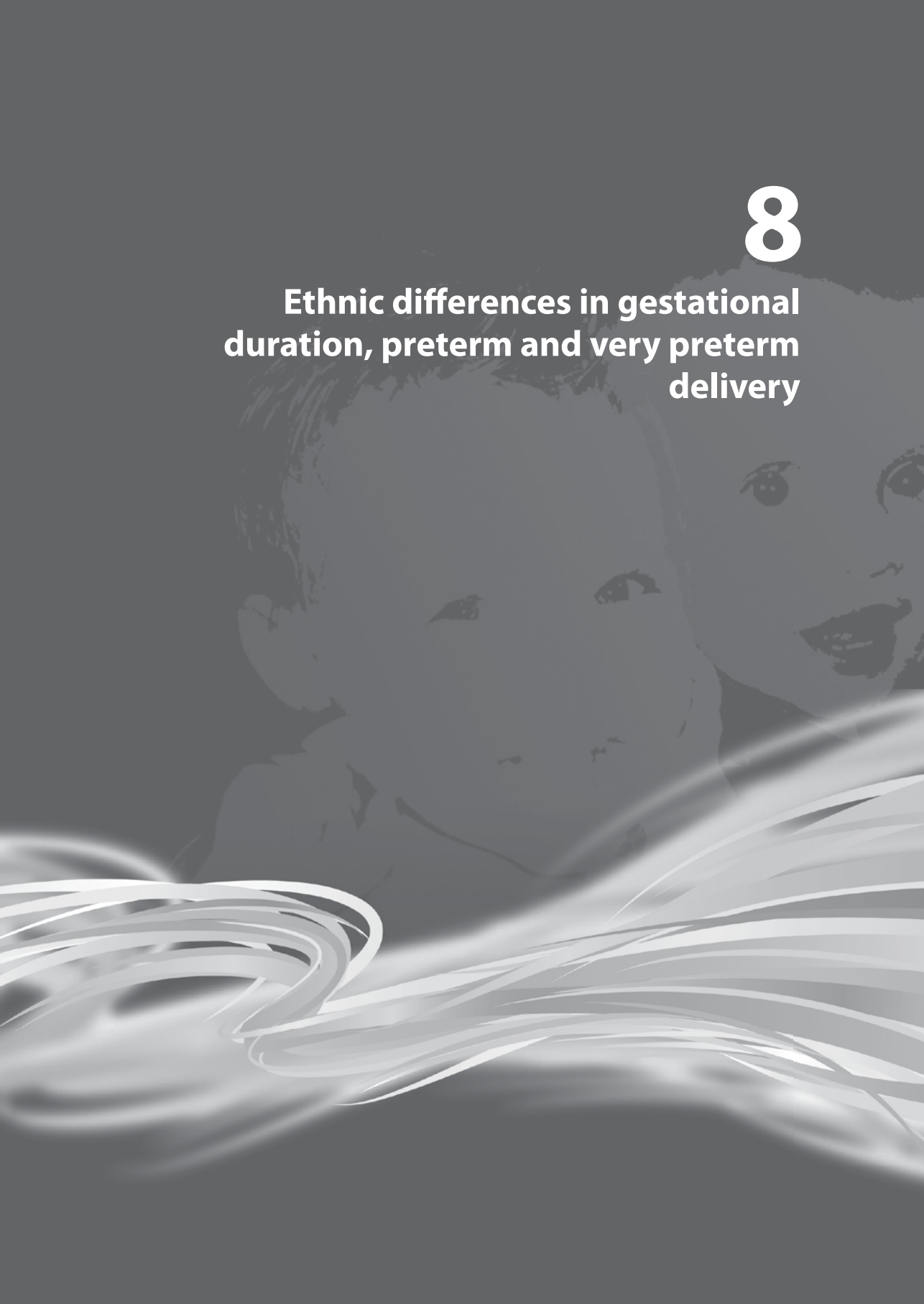

1. Armstrong BG, McDonald AD, Sloan M. Cigarette, alcohol, and coffee consumption and spontaneous abortion. Am J Public Health. 1992 Jan;82(1):85-7.
2. Cliver SP, Goldenberg RL, Cutter GR, Hoffman HJ, Davis RO, Nelson KG. The effect of cigarette smoking on neonatal anthropometric measurements. Obstet Gynecol. 1995 Apr;85(4):625-30.
3. Bernstein IM, Mongeon JA, Badger GJ, Solomon L, Heil SH, Higgins ST. Maternal smoking and its association with birth weight. Obstet Gynecol. 2005 Nov;106(5 Pt 1):986-91.
4. Shah NR, Bracken MB. A systematic review and meta-analysis of prospective studies on the association between maternal cigarette smoking and preterm delivery. Am J Obstet Gynecol. 2000 Feb; 182(2):465-72.
5. Kleinman JC, Pierre MB, Jr., Madans JH, Land GH, Schramm WF. The effects of maternal smoking on fetal and infant mortality. Am J Epidemiol. 1988 Feb;127(2):274-82.
6. Jaakkola JJ, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. Am J Public Health. 2004 Jan;94(1):136-40.
7. Ernst M, Moolchan ET, Robinson ML. Behavioral and neural consequences of prenatal exposure to nicotine. J Am Acad Child Adolesc Psychiatry. 2001 Jun;40(6):630-41.
8. Wakschlag LS, Leventhal BL, Pine DS, Pickett KE, Carter AS. Elucidating early mechanisms of developmental psychopathology: the case of prenatal smoking and disruptive behavior. Child Dev. 2006 Jul-Aug;77(4):893-906.
9. Morasco BJ, Dornelas EA, Fischer EH, Oncken C, Lando HA. Spontaneous smoking cessation during pregnancy among ethnic minority women: a preliminary investigation. Addict Behav. 2006 Feb; 31(2):203-10.
10. Ockene J, Ma Y, Zapka J, Pbert L, Valentine Goins K, Stoddard A. Spontaneous cessation of smoking and alcohol use among low-income pregnant women. Am J Prev Med. 2002 Oct;23(3):150-9.
11. Quinn VP, Mullen PD, Ershoff DH. Women who stop smoking spontaneously prior to prenatal care and predictors of relapse before delivery. Addict Behav. 1991;16(1-2):29-40.
12. Lumley J, Oliver SS, Chamberlain C, Oakley L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev. 2004(4):CD001055.

13. Fingerhut LA, Kleinman JC, Kendrick JS. Smoking before, during, and after pregnancy. Am J Public Health. 1990 May;80(5):541-4.
14. Andreski P, Breslau N, Med SS. Maternal smoking among blacks and whites. 1995 Jul;41(2):227-33.
15. Kahn RS, Certain L, Whitaker RC. A reexamination of smoking before, during, and after pregnancy. Am J Public Health. 2002 Nov;92(11):1801-8.
16. Wagenknecht LE, Perkins LL, Cutter GR, Sidney S, Burke GL, Manolio TA, et al. Cigarette smoking behavior is strongly related to educational status: the CARDIA study. Prev Med. 1990 Mar;19(2): 158-69.
17. McBride CM, Curry SJ, Grothaus LC, Nelson JC, Lando H, Pirie PL. Partner smoking status and pregnant smoker's perceptions of support for and likelihood of smoking cessation. Health Psychol. 1998 Jan;17(1):63-9.
18. McBride CM, Pirie PL. Postpartum smoking relapse. Addict Behav. 1990;15(2):165-8.
19. Pickett KE, Wakschlag LS, Rathouz PJ, Leventhal BL, Abrams B. The working-class context of pregnancy smoking. Health Place. 2002 Sep;8(3):167-75.
20. Cnattingius S, Thorslund M. Smoking behaviour among pregnant women prior to antenatal care registration. Soc Sci Med. 1990;31(11):1271-5.
21. Shankar S, Gutierrez-Mohamed ML, Alberg AJ. Cigarette smoking among immigrant Salvadoreans in Washington, DC: behaviors, attitudes, and beliefs. Addict Behav. 2000 Mar-Apr;25(2):275-81.
22. Land GH, Stockbauer JW. Smoking and pregnancy outcome: trends among black teenage mothers in Missouri. Am J Public Health. 1993 Aug;83(8):1121-4.
23. Teagle SE, Brindis CD. Substance use among pregnant adolescents: A comparison of self-reported use and provider perception. Journal of Adolescent Health. 1998 1998/3;22(3):229-38.
24. Ventura SJ, Hamilton BE, Mathews TJ, Chandra A. Trends and variations in smoking during pregnancy and low birth weight: evidence from the birth certificate, 1990-2000. Pediatrics. 2003 May; 111(5 Part 2):1176-80.
25. Camilli AE, McElroy LF, Reed KL. Smoking and pregnancy: a comparison of Mexican-American and non-Hispanic white women. Obstet Gynecol. 1994 Dec;84(6):1033-7.
26. Colman GJ, Joyce T. Trends in smoking before, during, and after pregnancy in ten states. Am J Prev Med. 2003 Jan;24(1):29-35.
27. Heaman MI, Chalmers K. Prevalence and correlates of smoking during pregnancy: a comparison of aboriginal and non-aboriginal women in manitoba. Birth. 2005 Dec;32(4):299-305.
28. Acevedo-Garcia D, Pan J, Jun HJ, Osypuk TL, Emmons KM. The effect of immigrant generation on smoking. Soc Sci Med. 2005 Sep;61(6):1223-42.
29. Hofman A, Jaddoe VW, Mackenbach JP, Moll HA, Snijders RF, Steegers EA, et al. Growth, development and health from early fetal life until young adulthood: the Generation R Study. Paediatr Perinat Epidemiol. 2004 Jan;18(1):61-72.
30. Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, et al. The Generation R Study: Design and cohort profile. Eur J Epidemiol. 2006;21(6):475-84.
31. Statistics Netherlands. Migrants in the Netherlands, 2003; 2003.
32. Lopez AD, Collishaw NE, Piha T. A descriptive model of the cigarette epidemic in developed countries. Tob Control. 1994 September 1, 1994;3(3):242-7.
33. Nierkens V. Smoking in a multicultural society: Implications for prevention [Dissertation]. Amsterdam: Academic Medical Center, University of Amsterdam; 2006.
34. van Leest LATM, van Dis SJ, Verschuren WMM. Cardiovascular diseases in non-western immigrants in the Netherlands. An exploratory study into lifestyle- and risk factors, morbidity and mortality [In Dutch]. Bilthoven: National Institute for Public Health and the Environment; 2002.
35. Curry SJ, Wagner EH, Cheadle A, Diehr P, Koepsell T, Psaty B, et al. Assessment of community-level influences on individuals' attitudes about cigarette smoking, alcohol use, and consumption of dietary fat. Am J Prev Med. 1993 Mar-Apr;9(2):78-84.

36. Carmichael SL, Ahluwalia IB. Correlates of postpartum smoking relapse. Results from the Pregnancy Risk Assessment Monitoring System (PRAMS). Am J Prev Med. 2000 Oct;19(3):193-6.
37. Ratner PA, Johnson JL, Bottorff JL, Dahinten S, Hall W. Twelve-month follow-up of a smoking relapse prevention intervention for postpartum women. Addict Behav. 2000 Jan-Feb;25(1):81-92.
38. Ogawa H, Tominaga S, Hori K, Noguchi K, Kanou I, Matsubara M. Passive smoking by pregnant women and fetal growth. J Epidemiol Community Health. 1991 June 1, 1991;45(2):164-8.
39. Hofhuis W, de Jongste JC, Merkus PJFM. Adverse health effects of prenatal and postnatal tobacco smoke exposure on children. Arch Dis Child. 2003 December 1, 2003;88(12):1086-90.
40. Severson HH, Andrews JA, Lichtenstein E, Wall M, Akers L. Reducing maternal smoking and relapse: long-term evaluation of a pediatric intervention. Prev Med. 1997 Jan-Feb;26(1):120-30.
41. McDonald AD, Armstrong BG, Sloan M. Cigarette, alcohol, and coffee consumption and prematurity. Am J Public Health. 1992 Jan;82(1):87-90.
42. Stotts AL, Shipley SL, Schmitz JM, Sayre SL, Grabowski J. Tobacco, alcohol and caffeine use in a low-income, pregnant population. J Obstet Gynaecol. 2003 May;23(3):247-51.
43. Lundsberg LS, Bracken MB, Saftlas AF. Low-to-moderate gestational alcohol use and intrauterine growth retardation, low birthweight, and preterm delivery. Ann Epidemiol. 1997 Oct;7(7):498-508.
44. Mariscal M, Palma S, Llorca J, Perez-Iglesias R, Pardo-Crespo R, Delgado-Rodriguez M. Pattern of alcohol consumption during pregnancy and risk for low birth weight. Ann Epidemiol. 2006 Jun; 16(6):432-8.
45. Cabral H, Fried LE, Levenson S, Amaro H, Zuckerman B. Foreign-born and US-born black women: differences in health behaviors and birth outcomes. Am J Public Health. 1990 Jan;80(1):70-2.
46. Marin G, Perez-Stable EJ, Marin BV. Cigarette smoking among San Francisco Hispanics: the role of acculturation and gender. Am J Public Health. 1989 Feb;79(2):196-8.
47. Wolff CB, Portis M. Smoking, acculturation, and pregnancy outcome among Mexican Americans. Health Care Women Int. 1996 Nov-Dec;17(6):563-73.
48. Klebanoff MA, Levine RJ, Morris CD, Hauth JC, Sibai BM, Ben Curet L, et al. Accuracy of self-reported cigarette smoking among pregnant women in the 1990s. Paediatr Perinat Epidemiol. 2001 Apr; 15(2):140-3.
49. Hebel JR, Fox NL, Sexton M. Dose-response of birth weight to various measures of maternal smoking during pregnancy. J Clin Epidemiol. 1988;41(5):483-9.
50. Perez-Stable EJ, Benowitz NL, Marin G. Is serum cotinine a better measure of cigarette smoking than self-report? Prev Med. 1995 Mar;24(2):171-9.
51. Wang X, Tager IB, Van Vunakis H, Speizer FE, Hanrahan JP. Maternal smoking during pregnancy, urine cotinine concentrations, and birth outcomes. A prospective cohort study. Int J Epidemiol. 1997 Oct; 26(5):978-88.
52. England LJ, Kendrick JS, Gargiullo PM, Zahniser SC, Hannon WH. Measures of maternal tobacco exposure and infant birth weight at term. Am J Epidemiol. 2001 May 15;153(10):954-60.
53. Haddow JE, Knight GJ, Palomaki GE, Kloza EM, Wald NJ. Cigarette consumption and serum cotinine in relation to birthweight. Br J Obstet Gynaecol. 1987 Jul;94(7):678-81.
54. Bauman KE, Ennett SE. Tobacco use by black and white adolescents: the validity of self-reports. Am J Public Health. 1994 Mar;84(3):394-8.
55. Clark PI, Gautam SP, Hlaing WM, Gerson LW. Response error in self-reported current smoking frequency by black and white established smokers. Ann Epidemiol. 1996 Nov;6(6):483-9.
56. Wagenknecht LE, Burke GL, Perkins LL, Haley NJ, Friedman GD. Misclassification of smoking status in the CARDIA study: a comparison of self-report with serum cotinine levels. Am J Public Health. 1992 Jan;82(1):33-6.
57. England LJ, Kendrick JS, Wilson HG, Merritt RK, Gargiullo PM, Zahniser SC, et al. Effects of smoking reduction during pregnancy on the birth weight of term infants. 2001 Oct 15;154(8):694-701.

# 8

# Ethnic differences in gestational duration, preterm and very preterm delivery



## Abstract

*Objectives:* The aim of this study was to examine whether ethnic differences in gestational duration, preterm and very preterm delivery may be explained by biological, socio-demographic, lifestyle and medical determinants.

*Methods:* Multivariate linear (gestational duration) and logistic (preterm and very preterm) regression models were used to examine the impact of biological, socio-demographic, lifestyle and obstetrical determinants on ethnic differences in gestational duration, preterm (32-37 weeks) and very preterm (< 32 weeks) birth. We compared women with a Dutch ethnic background to women with a Moroccan, Turkish, Antillean, Capeverdean, Surinamese-creole and Surinamese-hindustani ethnic background.

*Results:* Compared to Dutch women, we observed that gestational duration is longer in Moroccan women and shorter in Antillean, Surinamese-creole and Surinamese-hindustani women. The odds ratios for preterm delivery were increased in Antillean (OR 1.5, 95% CI: 0.9, 2.4) and Surinamese-hindustani populations (OR 1.6, 95% CI: 1.0, 2.4) compared to the Dutch population. The increased odds ratios in these populations were largely explained by maternal height. Moroccan women had a decreased odds ratio for preterm delivery (adjusted OR 0.5, 95% CI: 0.3, 0.9) compared to Dutch women. Surinamese-creole women had an increased risk of delivering very preterm (OR 3.1, 95% CI: 1.2, 8.2) compared to Dutch women, which was only partly explained by the explanatory determinants.

*Conclusions:* Our findings suggest that ethnic differences in gestational duration and preterm delivery are for a large part determined by biological factors. Ethnic differences in very preterm delivery could not be completely understood, and further study is wanted in order to obtain a fuller understanding.

## Introduction

Preterm delivery is considered as the most important cause of perinatal morbidity and mortality (1). In many industrialized countries ethnic differences in (very) preterm delivery has been observed (2-4). In the United States several studies have shown that risk of preterm or very preterm delivery is increased in black, Mexican-American and Asian women (2, 3). In the United Kingdom an increased risk of preterm delivery is observed in Afro-Caribbean and African women (4). Also in the Netherlands differences in rates of preterm delivery between ethnic populations have been found (5). Besides these differences in preterm and very preterm delivery, also ethnic variations in gestational duration have been observed. Previous studies have indicated that gestational duration is shorter in black and Asian women compared to white women (6, 7).

Several investigators have tried to elucidate the underlying mechanisms of these differences by looking at socio-demographic, lifestyle, medical and genetic factors. Known socio-demographic and lifestyle determinants that are associated with preterm delivery are: teenage or older mothers (8), low education (8), unmarried or single motherhood (9), low maternal prepregnancy body mass index (9), cigarette smoking (9, 10), alcohol consumption (11, 12), and short stature (13). Obstetrical factors such as previous preterm delivery and pre-eclampsia are also associated with preterm deliveries (9, 14, 15). Still, the reasons for ethnic differences in gestational duration, preterm and very preterm delivery are still largely unknown. This is probably the result of the complex multifactorial pathophysiology.

With this study we aim to disentangle the mechanisms underlying the ethnic differences in gestational duration, preterm and very preterm delivery. Identifying these determinants may be of importance for ethnic specific strategies for the prevention of preterm and very preterm delivery.

In a population-based multi-ethnic cohort study among pregnant women we examined the association of ethnic background with gestational duration, preterm and very preterm delivery. Furthermore, we examined whether ethnic differences in gestational duration, preterm and very preterm delivery may be explained by biological, socio-demographic, lifestyle and obstetrical determinants.

## Methods

### Design

This study is embedded in the Generation R study, a population-based prospective cohort study from fetal life until young adulthood. The Generation R Study is designed to identify early environmental and genetic determinants of growth, development and

health in fetal life, childhood and adulthood and has been described previously in detail (16, 17). Briefly, all pregnant women and their partners in a previously defined area in Rotterdam, the Netherlands, were approached, either by community midwife or hospital based Generation R staff, at their first antenatal visit. Most women spoke Dutch and if otherwise, the study was explained and questionnaires were available in their own language. In total, 9,778 women participated, of which 8,880 enrolled during pregnancy and 898 at birth of their child. All participating women had a delivery date between April 2002 and January 2006. Data in pregnancy were collected from physical examinations, fetal ultrasounds and questionnaires. Women were usually seen for the first time before the 18th week of the pregnancy and in total three times during pregnancy, in early (gestational age < 18 weeks), mid (gestational age 18 - 25 weeks) and late pregnancy (gestational age ≥ 25 weeks) in a research setting. The individual time scheme of these assessments depended on the specific gestational age at enrolment. Of all eligible children in the study area, 61% participated at birth (17). The Medical Ethics Committee of the Erasmus Medical Center approved the Generation R Study. Written informed consent was obtained from all participants.

**Ethnic background**

Ethnic background of the participating pregnant woman was assessed by the country of birth of the woman herself and her parents. Information about countries of birth was obtained by questionnaire. The participating pregnant woman was of non-Dutch ethnic origin if one of her parents was born abroad (18). If both parents were born abroad, the country of birth of the participant's mother decided on the ethnic background.

Besides women of Dutch ethnic background, a distinction was made among the non-Dutch populations included in this study: Moroccan, Turkish, Capeverdean, Antillean and Surinamese. Women with an ethnic background other than these were grouped as other-western for European, North American, Oceanean, Japanese and Indonesian, and as other non-western for African, Asian (except Japanese and Indonesian) and South- and Central American. Women with a Surinamese background are of mixed ethnic origin, mainly consisting of Hindustanis originating from India, and Creoles from Africa. These women were asked about their ethnic origin and further classified as Surinamese-hindustani, Surinamese-creole or Surinamese-other.

**Gestational duration, preterm and very preterm delivery**

Gestational duration was established by fetal ultrasound examination because using the last menstrual period has several limitations, including the large number of women who do not know the exact date of their last menstrual period or have irregular menstrual cycles (19). Pregnancy dating curves were constructed for subjects with complete data on gestational age measured by ultrasonography and the last menstrual period. Crown-

rump length was used for pregnancy dating up to a gestational age of 12 weeks and 5 days (crown-rump length < 65 mm), and biparietal diameter was used for pregnancy dating thereafter (gestational age from 12 weeks and 5 days onwards, biparietal diameter > 23 mm) (20).

Full-term birth was defined as birth between 37 completed weeks and before 42 completed weeks of gestation. Preterm delivery was defined as birth between 32 completed weeks and before 37 completed weeks of pregnancy and very preterm as birth before 32 completed weeks of pregnancy.

**Determinants**

Information on the biological determinant (maternal height) was obtained at time of enrolment. The height of the participating women was measured without shoes. Information on the socio-demographic (maternal age, marital status, educational level) and lifestyle (maternal smoking and alcohol consumption during pregnancy) determinants was obtained by questionnaires. The third lifestyle-related determinant, maternal body mass index, was calculated from maternal weight and maternal height (weight/height$^2$ (kg/m$^2$)), and adjusted for gestational age at intake. Information on the obstetric determinants (pre-eclampsia, gestational hypertension, parity) was retrieved from the medical records of the participating women.

Except for maternal height and maternal age, all determinants were dichotomized for analyses. Marital status was classified as: (1) single mother and (2) married/cohabiting; Educational level was classified by highest completed education: (1) low for primary school and (2) high for secondary school or higher; Maternal body mass index was classified as: (1) <= 30 kg/m$^2$ and (2) > 30 kg/m$^2$; Maternal smoking, alcohol consumption, pre-eclampsia and gestational hypertension were classified as: (1) yes and (2) no.

**Population for analysis**

Of the women who enrolled in the Generation R Study (n=8880), those with missing data on their ethnic background (n=653, 7.4%) were excluded from present study. Of the remaining 8,227 women, we excluded those with twin pregnancies (n=93), abortion (n=29), intra-uterine or perinatal death (n=75) and missing birth outcomes (n=45) were excluded from analyses. The results of women with a 'Surinamese-other' (n=166), 'other-western' (n=919) and 'other non-western' (n=506) ethnic background are not presented, because of the mixed composition of these populations. This left 6,349 pregnant women with a Dutch, Turkish, Moroccan, Surinamese-creole, Surinamese-hindustani, Antillean or Capeverdean ethnic background for the current study.

### Data analyses

The non-Dutch populations under consideration were compared with the reference (Dutch) population. The differences in baseline characteristics were compared using the Chi-square statistic for categorical variables and analysis of variance (ANOVA) for continuous variables.

First we examined the associations of the biological, socio-demographic, lifestyle and obstetrical determinants with gestational age, preterm and very preterm delivery. In these analyses ethnic background, maternal age and parity were considered as confounders. Secondly, multivariate linear and logistic regression analyses were used to examine the association of ethnic background with gestational duration, preterm and very preterm delivery, comparing the non-Dutch populations with the reference population. In these analyses maternal age and parity were considered as confounders. In these regression analyses, a basic model was constructed adjusted for confounders. Additionally, by adding each determinant solely to this model, we examined the individual effect of the separate determinants on the ethnic differences in gestational duration, preterm and very preterm delivery. Finally, a full model was constructed by adding all determinants to the basic model. All measures of association are presented with their 95 % confidence interval (CI). The statistical analyses were performed using Statistical Package of Social Sciences version 11.0 for Windows (SPSS Inc, Chicago, IL, USA).



## Results

### Subject characteristics

Of the total of 6,394 pregnant women, 3,958 women were Dutch (61.9%), 541 Moroccan (8.5%), 734 Turkish (11.5%), 333 Capeverdean (5.2%), 274 Antillean (4.3%), 272 Surinamese-creole (4.3%), 282 Surinamese-hindustani (4.4%)(table1). Non-Dutch pregnant women had a lower age, were shorter of height and were lower educated compared to Dutch pregnant women ($p < 0.001$). Mean body mass index at enrolment was highest for Moroccan women (26.1 kg/m2). Moroccan and Turkish women were more frequently married than Dutch women ($p < 0.001$). Single motherhood was more common among the Capeverdean, Antillean and Surinamese women compared to Dutch women ($p < 0.001$). Maternal smoking during pregnancy was more frequently observed among the Turkish women compared to the Dutch women ($p < 0.001$). Non-Dutch women were less likely to consume alcohol during pregnancy compared to Dutch women ($p < 0.001$). Multiparity was most common amongst Moroccan (61.3%) and Turkish women (54.8%), compared to 40.5% among Dutch women ($p < 0.001$). Pre-eclampsia was most frequently observed among Surinamese-hindustani women (3.9%), while gestational hypertension was most frequent among Surinamese-creole women (5.7%).

**Table 1.** Subject characteristics.

| | Dutch | Moroccan | Turkish | Cape-verdean | Antillean | Surinamese-creole | Surinamese-hindustani | P-value |
|---|---|---|---|---|---|---|---|---|
| N | n = 3958 | n = 541 | n = 734 | n = 333 | n = 274 | n = 272 | n = 282 | |
| age (years) | 31.3 (4.5) | 28.0 (5.3) | 27.1 (4.9) | 27.3 (6.0) | 26.2 (5.4) | 27.7 (6.4) | 27.5 (5.0) | p < 0.001 |
| maternal height (cm) | 171 (6.4) | 163 (5.6) | 162 (5.8) | 165 (6.6) | 165 (6.2) | 166 (6.7) | 161 (5.9) | p < 0.001 |
| body mass index (kg/m$^2$) | 24.2 (4.1) | 26.1 (4.7) | 25.9 (4.9) | 24.5 (4.3) | 26.0 (5.4) | 25.6 (5.6) | 24.2 (5.0) | p < 0.001 |
| educational level (%) | | | | | | | | p < 0.001 |
| *lower education* | 3.8 | 23.7 | 29.4 | 21.6 | 16.4 | 10.7 | 13.5 | |
| *higher education* | 90.6 | 62.3 | 59.3 | 68.8 | 77.0 | 86.4 | 85.1 | |
| *missing* | 5.6 | 14.0 | 11.3 | 9.6 | 6.6 | 2.9 | 1.4 | |
| marital status (%) | | | | | | | | p < 0.001 |
| *married/cohabiting* | 85.4 | 86.9 | 85.3 | 42.6 | 44.2 | 44.9 | 71.6 | |
| *single mother* | 7.3 | 3.1 | 4.9 | 46.8 | 48.2 | 53.7 | 24.8 | |
| *missing* | 7.3 | 10.0 | 9.8 | 10.5 | 7.7 | 1.5 | 3.5 | |
| smoking (%) | | | | | | | | p < 0.001 |
| *non-smoker* | 75.7 | 85.2 | 61.3 | 68.5 | 73.7 | 76.8 | 80.9 | |
| *smoker during pregnancy* | 16.8 | 5.2 | 29.8 | 19.2 | 18.6 | 21.3 | 17.0 | |
| *missing* | 7.5 | 9.6 | 8.9 | 12.3 | 7.7 | 1.8 | 2.1 | |
| alcohol consumption (%) | | | | | | | | p < 0.001 |
| *no* | 44.2 | 87.6 | 83.8 | 58.6 | 59.5 | 54.4 | 74.8 | |
| *yes* | 49.0 | 3.1 | 6.8 | 29.1 | 29.2 | 35.3 | 17.7 | |
| *missing* | 6.8 | 9.2 | 9.4 | 12.3 | 11.3 | 10.3 | 7.4 | |
| parity (%) | | | | | | | | p < 0.001 |
| *0* | 59.0 | 38.6 | 44.8 | 55.3 | 57.7 | 55.1 | 58.2 | |
| *>= 1* | 40.3 | 60.8 | 53.8 | 42.9 | 41.6 | 44.5 | 41.5 | |
| *missing* | 0.8 | 0.6 | 1.4 | 1.8 | 0.7 | 0.4 | 0.4 | |
| pre-eclampsia (%) | | | | | | | | p = 0.004 |
| *no* | 96.1 | 97.2 | 96.2 | 94.9 | 91.6 | 93.4 | 94.3 | |
| *yes* | 1.8 | 0.9 | 2.0 | 3.3 | 3.6 | 3.3 | 3.9 | |
| *missing* | 2.1 | 1.8 | 1.8 | 1.8 | 4.7 | 3.3 | 1.8 | |
| pregnancy induced hypertension (%) | | | | | | | | p < 0.001 |
| *no* | 92.9 | 96.7 | 96.6 | 95.2 | 92.7 | 91.2 | 95.4 | |
| *yes* | 5.0 | 1.5 | 1.6 | 3.0 | 2.6 | 5.5 | 2.8 | |
| *missing* | 2.1 | 1.8 | 1.8 | 1.8 | 4.7 | 3.3 | 1.8 | |
| gestational age (weeks) | 39.9 (1.8) | 40.2 (1.6) | 39.8 (1.7) | 39.7 (1.9) | 39.4 (1.9) | 39.5 (2.2) | 39.3 (1.8) | p < 0.001 |
| preterm birth (%) | 4.7 | 2.8 | 5.3 | 5.1 | 7.7 | 5.5 | 8.2 | p = 0.02 |
| very preterm birth (%) | 0.6 | 0.6 | 0.3 | 0.9 | 1.1 | 1.8 | 0.4 | p = 0.13 |

Values are means (standard deviation) or percentages.

P-values are result of $\chi^2$ test for categorical variables or analysis of variance (ANOVA) for continuous variables, Dutch is reference.

The highest rates of preterm delivery were observed among the Antillean (8.2%), Surinamese-creole (7.3%), Surinamese-hindustani (8.5%) and Surinamese-other women (7.2%). The rate of very preterm deliveries was highest among the Surinamese-creole women (1.8%).

### Associations of determinants with gestational duration, preterm and very preterm birth

Table 2 presents the associations of the studied determinants with gestational duration, preterm and very preterm birth. Low maternal height, single motherhood, maternal smoking, body mass index above 30 kg/m$^2$ and pre-eclampsia were all associated with shorter gestational duration. Only maternal alcohol consumption during pregnancy was associated with longer gestational duration.

Low maternal height, single motherhood, maternal smoking during pregnancy and pre-eclampsia were all associated with an increased risk of preterm birth. Only presence of pre-eclampsia was significantly associated with very preterm birth, but non-significant associations were found between marital status and maternal smoking and very preterm birth.



**Table 2.** Associations of explanatory variables with gestational age, preterm birth (32-37 weeks) and very preterm birth (< 32 weeks).

| | Gestational age | Preterm birth | Very preterm birth |
|---|---|---|---|
| | Change in weeks | OR (95% CI) | OR (95% CI) |
| **Maternal height (per 10 cm)** | 0.21 (0.14, 0.28)** | 0.7 (0.5, 0.8)** | 1.0 (0.6, 1.6) |
| **Educational level (low vs high)** | -0.13 (-0.28, 0.02) | 1.0 (0.6, 1.5) | 0.9 (0.3, 3.0) |
| **Marital status (single mother vs married/ cohabiting)** | -0.25 (-0.40, -0.10)** | 1.5 (1.1, 2.1)* | 1.7 (0.7, 4.3) |
| **Maternal smoking (yes vs no)** | -0.23 (-0.35, -0.11)** | 1.5 (1.2, 2.5)* | 1.6 (0.8, 3.4) |
| **Maternal alcohol consumption (yes vs no)** | 0.17 (0.7, 0.27)** | 1.0 (0.8, 1.3) | 0.6 (0.3, 1.4) |
| **Maternal BMI (> 30 vs <=30)** | -0.19 (-0.33, -0.05)* | 0.7 (0.5, 1.1) | 0.8 (0.3, 2.0) |
| **Pre-eclampsia (yes vs no)** | -2.17 (-2.47, -1.87)** | 5.8 (3.7, 8.9)** | 18.9 (8.7, 41.4)** |
| **Gestational hypertension (yes vs no)** | -0.12 (-0.34, 0.10) | 0.8 (0.4, 1.5) | 0.6 (0.1, 4.2) |

All associations were adjusted for ethnic background, parity and age of the mother.
** p-value < 0.001, * p-value < 0.05

### Ethnic differences in gestational duration, preterm and very preterm delivery

Table 3 presents the differences in gestational duration of the non-Dutch populations compared to the Dutch population. The gestational duration in Moroccan women was significantly longer than in Dutch women (0.32 weeks, 95% CI: 0.16, 0.48). Gestational duration in women with an Antillean, Surinamese-creole and Surinamese-hindustani ethnic background was significant shorter compared to Dutch women (Antillean: -0.51 weeks, 95% CI:-0.72, -0.29; Surinamese-creole: -0.47 weeks, 95% CI:-0.69, -0.26; Surinam-

**Table 3.** The difference in gestational length (weeks) of the non-Dutch populations compared to the Dutch population and the effect of the individual determinants in explaining ethnic differences in gestational length.

| | Moroccan | Turkish | Capeverdean | Antillean | Surinamese-creole | Surinamese-hindustani |
|---|---|---|---|---|---|---|
| | Difference in gestational length in weeks (95% CI) | | | | | |
| **Unadjusted** | 0.32 (0.16, 0.48)** | -0.08 (-0.22, 0.06) | -0.19 (-0.38, 0.01) | -0.51 (-0.72, -0.29)** | -0.47 (-0.69, -0.26)** | -0.67 (-0.88, -0.46)** |
| **Adjusted for confounders** | 0.34 (0.18, 0.51)** | -0.05 (-0.20, 0.10) | -0.14 (-0.34, 0.06) | -0.45 (-0.67, -0.23)** | -0.43 (-0.65, -0.21)** | -0.63 (-0.85, -0.42)** |
| **+ Maternal height (per 10 cm)** | 0.52 (0.35, 0.70)** | 0.15 (-0.01, 0.31) | -0.00 (-0.21, 0.20) | -0.32 (-0.55, -0.09)* | -0.32 (-0.55, -0.10)* | -0.43 (-0.66, -0.20)** |
| **+ Educational level (low vs high)** | 0.38 (0.21, 0.54)** | -0.01 (-0.16, 0.14) | -0.11 (-0.32, 0.09) | -0.44 (-0.66, 0.21)** | -0.42 (-0.65, -0.20)** | -0.63 (-0.85, -0.41)** |
| **+ Marital status (single mother vs married/ cohabiting)** | 0.33 (0.17, 0.50)** | -0.06 (-0.21, 0.09) | -0.05 (-0.26, 0.16) | -0.36 (-0.59, -0.13)* | -0.33 (-0.56, -0.10)* | -0.60 (-0.82, -0.39)** |
| **+ Maternal smoking (yes vs no)** | 0.31 (0.15, 0.48)** | -0.03 (-0.17, 0.12) | -0.13 (-0.33, 0.07) | -0.46 (-0.68, 0.23)** | -0.44 (-0.66, -0.22)** | -0.65 (-0.87, -0.44)** |
| **+ Maternal alcohol consumption (yes vs no)** | 0.41 (0.24, 0.58)** | 0.01 (-0.14, 0.16) | -0.11 (-0.31, 0.09) | -0.42 (-0.65, -0.20)** | -0.41 (-0.63, -0.19)** | -0.59 (-0.81, -0.37)** |
| **+ Maternal BMI (> 30 vs <=30)** | 0.35 (0.19, 0.52)** | -0.04 (-0.19, 0.11) | -0.14 (-0.34, 0.07) | -0.44 (-0.66, -0.22)** | -0.41 (-0.63, -0.19)** | -0.63 (-0.85, -0.41)** |
| **+ Pre-eclampsia (yes vs no)** | 0.33 (0.17, 0.49)** | -0.04 (-0.19, 0.10) | -0.11 (-0.31, 0.09) | -0.40 (-0.62, -0.18)** | -0.39 (-0.61, -0.17)** | -0.59 (-0.80, -0.38)** |
| **+ Gestational hypertension (yes vs no)** | 0.34 (0.17, 0.50)** | -0.06 (-0.20, 0.09) | -0.15 (-0.35, 0.06) | -0.44 (-0.67, -0.22)** | -0.42 (-0.64, -0.20)** | -0.64 (-0.86, -0.42)** |
| **Full Model** | 0.41 (0.24, 0.58)** | 0.10 (-0.05, 0.26) | 0.03 (-0.34, 0.06) | -0.28 (-0.67, -0.23)** | -0.27 (-0.50, -0.05)* | -0.46 (-0.68, -0.24)** |

** p-value < 0.001, * p-value < 0.05.

ese-hindustani: -0.67 weeks, 95% CI:-0.88, -0.46). These differences in gestational duration remained approximately the same adjusted for the confounding determinants. Of the explanatory determinants, maternal height had the most substantial effect on the differences in gestational duration. After full adjustment a shorter gestational duration was observed in the Antillean, Surinamese-creole and Surinamese-hindustani populations and a longer gestational duration was observed in the Moroccan population.

Table 4 presents the associations of ethnic background with preterm delivery and the individual effects of the separate determinants on the ethnic differences in preterm delivery. The odds ratios for preterm delivery were increased in the Antillean (OR 1.6, 95% CI: 1.0, 2.6) and Surinamese-hindustani populations (OR 1.7, 95% CI: 1.1, 2.7) compared to the Dutch population. The increased odds ratios in these populations were largely explained by maternal height. Moroccan women had a decreased odds ratio for preterm delivery (unadjusted OR 0.6, 95% CI: 0.3, 1.0) compared to Dutch women. The

**Table 4.** The association of ethnic background with preterm delivery and the effect of the individual determinants in explaining ethnic differences in with preterm delivery (32-37 weeks, Dutch is reference).

| | Moroccan | Turkish | Capeverdean | Antillean | Surinamese-creole | Surinamese-hindustani |
|---|---|---|---|---|---|---|
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| **Unadjusted** | 0.6 (0.3, 1.0) * | 1.1 (0.8, 1.6) | 1.1 (0.6, 1.8) | 1.6 (1.0, 2.6) * | 1.2 (0.7, 2.0) | 1.7 (1.1, 2.7) * |
| **Adjusted for confounders** | 0.6 (0.3, 1.0) | 1.1 (0.8, 1.7) | 1.0 (0.6, 1.7) | 1.5 (0.9, 2.4) | 1.1 (0.6, 1.8) | 1.6 (1.0, 2.6) * |
| **+ Maternal height (per 10 cm)** | 0.4 (0.2, 0.8) * | 0.8 (0.5, 1.2) | 0.8 (0.5, 1.3) | 1.2 (0.7, 1.9) | 0.9 (0.5, 1.5) | 1.1 (0.7, 1.8) |
| **+ Educational level (low vs high)** | 0.6 (0.3, 1.0) | 1.1 (0.8, 1.7) | 1.0 (0.6, 1.7) | 1.5 (0.9, 2.4) | 1.1 (0.6, 1.8) | 1.6 (1.0, 2.6) * |
| **+ Marital status (single mother vs married/cohabiting)** | 0.6 (0.4, 1.1) | 1.2 (0.8, 1.7) | 0.9 (0.5, 1.5) | 1.3 (0.8, 2.1) | 0.9 (0.5, 1.6) | 1.5 (1.0, 2.4) |
| **+ Maternal smoking (yes vs no)** | 0.6 (0.4, 1.1) | 1.1 (0.8, 1.6) | 1.0 (0.6, 1.6) | 1.5 (0.9, 2.5) | 1.1 (0.6, 1.9) | 1.7 (1.1, 2.7) * |
| **+ Maternal alcohol consumption (yes vs no)** | 0.6 (0.3, 1.0) | 1.1 (0.8, 1.7) | 1.0 (0.6, 1.7) | 1.5 (0.9, 2.4) | 1.1 (0.6, 1.8) | 1.6 (1.0, 2.6) * |
| **+ Maternal BMI (> 30 vs <=30)** | 0.6 (0.3, 1.0) | 1.1 (0.8, 1.6) | 1.0 (0.6, 1.7) | 1.5 (0.9, 2.4) | 1.0 (0.6, 1.8) | 1.6 (1.0, 2.6) * |
| **+ Pre-eclampsia (yes vs no)** | 0.6 (0.4, 1.1) | 1.1 (0.8, 1.6) | 0.9 (0.6, 1.6) | 1.4 (0.9, 2.3) | 1.0 (0.6, 1.8) | 1.5 (1.0, 2.4) |
| **+ Gestational hypertension (yes vs no)** | 0.6 (0.3, 1.0) | 1.1 (0.8, 1.7) | 1.0 (0.6, 1.7) | 1.4 (0.9, 2.4) | 1.0 (0.6, 1.8) | 1.6 (1.0, 2.6) * |
| **Full Model** | 0.5 (0.3, 0.9)* | 0.8 (0.5, 1.2) | 0.7 (0.4, 1.2) | 1.0 (0.6, 1.7) | 0.8 (0.4, 1.4) | 1.0 (0.6, 1.7) |

Values are odds ratios and 95% confidence intervals. ** p-value < 0.001, * p-value < 0.05





decreased odds ratio for Moroccan women was hardly affected by the studied determinants. After full adjustment only a significant lower odds ratio was observed in the Moroccan population (OR 0.5, 95% CI: 0.3, 0.9).

Table 5 presents the associations of ethnic background with very preterm delivery and the individual effects of the separate determinants on the ethnic differences in very preterm delivery. Surinamese-creole women had an increased risk of delivering very preterm (OR 3.3, 95% CI: 1.2, 8.7) compared to Dutch women, which was not affected by maternal height and could only be partly explained by marital status and pre-eclampsia. After full adjustment a non-significant association was observed in the Surinamese-creole population (OR 2.0, 95% CI: 0.6, 6.3).

**Table 5.** The association of ethnic background with very preterm delivery and the effect of the individual determinants in explaining ethnic differences in very preterm delivery (< 32 weeks, Dutch is reference).

| | Moroccan | Turkish | Capeverdean | Antillean | Surinamese-creole | Surinamese-hindustani |
|---|---|---|---|---|---|---|
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| **Unadjusted** | 1.0 (0.3, 3.3) | 0.5 (0.1, 2.1) | 1.6 (0.5, 5.4) | 2.0 (0.6,6.7) | 3.3 (1.2, 8.7) * | 0.6 (0.1, 4.7) |
| **Adjusted for confounders** | 0.9 (0.3, 3.2) | 0.5 (0.1, 2.0) | 1.4 (0.4, 4.8) | 1.7 (0.5, 5.8) | 2.8 (1.0, 7.8) * | 0.6 (0.1, 4.2) |
| **+ Maternal height (per 10 cm)** | 0.9 (0.2, 3.3) | 0.4 (0.1, 2.1) | 1.4 (0.4, 4.9) | 1.6 (0.5, 5.9) | 2.8 (1.0, 7.8) | 0.5 (1.0, 4.3) |
| **+ Educational level (low vs high)** | 0.8 (0.2, 2.9) | 0.4 (0.1, 1.8) | 1.3 (0.4, 4.7) | 1.6 (0.5, 5.8) | 3.0 (1.1, 8.2) * | 0.6 (0.1, 4.6) |
| **+ Marital status (single mother vs married)** | 1.0 (0.3, 3.3) | 0.5 (0.1, 2.0) | 1.1 (0.3, 4.0) | 1.4 (0.4, 5.0) | 2.4 (0.8, 7.3) | 0.5 (0.1, 4.1) |
| **+ Maternal smoking (yes vs no)** | 1.0 (0.3, 3.6) | 0.4 (0.1, 1.9) | 1.4 (0.4, 4.8) | 1.7 (0.5, 5.9) | 2.9 (1.0, 7.9) * | 0.6 (0.1, 4.4) |
| **+ Maternal alcohol use (yes vs no)** | 0.8 (0.2, 2.8) | 0.4 (0.1, 1.8) | 1.3 (0.4, 4.4) | 1.5 (0.4, 5.3) | 2.6 (1.0, 7.3) | 0.5 (0.1, 3.9) |
| **+ Maternal BMI (> 30 vs <=30)** | 0.9 (0.3, 3.2) | 0.4 (0.1, 2.0) | 1.4 (0.4, 4.8) | 1.6 (0.5, 5.7) | 2.7 (1.0, 7.6) | 0.6 (0.1, 4.2) |
| **+ Pre-eclampsia (yes vs no)** | 1.0 (0.3, 3.5) | 0.4 (0.1, 1.9) | 1.2 (0.3, 4.3) | 1.4 (0.4, 5.2) | 2.3 (0.8, 6.7) | 0.5 (0.1, 3.6) |
| **+ Gestational hypertension (yes vs no)** | 0.9 (0.3, 3.2) | 0.4 (0.1, 2.0) | 1.4 (0.4, 4.8) | 1.6 (0.5, 5.8) | 2.8 (1.0, 7.8) * | 0.6 (0.1, 4.2) |
| **Full Model** | 0.9 (0.2, 3.5) | 0.4 (0.1, 1.8) | 1.1 (0.3, 4.1) | 1.2 (0.3, 4.6) | 2.0 (0.6, 6.3) | 0.5 (0.1, 4.2) |

Values are odds ratios and 95% confidence intervals. ** p-value < 0.001, * p-value < 0.05

## Discussion

Our results suggest that differences in gestational duration between ethnic groups exist, that could not be explained by the known determinants. The increased risk of preterm delivery in Antillean and Surinamese-hindustani women is for a large part attributable to the shorter height of these women. The increased risk of very preterm deliveries in Surinamese-creole women is only partly understood by the higher rates of single motherhood and pre-eclampsia in this ethnic group. Finally, we observed that gestational duration is longer in Moroccan women compared to Dutch women and that the risk of preterm delivery is decreased in this group. These latter finding could not be understood by the studied determinants.

**Methodological considerations**

The strengths of this study are the prospective population-based design and the detailed information of gestational duration and the information on numerous determinants that may explain the association between ethnic background and gestational age at delivery.

Some limitations, however, need to be addressed. Pregnancy dating was established by fetal ultrasound by using the crown rump length (up to 12 weeks and 5 days) or the biparietal diameter (above 12 weeks and 5 days). Because of the increasing variation in BPD there is increasing uncertainty in pregnancy dating as pregnancy proceeds (21). This misclassification of gestational duration in specific ethnic populations could therefore bias our results. However, no substantial differences in our estimates were observed in a separate analysis of pregnant women that enrolled in early pregnancy, suggesting that misclassification of gestational duration did not largely affect our results.

Information about ethnic background was obtained by questionnaires. Misclassification of ethnic background could be introduced by missing countries of birth of the pregnant woman or her parents. However, in less than 3% the women's ethnic background was defined while one or more countries of birth of herself or her parents were missing. Therefore it seems unlikely that misclassification of ethnic background would alter the observed findings.





**Gestational duration and preterm delivery**

In our study we observed that the gestational duration is shorter in the Antillean, Surinamese-creole and Surinamese-hindustani groups, even after full adjustment. It has been suggested that normal gestational duration varies according to ethnic background. Previous studies have found a shorter gestational duration in black and Asian women and even found indications of earlier fetal maturation in utero in Black and Asian infants (6, 7). Patel et al found that meconium stained amniotic fluid, which is a sign of fetal maturity, is more frequent in preterm Black and Asian infants compared with white European infants [13]. Variations in normal gestational duration and earlier fetal maturation is further supported by studies that observed that gestational age specific mortality rates in black infants are lower than in white infants, which suggests earlier maturation that enhances their survival (22, 23). Our findings imply that normal gestational duration might be shorter in Antillean, Surinamese-creole and Surinamese-hindustani women. Research on fetal maturation and gestational age specific morbidity and mortality is wanted in these populations to obtain a fuller understanding.

We found an increased risk for preterm delivery in the Surinamese-hindustani and Antillean populations compared to the Dutch population. These results are in line with a previous study that reported increased rates of preterm delivery in Blacks and Hindustani women (5). The increased risks in our study were mainly explained by the

lower maternal height of the women in these populations. Several other studies have described an association between low maternal height and preterm delivery (13, 24, 25). If low maternal height is the main determinant of preterm delivery in these specific populations, then it seems that the increased risk of preterm deliveries in these populations is the result of normal physiology. It might be that lower maternal height causes a shift in the gestational age distribution towards lower gestational ages at delivery. We hypothesize that this shift in the gestational age distribution leads to lower gestational age specific morbidity and mortality in these population compared to the Dutch native populations. As a consequence, not all infants born preterm in the Antillean and Surinamese-hindustani populations have to be at increased risk of morbidity and mortality. This hypothesis however needs to be tested in further research.

We observed a longer gestational duration and a decreased risk of preterm delivery in Moroccan women compared to Dutch women. None of the previous studies on ethnic disparities found indications of longer gestational duration in specific ethnic subgroups (6, 7). Our results suggest that the gestational duration in Moroccan women is longer than in Dutch women. We also observed an increased risk of postterm births in Moroccan women (OR 1.8, 95% CI: 1.2, 2.6, data not shown). This finding is remarkable, because pregnant women in the Netherlands are induced to labour at 42 weeks of gestation.

**Very preterm delivery**

We found an increased risk of very preterm delivery, but not preterm delivery, in Surinamese-creole women compared to Dutch women that was only partially explained by the studied determinants. The part that is explained points to the importance of single motherhood in this population. Over 50% of the Surinamese-creole pregnant women are single mother at time of delivery. Single motherhood might be associated with several factors that may increase the risk of very preterm deliveries. Single mothers might be exposed to more stress during pregnancy than mothers who have a partner. Maternal stress during pregnancy seems to be associated with preterm delivery (26, 27). Besides, single mothers might engage in more risk full sexual behaviour, which may lead to a higher prevalence of urogenital infections. Several studies have found associations between urogenital infections and preterm delivery (28-31). In our data we had information on chlamydia trachomatis infection in a sub sample of our study population. Within this sub sample, we observed an increased prevalence of chlamydia trachomatis among Surinamese-creole pregnant women compared to Dutch pregnant women (12.1% versus 1.9%, respectively, data not shown). In a separate analysis, chlamydia trachomatis was strongly associated with very preterm delivery (OR 5.1, 95% CI: 1.7, 15.0, data not shown). In the multivariate analysis in this sub sample, chlamydia trachomatis also reduced the risk of very preterm delivery in Surinamese-creole women by 16%. Further research in this population is wanted to further elucidate the underlying

factors that cause the increased risk of very preterm delivery and find possible pathways for prevention.

**Conclusions**

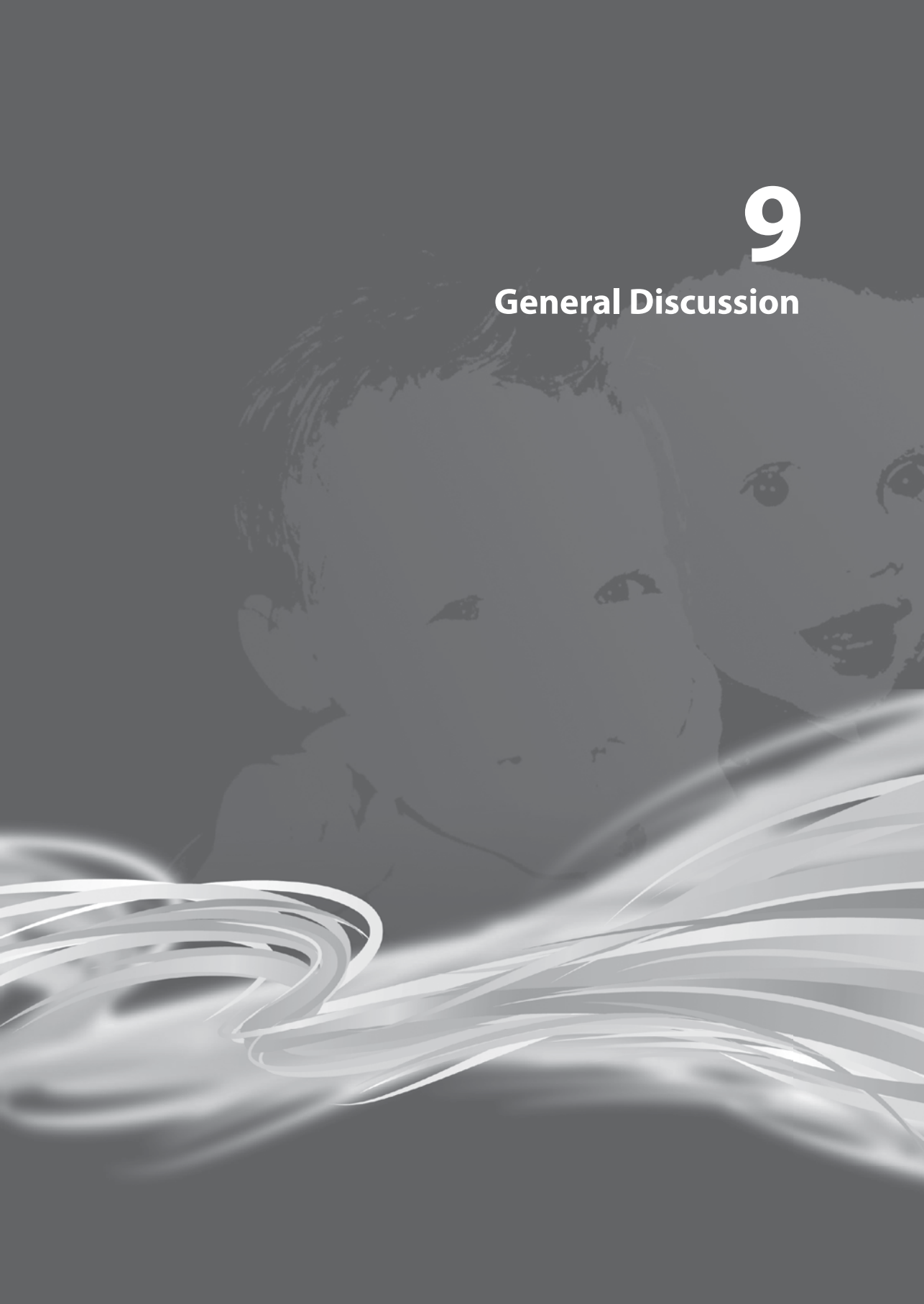
Our study shows that ethnic differences in gestational duration cannot be understood from known determinants of gestational duration. This finding suggests that normal variations may exist in gestational duration between ethnic groups. We found that ethnic differences in preterm delivery were mainly explained by maternal height, suggesting that these differences are for a large part determined by biological factors and therefore are less amenable to modification. Ethnic differences in very preterm delivery could not be completely understood, and further studies are wanted to disentangle the underlying mechanisms.

## References


1. Wilcox AJ, Skjaerven R. Birth weight and perinatal mortality: the effect of gestational age. Am J Public Health. 1992 Mar;82(3):378-82.
2. Schieve LA, Handler A. Preterm delivery and perinatal death among black and white infants in a Chicago-area perinatal registry. Obstet Gynecol. 1996 Sep;88(3):356-63.
3. Shiono PH, Klebanoff MA. Ethnic differences in preterm and very preterm delivery. Am J Public Health. 1986 Nov;76(11):1317-21.
4. Aveyard P, Cheng KK, Manaseki S, Gardosi J. The risk of preterm delivery in women from different ethnic groups. BJOG. 2002 Aug;109(8):894-9.
5. van Enk A, Buitendijk SE, van der Pal KM, van Enk WJ, Schulpen TW. Perinatal death in ethnic minorities in The Netherlands. J Epidemiol Community Health. 1998 Nov;52(11):735-9.
6. Papiernik E, Alexander GR, Paneth N. Racial differences in pregnancy duration and its implications for perinatal care. Med Hypotheses. 1990 Nov;33(3):181-6.
7. Patel RR, Steer P, Doyle P, Little MP, Elliott P. Does gestation vary by ethnic group? A London-based study of over 122,000 pregnancies with spontaneous onset of labour. Int J Epidemiol. 2004 Feb; 33(1):107-13.
8. Astolfi P, Zonta LA. Risks of preterm delivery and association with maternal age, birth order, and fetal gender. Hum Reprod. 1999 Nov;14(11):2891-4.
9. Wen SW, Goldenberg RL, Cutter GR, Hoffman HJ, Cliver SP. Intrauterine growth retardation and preterm delivery: prenatal risk factors in an indigent population. Am J Obstet Gynecol. 1990 Jan;162(1): 213-8.
10. Jaddoe VW, Troe EJWM, Hofman A, Mackenbach JP, Moll HA, Steegers EA, et al. Active and passive maternal smoking patterns in pregnancy and the risk of low birth weight and preterm birth. The Generation R Study. Paediatr Perinat Epidemiol. 2007;Accepted.
11. Lundsberg LS, Bracken MB, Saftlas AF. Low-to-moderate gestational alcohol use and intrauterine growth retardation, low birthweight, and preterm delivery. Ann Epidemiol. 1997 Oct;7(7):498-508.
12. Jaddoe VW, Bakker R, Hofman A, Mackenbach JP, Moll HA, Steegers EA, et al. Moderate Alcohol Consumption During Pregnancy and the Risk of Low Birth Weight and Preterm Birth. The Generation R Study. Ann Epidemiol. 2007 Jun 27.
13. Kramer MS, Coates AL, Michoud MC, Dagenais S, Hamilton EF, Papageorgiou A. Maternal anthropometry and idiopathic preterm labor. Obstet Gynecol. 1995 Nov;86(5):744-8.

14. Villar J, Carroli G, Wojdyla D, Abalos E, Giordano D, Ba'aqeel H, et al. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? Am J Obstet Gynecol. 2006 Apr;194(4):921-31.
15. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005 Feb 26-Mar 4;365(9461):785-99.
16. Hofman A, Jaddoe VW, Mackenbach JP, Moll HA, Snijders RF, Steegers EA, et al. Growth, development and health from early fetal life until young adulthood: the Generation R Study. Paediatr Perinat Epidemiol. 2004 Jan;18(1):61-72.
17. Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, et al. The Generation R Study: Design and cohort profile. Eur J Epidemiol. 2006;21(6):475-84.
18. Statistics Netherlands. Migrants in the Netherlands, 2003; 2003.
19. Tunon K, Eik-Nes SH, Grottum P. A comparison between ultrasound and a reliable last menstrual period as predictors of the day of delivery in 15,000 examinations. Ultrasound Obstet Gynecol. 1996 Sep;8(3):178-85.
20. Verburg BO, Steegers EAP, de Ridder MA, R.J.M. S, A. H, H.A. M, et al. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. Ultrasound in obstetrics and gynecology. 2007;In press.
21. Altman DG, Chitty LS. New charts for ultrasound dating of pregnancy. Ultrasound Obstet Gynecol. 1997 Sep;10(3):174-91.
22. Mittendorf R, Williams MA, Kennedy JL, Jr., Berry RE, Herschel M, Aronson MP, et al. A hypothesis to explain paradoxical racial differences in neonatal mortality. Am J Prev Med. 1993 Nov-Dec;9(6): 327-30.
23. Lyon AJ, Clarkson P, Jeffrey I, West GA. Effect of ethnic origin of mother on fetal outcome. Arch Dis Child Fetal Neonatal Ed. 1994 Jan;70(1):F40-3.
24. Smith GC, Shah I, White IR, Pell JP, Crossley JA, Dobbie R. Maternal and biochemical predictors of spontaneous preterm birth among nulliparous women: a systematic analysis in relation to the degree of prematurity. Int J Epidemiol. 2006 Oct;35(5):1169-77.
25. Harlow BL, Frigoletto FD, Cramer DW, Evans JK, LeFevre ML, Bain RP, et al. Determinants of preterm delivery in low-risk pregnancies. The RADIUS Study Group. J Clin Epidemiol. 1996 Apr;49(4):441-8.
26. Copper RL, Goldenberg RL, Das A, Elder N, Swain M, Norman G, et al. The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1996 Nov;175(5):1286-92.
27. Dole N, Savitz DA, Hertz-Picciotto I, Siega-Riz AM, McMahon MJ, Buekens P. Maternal stress and preterm birth. Am J Epidemiol. 2003 Jan 1;157(1):14-24.
28. Andrews WW, Goldenberg RL, Mercer B, Iams J, Meis P, Moawad A, et al. The Preterm Prediction Study: association of second-trimester genitourinary chlamydia infection with subsequent spontaneous preterm birth. Am J Obstet Gynecol. 2000 Sep;183(3):662-8.
29. Fiscella K. Racial disparities in preterm births. The role of urogenital infections. Public Health Rep. 1996 Mar-Apr;111(2):104-13.
30. Ugwumadu AH. Bacterial vaginosis in pregnancy. Curr Opin Obstet Gynecol. 2002 Apr;14(2):115-8.
31. Hillier SL, Nugent RP, Eschenbach DA, Krohn MA, Gibbs RS, Martin DH, et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group. N Engl J Med. 1995 Dec 28;333(26):1737-42.

# 9
# General Discussion



The general aim of the studies presented in this thesis, was to improve the understanding of the ethnic differences in perinatal and infant mortality by examining ethnic differences in fetal growth, birth weight, gestational age and infant mortality, and by identifying their specific determinants in the non-Dutch populations in the Netherlands.

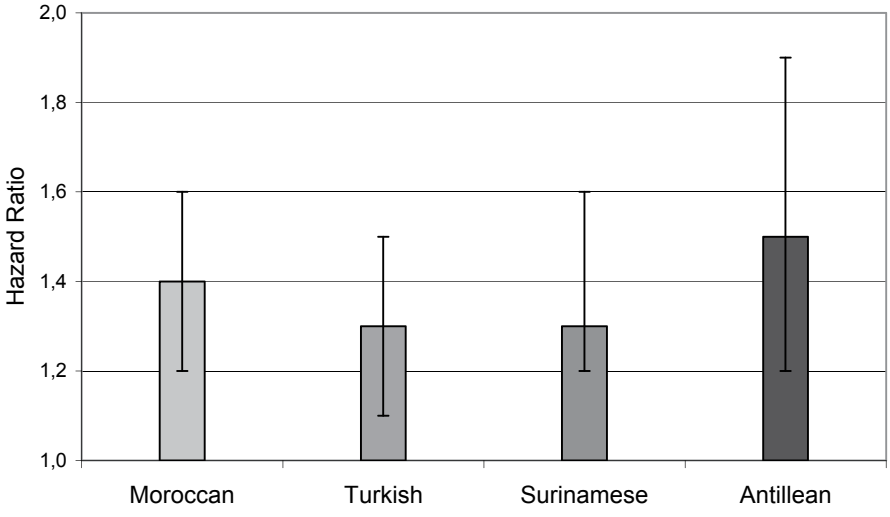
The research questions outlined in the Introduction section are addressed in the previous chapters of this thesis. This chapter provides a general discussion in which way our findings can help to improve the understanding of the differences in perinatal and infant mortality between the non-Dutch and Dutch populations. Furthermore, general methodological issues will be considered and implications for future research and health policy are discussed.

## Ethnic differences in infant mortality, fetal growth, birth weight and gestational age.

Results on ethnic differences in infant mortality are presented in part 1 of this thesis. We demonstrated that the Moroccan, Turkish, Antillean and Surinamese populations in the Netherlands all have an increased risk of infant mortality compared to the Dutch population (figure 1). The risk of infant mortality was highest for the Antillean population (HR 1,5, 95% CI: 1.2, 1.9), followed by the Moroccan population (HR 1.4, 95% CI: 1.2, 1.6) and lowest for the Turkish (HR 1.3, 95% CI: 1.1, 1.5) and Surinamese populations (HR 1.3, 95% CI: 1.2, 1.6).

The risk of infant mortality in the Capeverdean population was not examined in our study on total and cause-specific infant mortality (chapter 2). With data from the Center of Statistics and Research in Rotterdam we could estimate the infant mortality

**Figure 1.** Hazard ratios (and 95% CI) for infant mortality in the non-Dutch populations (Dutch population is reference group).



rate for the Capeverdean population in Rotterdam over the period 2000-2006. Although the numbers of live births and infant deaths were small, which limited an accurate statistical analysis, we found a higher infant mortality rate in the Capeverdean population (5.9/1000 live births) compared to the infant mortality rate in the Dutch population (4.8/1000 live births). These findings suggest that the Capeverdean population also has an increased risk of infant mortality compared to the Ducth population.

Since fetal growth, birth weight and gestational age are determinants that are strongly related to perinatal and infant mortality, the increased risk in infant mortality in these populations might be mediated by these determinants. We demonstrated that differences exist in birth weight in the offspring of several non-Dutch populations compared to the Dutch population (chapter 5). After controlling for gender and gestational age, we observed a significantly lower birth weight in the infants of the Turkish, Antillean, Surinamese-creole, Surinamese-hindustani and Capeverdean populations compared to infants of the Dutch population. No significant difference in birth weight was found between the infants of the Moroccan population and the infants of the Dutch population (figure 2). In line with these findings, we showed that ethnic differences exist in prenatal growth as well. Differences in fetal size were found for the Turkish, Capeverdean, Surinamese-creole and Surinamese-hindustani populations as compared to the Dutch population (chapter 4).





Furthermore, we found that gestational duration is longer in Moroccan women and shorter in Surinamese-creole, Surinamese-hindustani and Antillean women (figure 3).

**Figure 2.** Differences in mean birth weight (grams) of the non-Dutch populations compared to the Dutch population (adjusted for gender of infant and gestational age).

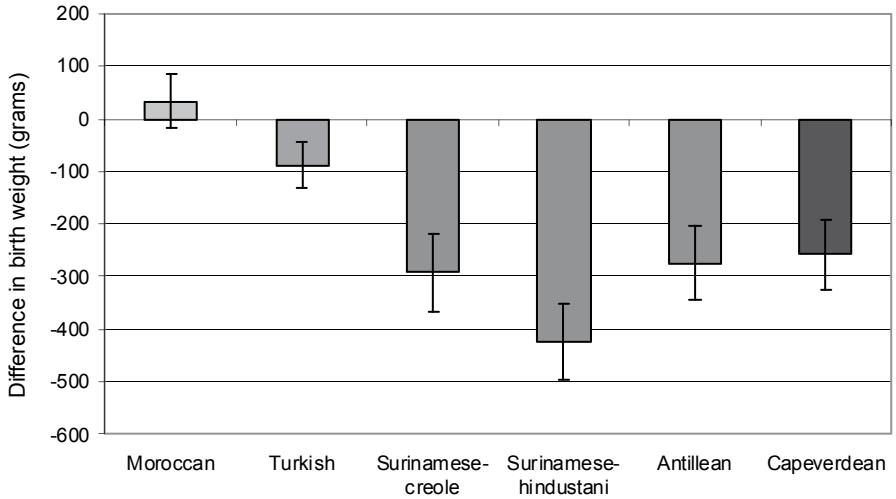
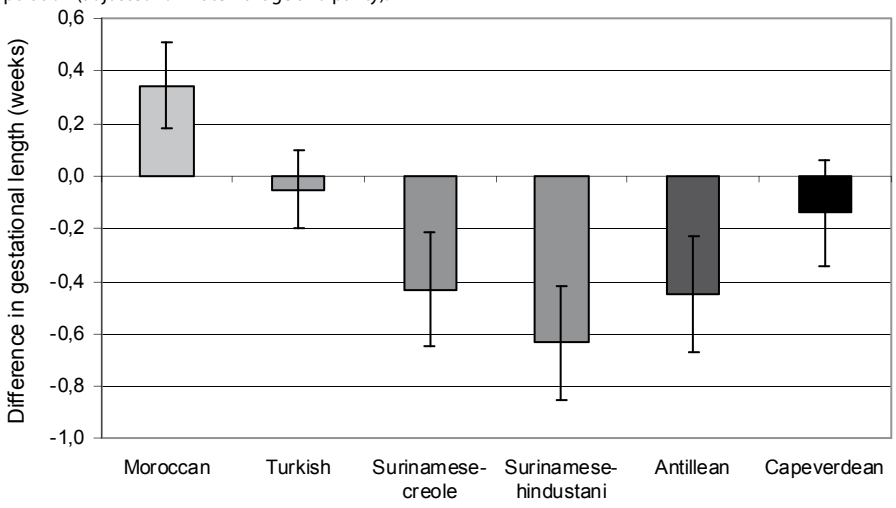


**Figure 3.** Difference in mean gestational length (weeks) of the non-Dutch populations compared to the Dutch population (adjusted for maternal age and parity).




We observed an increased risk of preterm birth (< 37 weeks) among the Surinamese-hindustani and Antillean populations compared to the Dutch population. The Surinamese-creole population had an increased risk of very preterm birth (< 32 weeks) compared to the Dutch population. No increased risks of (very) preterm birth was observed for the Turkish and Moroccan populations compared to the Dutch population (chapter 8).

Our results support the hypothesis that the increased risk of perinatal and infant mortality in the Surinamese-creole, Surinamese-hindustani, Antillean and Capeverdean populations is at least partly mediated by birth weight and gestational age, while the increased risk of perinatal and infant mortality in the Turkish and Moroccan populations seems to be mediated by different causal pathways.

**Determinants in the Surinamese, Antillean and Capeverdean populations that contribute to the lower birth weight and shorter gestational age in these populations.**

We examined the determinants of fetal growth, birth weight and gestational age in the Surinamese-creole, Surinamese-hindustani, Antillean and Capeverdean populations in chapter 4, 5 and chapter 8. We showed that the most important determinants in explaining the differences in fetal growth and birth weight between these populations and the Dutch population are maternal and paternal height, educational level of the mother, maternal age and marital status. Determinants of differences in (very) preterm birth between these populations and the Dutch population are maternal height, marital status and pre-eclampsia (table 1).

**Table 1.** The role of specific determinants in explaining the lower birth weight and shorter gestational age of the Surinamese, Antillean and Capeverdean populations.

| | Birth weight | | | | Gestational age | | | |
|---|---|---|---|---|---|---|---|---|
| | Cape-verdean | Antillean | Surinamese-creoles | Surinamese-hindustani | Cape-verdean | Antillean | Surinamese-creoles | Surinamese-hindustani |
| **Maternal height** | +++ | +++ | ++ | +++ | +++ | ++ | ++ | +++ |
| **Paternal height** | + | +++ | +++ | ++ | NI | NI | NI | NI |
| **Educational level** | + | + | + | - | ++ | - | - | - |
| **Maternal age** | + | + | + | - | NI | NI | NI | NI |
| **Marital status** | + | ++ | ++ | - | +++ | ++ | ++ | - |
| **Pre-eclampsia** | NI | NI | NI | NI | ++ | + | - | - |

NI = Not Investigated

Relative importance (percentage change in the association between ethnic background and birth weight/ gestational age; data were used from chapter 4, Appendix and chapter 7, table 3):

- \- change < 10%
- \+ change 10-20%
- ++ change 20-30%
- +++ change > 30%

We observed that pregnant women and their partners of the non-Dutch populations are shorter of height compared to the Dutch population. Low maternal and paternal height were associated with a lower birth weight. Several other studies have documented that maternal height is associated with birth weight (1, 2). We showed that, besides maternal height, paternal height is also a determinant of birth weight in offspring. Several previous studies also have found an association between paternal height and birth weight (3-5). We observed that low maternal height largely explained the increased risk of preterm birth in the Surinamese-hindustani and Antillean populations. This is in line with the findings of previous studies that described an association between low maternal height and preterm birth (6-8). Maternal and paternal height are the result of a complex conjuncture of environmental (especially long-term dietary intake and nutritional status) and genetic factors (9). The observed shorter height in the non-Dutch populations might reflect the multigenerational long-term poorer dietary intake and adverse living conditions they were exposed to.

In a separate analysis, maternal height of second-generation women in our study showed to be significantly higher compared to their first generation counterparts (results not shown). This is consistent with the hypothesis that environmental influences might affect the mean height of populations (9). Reducing the socio-economic and environmental inequalities between ethnic populations could in long-term decrease differences in maternal and paternal height, and as a result lead to a decrease in ethnic differences in birth weight and gestational age. All together, our findings suggest that the lower mean birth weight and increased risk of preterm birth in the Surinamese, Antillean and Capeverdean populations are attributable for a substantial part to the

lower maternal and paternal height in these populations. Since maternal and paternal height cannot easily be modified, these determinants are not suitable for the prevention of ethnic differences in birth weight and gestational age, but their importance should be taken into account when interpreting ethnic differences in birth weight and gestational age at the population level.

We observed that all non-Dutch populations are in general lower educated compared to the Dutch native population. In general the non-Dutch populations in the Netherlands have a lower socio-economic position than the native Dutch population (10). Low socio-economic status has been shown to be related to low birth weight and preterm birth (11, 12). There are several etiological factors that can mediate the associations between maternal socio-economic status and birth weight, gestational age and infant mortality. These factors include smoking habits, bacterial vaginosis, low gestational weight gain, short stature and psychosocial stressors (12, 13). The low socio-economic status of the non-Dutch populations, and the above-mentioned adverse factors associated with low socio-economic status, may contribute to the excess of low birth weight and preterm birth in these specific populations.

Marital status of the pregnant women and maternal age are associated with adverse pregnancy outcomes, such as low birth weight and preterm birth (14, 15). Especially single motherhood and teenage pregnancy are associated with these adverse pregnancy outcomes (14-17). We observed a high prevalence of single motherhood among the pregnant women in the non-Dutch populations. About 50% of the pregnant women were single in the Surinamese-creole (52.9%), Antillean (49.2%) and Capeverdean (50.8%) populations and over 20% in the Surinamese-hindustani population (21.9%). Single motherhood showed to be an important determinant in explaining the lower birth weight of the Surinamese-creole, Surinamese-hindustani, Antillean and Capeverdean populations. Furthermore, single motherhood was an important determinant in explaining the increased risk of very preterm birth in the Surinamese-creole population. Secondly, we observed that mean maternal age was lower in the participating Surinamese, Antillean and Capeverdean women compared to the Dutch native women. In these populations we also observed a higher prevalence of teenage pregnancies (defined as maternal age below 20 years) compared to the Dutch native population (Surinamese-creole 10.7%; Surinamese-hindustani 5.9%; Antillean 11.7%; Capeverdean 13.8%; compared to Dutch 1.7%). Although the exact pathways of single motherhood and teenage motherhood to lower birth weight and (very) preterm birth are unclear, several risk factors might account for the increased risk in these groups, like less optimal use of prenatal care, more unhealthy behaviours (smoking, drug use, risk full sexual behaviour), more stress and unfavourable material conditions. Our findings suggest that single motherhood and teenage pregnancy are significant mediators that explain

impaired fetal growth, and increased risks of low birth weight and short gestational age among the Surinamese, Antillean and Capeverdean populations.

Pre-eclampsia is a major obstetric problem leading to substantial maternal and perinatal morbidity and mortality (18). First pregnancy, obesity and limited sperm exposure by the same partner are risk factors of pre-eclampsia (18). These risk factors might be more prevalent in the Surinamese-creole, Surinamese-hindustani, Antillean and Capeverdean populations, since we observed a higher body mass index, a high prevalence of teenage pregnancies and single motherhood in these populations. We observed a higher prevalence of pre-eclampsia in the Surinamese-creole, Surinamese-hindustani, Antillean and Capeverdean populations compared to the Dutch native population, although the differences were not statistically significant (table 2).

**Table 2.** Prevalence in the Generation R Study of pre-eclampsia in the Dutch and non-Dutch populations.

| | Dutch | Capeverdean | Antillean | Surinamese-creole | Surinamese-hindustani |
|---|---|---|---|---|---|
| Pre-eclampsia (%) | 1.9 | 3.5 | 3.3 | 3.1 | 4.6 |

p-value = 0.15, result of chi-square test

We showed that the increased risk of very preterm birth in the Surinamese-creole population is partially explained by the relatively high prevalence of pre-eclampsia (chapter 8). The relatively high prevalence of pre-eclampsia might contribute to the increased risk of (very) preterm birth in the Surinamese-creole population, and might also contribute to the adverse pregnancy outcomes in the Surinamese-hindustani, Antillean and Capeverdean populations.



**Determinants in the Turkish and Moroccan populations that might contribute to the increased risk of infant mortality.**

In the Turkish and Moroccan populations we did not observe a lower birth weight (except a slightly lower birth weight in infants of Turkish pregnant women) or an increased risk of preterm birth. These results suggest that the increased risk of perinatal and infant mortality in these populations is not mediated by birth weight and/or gestational age. However, we found several potential determinants that might contribute to a better understanding of the increased risk of perinatal and infant mortality in the Turkish and Moroccan populations. The determinants that might be of importance are smoking during pregnancy and consanguinity.

First, we found that a relatively high percentage of Turkish pregnant women continue smoking during pregnancy. Over 30% of the Turkish pregnant women continued smoking during pregnancy compared to 17 % of the Dutch pregnant women (chapter 7). Maternal smoking during pregnancy is associated with infant mortality, childhood asthma and psychopathology (19-22). Additionally, exposure to environmental tobacco

smoke is a major risk factor for sudden infant death syndrome (SIDS); Maternal smoking doubles the risk of SIDS. (23). Since prenatal smoking is associated with postnatal smoking, the high percentage of smoking during pregnancy among Turkish women might contribute to the increased risk of total infant mortality in this population. It might also add to the increased risk of post neonatal mortality and SIDS we found in the Turkish population (chapter 2).

Secondly, we found that over 20% of the pregnant women in the Turkish and Moroccan populations had a consanguineous partner (chapter 6). We observed that consanguinity in the Turkish and Moroccan populations is associated with an increase in mean birth weight (chapter 6). Although we were unable to study the association of consanguinity with other health outcomes, we also found that infants of the Turkish and Moroccan populations in the Netherlands have an increased risk of dying from congenital anomalies (chapter 2). Consanguinity has been shown to be a risk factor for congenital anomalies (24, 25). Moreover, consanguinity is associated with perinatal and infant mortality (26-29). In the literature relative risks of infant mortality associated with parent's consanguinity are described ranging from 1.3 to 2.1 for first cousin relationships and from 1.2 to 2.4 for second cousin relationships (26, 28, 30). If we assume an increased relative risk of infant mortality in the subgroups of the Turkish and Moroccan populations in our studies, we can estimate the Population Attributable Risk (PAR) of consanguinity in these populations. Given these assumptions, we estimated that the proportion of infant mortality that could be attributed to consanguinity ranges from 5% to 23% (table 3). All together, this relatively high frequency of consanguinity in the Turkish and Moroccan population potentially contributes to the increased risk for infant death from congenital anomalies and to the excess infant mortality observed in the Turkish and Moroccan populations.

**Methodological considerations**

For our studies of total and cause-specific mortality in the Netherlands presented in this thesis we used registry data from Statistics Netherlands (chapter 2 and 3). The other studies in this thesis were embedded in the Generation R Study (chapter 4 to 8). Strengths of our database from Statistics Netherlands include national coverage of all births and infant deaths (including deaths abroad of infants born in the Netherlands). Strengths of the Generation R Study are the population-based prospective design and the large number of subjects in the non-Dutch populations that were studied from early pregnancy onwards. Detailed information about ethnic background, fetal growth, birth outcomes and numerous potential confounders and mediating variables was available. However, some methodological issues regarding the internal (selection bias, information bias, confounding) and external (generalizability) validity need to be considered.

**Table 3.** Population Attributable Risk (PAR) for infant mortality of consanguinity calculated on the basis of data from literature.

| | First cousin relationship | | |
|---|---|---|---|
| Pc | 0,12 | 0,12 | 0,12 |
| RRc | 1,30 [1] | 1,70 [2] | 2,10 [3] |
| PARc | 0,03 | 0,08 | 0,12 |
| | **Second cousin relationship** | | |
| Pc | 0,09 | 0,09 | 0,09 |
| RRc | 1,20 [1] | 1,40 [2] | 2,40 [3] |
| PARc | 0,02 | 0,03 | 0,11 |
| | **First and second cousin relationship** | | |
| PARc | 0,05 | 0,11 | 0,23 |

Pc = proportion of population that has consanguineous relationship
RRc = relative risk of infant mortality for infants of consanguineous partners
PARc = the attributable risk for the effect of consanguinity on infant mortality
References

1. The comparative role of consanguinity in infant and childhood mortality, JC Grant et al, Ann Hum Genet, 1997
2. An epidemiologic approach to the evaluation of the effect of inbreeding on prereproductive mortality, MJ Khoury et al, Am J Epi, 1987
3. Influence of consanguinity and maternal education on risk of stillbirth and infant deat in Norway, 1967-1993, C Stoltenberg, Am J Epi, 1998



### *Selection bias*

The studies with total and cause-specific infant mortality as outcome were conducted in a database from Statistics Netherlands, including complete national coverage of all births and infant deaths. There are two selection effects that might have influenced our findings. These are the presence of illegal persons and selective remigration. Persons whose residence is illegal in the Netherlands are not present in the database from Statistics Netherlands. Illegal persons, whose ethnic background will be non-Dutch, are likely to have a higher risk of infant mortality due to the unfavourable socio-economic and living conditions. This might have lead to an underestimation of the mortality differences between the ethnic populations. Secondly, the selective remigration of a relatively (un) healthy sub sample of migrants might act upon our findings. If people who are either relatively healthy or relatively unhealthy remigrate from the host country to the country of origin, than the persons who remained in the Netherlands might be a selective group. If so, this may have influenced the levels of infant mortality in the non-Dutch ethnic populations.

The studies with fetal growth, birth weight and gestational age as outcome were conducted in the Generation R Study. Of all eligible children in the study area, 61%

participated at birth in the Generation R Study (31). Response-rates among the non-Dutch populations can be expected to be lower. Non-response due to non-participation may introduce selection bias. We were able to do a crude non-response analysis by comparing data from the Generation R Study with data from the Center of Research and Statistics, Rotterdam. We observed that the ethnic specific response rates for the non-Dutch populations were lower compared to the Dutch population. In general, we observed that women with higher socio-economic status, first pregnancy and lower age were over-represented in the Generation R cohort compared to population figures in Rotterdam. However, this picture was generally seen in both the Dutch and non-Dutch populations, suggesting that selection mechanisms were the same across the ethnic populations. Since the selection mechanisms seem to act upon all ethnic populations, we believe that the magnitude of differences in fetal growth, birth weight and gestational age are not largely biased.

***Information bias***

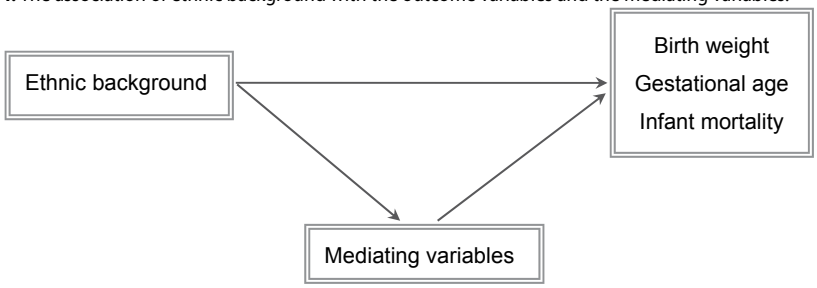
Information bias in our studies conducted with data of Statistics Netherlands is unlikely to have a major influence on our results. In these studies we used registry data and it is possible that misclassification is present in the routinely collected data of Statistics Netherlands. This misclassification is likely to be non-differential and this would have led to underestimation of our results.

Within our studies in the Generation R Study, information bias might be present. Ethnic background of the women under study was based on the Dutch standard classification. This classification is based on the county of birth of the women and her parents. Within the Generation R Study, information of country of birth of the pregnant women and her parents was collected by questionnaire. Misclassification of ethnic background could be introduced by missing countries of birth of the pregnant woman or her parents. However, in less than 3%, the women's ethnic background was defined while the country of birth of herself or one or both of her parents was missing. Therefore it seems unlikely that misclassification of ethnic background would have altered the observed findings. Finally, misclassification of explanatory determinants might be present since data collection among the non-Dutch populations was in some cases different than in the Dutch population (interview versus questionnaire). This might have led to incomplete control for possible explanatory determinants in our analyses.

***Confounding***

One of the strengths of the Generation R Study is the detailed information and large amount of potential covariates that is available. The examination of pathways explaining ethnic differences in health outcomes is not straightforward. The covariates could be considered as mediator, moderator (effect modifier), confounder or as antecedent

**Figure 4.** The association of ethnic background with the outcome variables and the mediating variables.




variable (32). In our studies on ethnic differences in birth weight, gestational age and infant mortality most of the available variables were considered as mediating variables of the studied association. Thus ethnic background is thought to have a direct effect on the outcomes and (or) an indirect effect mediated through its effect on the mediating variables (figure 4). We believe that in our studies on ethnic differences in birth weight, gestational age and infant mortality, the studied associations are not largely affected by (residual) confounding. In our study on the association of consanguinity with birth weight we were able to control for a large amount of potential confounders. We cannot exclude some amount of residual confounding in this study, but we think that we were able to control for the most important confounders and that the effect of residual confounding on the studied association will be small.



***Unavailable information on determinants.***

Our main interest was in determining the determinants that may explain the associations between ethnic background and fetal growth, birth weight, gestational age and infant mortality. We were able to study numerous potential biological, socio-demographic, lifestyle and obstetrical determinants. However, some potential determinants were not available for this study. For example, information on infectious and prenatal care-related determinants of fetal growth, birth weight and gestational age could contribute to a fuller understanding of the ethnic disparities in health outcomes.

Previous studies have suggested that urogenital infections, like bacterial vaginosis and chlamydia trachomatis, increase the risk of preterm birth (33-36). In the Generation R Study, information was available in a sub sample of the study cohort on chlamydia trachomatis infection among pregnant women. Within this sub sample (n = 2878), we observed an increased prevalence of chlamydia trachomatis among non-Dutch pregnant women compared to Dutch pregnant women. Especially, pregnant women with a Capeverdean, Antillean, Surinamese-creole and Surinamese-other ethnic background had relatively high rates of chlamydia trachomatis infection (Capeverdean: 9.9%, Antillean: 16.1%, Surinamese-creole: 12.1% and Surinamese-other: 11.3% versus Dutch: 1.9%, $p < 0.05$). In a separate analysis, chlamydia trachomatis was strongly associated

with very preterm birth (OR 5.1, 95% CI: 1.7, 15.0). These findings suggest that urogenital infections might be of importance in elucidating the ethnic differences in (very) preterm birth. Studies on the role of urogenital infections in the non-Dutch populations are necessary to identify their exact role in the ethnic differences in (very) preterm birth and to assess their potential effect on perinatal morbidity.

Several studies have suggested that offspring of pregnant women with less optimal prenatal care are at increased risk of low birth weight and preterm birth (37-40). Previous studies also indicate that pregnant women of migrant populations are more likely to initiate prenatal care later in pregnancy compared to pregnant women of native populations (37, 38). Information on late prenatal care or inadequate prenatal care of pregnant women of the non-Dutch populations might add to the explanation of ethnic differences in pregnancy outcomes. Information on prenatal care characteristics was available for only 2,769 pregnant women. In this subgroup, we examined the association of late prenatal care and inadequate prenatal care with birth weight and gestational age. We found that inadequate prenatal care use (defined as late intake (> 15 weeks of gestation) and/or insufficient number of antenatal visits) was associated with a lower birth weight (-48 grams, 95% CI: -84, -13), but not with low birth weight (< 2500 grams), gestational age or preterm birth (< 37 weeks). Since these results reflect preliminary analyses we recommend evaluating the impact of quality of prenatal care on birth outcomes in future studies.

### *External validity*

External validity refers to the generalization of the results. We will discuss to what extent the findings can be generalized to the Turkish, Moroccan, Capeverdean, Antillean, Surinamese-creole and Surinamese-hindustani populations in the Netherlands and to ethnic minority populations living in other countries.

*Generalization in the Netherlands.* Most of the non-Dutch populations live in the major cities in the Netherlands. In several large cities (the Hague, Amsterdam) and in nation wide samples, ethnic differences in infant mortality, birth weight and gestational age have been studied (41-43). In line with our study, findings of most of these studies indicated that the perinatal and infant mortality was increased in the largest non-Dutch populations (Turkish, Moroccan, Surinamese and Antillean). These previous studies indicated that an increased risk of low birth weight and preterm birth was observed in the Surinamese and Antillean populations, while in the Turkish and Moroccan populations no differences in risks of low birth weight and preterm birth were found (44). Our studies were able to examine in more detail the magnitude of the differences in birth weight and gestational age and we were able to take into account information on numerous covariates. Our findings confirm the lower birth weight and shorter gestational duration in the Surinamese and Antillean populations, and not in the Turkish and Moroccan populations.

In our studies we present prevalence rates of several important determinants of birth weight, gestational age and infant mortality (e.g. maternal smoking, consanguinity, marital status). However, selective participation and missing data on ethnic background might have led to biased estimates of the prevalence of determinants in the different ethnic groups. Therefore, caution is needed in extrapolating the prevalence rates of several determinants to the general population.

*Generalization outside the Netherlands.* Whether our findings can be generalized to other ethnic minority populations in other European and non-European countries remains to be ascertained. In several other European and non-European countries increased risks of infant mortality, low birth weight and/or preterm birth were found in ethnic minority populations as compared to native populations (45-51). From these studies, it seems that the determinants explaining ethnic differences in infant mortality, low birth weight and preterm birth in the Netherlands, also seem to be of importance in the contribution of ethnic differences in the United Kingdom and the United States. However, it is important to notify that the living conditions, migration history, health care accessibility and life style behaviour of these ethnic minority populations in the UK and US might differ from the ethnic minority populations in the Netherlands. Therefore, generalization of our results to ethnic minority populations outside the Netherlands should be done carefully.



**Implications for policy**

*Smoking.* We observed that smoking prevalence during pregnancy was high among Turkish women. We also observed that Turkish and Moroccan women who smoked before pregnancy were more likely to continue smoking during pregnancy compared to Dutch women who smoked before pregnancy. Since maternal smoking during pregnancy is an important modifiable risk factor for unfavourable pregnancy outcomes and for childhood morbidity and mortality, these groups should form a priority in smoking prevention and intervention strategies. Pregnant women might be motivated to quit smoking and therefore pregnancy offers a window of opportunity to modify smoking behaviour of women. Smoking cessation programs in pregnancy have shown to reduce the rates of low birth weight and preterm birth (52). Dornelas et al. showed that intervention in a prenatal clinic increases the rates of smoking cessation at end of pregnancy in a low-income, ethnically diverse sample of pregnant smokers (53). Results of this study suggest that counselling might be most effective when started in early in pregnancy, as the odds of quitting smoking during pregnancy diminish over time (54, 55).These previous findings suggest that interventions for smoking cessation could be effective and are preferably undertaken before or in early pregnancy. We found that partner smoking and single motherhood are important correlates of smoking during pregnancies. We also observed a lack of an educational gradient in smoking behaviour in several non-

Dutch populations. These observations should be taken into account when designing maternal smoking prevention and intervention strategies.

*Teenage pregnancy and single motherhood.* The high rates of teenage pregnancies and single mothers among Surinamese-creole, Antillean and Capeverdean calls for special attention to these groups. Although the exact pathways of teenage pregnancy and single motherhood to unfavourable health outcomes in infants (infant mortality, low birth weight and preterm birth) are unclear, several risk factors might account for the increased risk in these groups, such as less optimal use of prenatal care, more unhealthy behaviours (smoking, drug use, riskfull sexual behaviour), more stress and unfavourable material conditions. Previous studies suggest that social support programs could improve both the health of the mother and the outcome of her pregnancy (56, 57). Comprehensive prenatal care programs for teenage pregnant women were associated with diminished risks of pregnancy induced hypertension, preterm delivery and caesarean delivery (56). The extension of prenatal care and more signalling and alertness on the presence of specific risk factors could improve the health outcomes of infants in these high-risk groups.

*Consanguinity.* We showed that consanguinity is commonly observed in the Turkish and Moroccan populations and that consanguinity is associated with a higher birth weight. Several studies have shown that consanguinity is associated with infant mortality and congenital anomalies, but we were unable to examine the association of consanguinity with these health outcomes. To overcome the health burden imposed by consanguinity, preventive factors should focus on several factors. One such factor relates to public education on the effects of consanguinity on genetic diseases. Premarital and preconception testing, prenatal diagnosis and termination of pregnancy (within the allowed limits in religion) should also be part of strategies to reduce the prevalence of congenital anomalies and birth defects (58). Strategies however, should be accompanied by careful and well-informed counselling to avoid stigmatisation. We recommend to routinely collect information on consanguinity of (future) parents by midwives/gynaecologists and in registry databases. A thorough (medical) family history by health care workers could help identifying consanguinity of parents and could improve the health outcomes of infants of consanguineous couples.

*Acculturation/generational status.* We showed that acculturation and generational status might influence the life style (e.g. smoking) and the mortality rates in the non-Dutch populations. We found that these patterns could lead to increasing inequalities in health outcomes of mother and infant. Therefore, efforts should be undertaken in non-Dutch populations, even in second generation migrants, in order to prevent the adaptation of unhealthy western lifestyles and to maintain their healthy elements of their more traditional lifestyles.

## Implications for future research

*Smoking during pregnancy.* We found that the rate of smoking during pregnancy was high among Turkish pregnant women and that continuation of smoking during pregnancy among women who smoked before pregnancy was high among the Turkish and Moroccan women. Studies are wanted to gain more information on beliefs and attitudes toward smoking behaviour and cessation, and possible contextual influences. This research could lead to the improvement of ethnic-specific smoking prevention and cessation strategies.

*Better understanding of the association of single motherhood and teenage pregnancy and unfavourable pregnancy outcomes.* Single motherhood and teenage pregnancy showed to be important determinants of unfavourable pregnancy outcomes. Research on the causal pathways through which single motherhood and teenage pregnancy lead to low birth weight and preterm birth is needed to support the development of specific prevention strategies. Furthermore, intervention studies on special prenatal care programs for teenage and single mothers are wanted in order to examine the effect of these programs on pregnancy outcomes.

*Consanguinity and other health outcomes.* We found that consanguinity is prevalent in the Turkish and Moroccan population. We were unable to adress several important associations of consanguinity with health outcomes (perinatal and infant mortality, congenital anomalies). Studies regarding the association of consanguinity with these health outcomes are needed. Next, studies are needed regarding strategies for the prevention of congenital anomalies and infant mortality.

*Determinants of pre-eclampsia.* We showed that pre-eclampsia is more frequently seen in several non-Dutch populations. More insight is wanted in the factors that are responsible for this higher prevalence in order to improve the prediction, prevention and management of pre-eclampsia in these populations.



## Conclusion

The studies presented in this thesis provide insight into ethnic disparities in total and cause-specific infant mortality, determinants of low birth weight and (very) preterm birth in the Antillean, Surinamese and Capeverdean populations, and the prevalence of determinants of perinatal and infant mortality in the Turkish and Moroccan populations.

We confirmed that there is an increased risk of infant mortality in the Turkish, Moroccan, Antillean and Surinamese populations in the Netherlands. The increased risks of infant mortality might be mediated by birth weight and gestational age in the Surinamese-creole, Surinamese-hindustani, Antillean and Capeverdean populations, while the increased risk of infant mortality in the Turkish and Moroccan populations seems to be mediated by different causal pathways.

We found that the most important determinants that explain the differences in fetal growth and birth weight between the Surinamese-creole, Surinamese-hindustani, Antillean and Capeverdean populations and the Dutch population are maternal and paternal height, educational level of the mother, maternal age and marital status. Important determinants that explain differences in (very) preterm birth between these populations and the Dutch population are maternal height, marital status and the presence of pre-eclampsia.

In the Turkish and Moroccan populations we did not observe a lower birth weight nor an increased risk of preterm birth. However, we found that smoking during pregnancy and consanguinity are determinants that might be of importance in the explanation of the increased risk of perinatal and infant mortality in the Turkish and Moroccan populations.

In conclusion, at the beginning of the 21th century there are still marked differences in fetal growth, birth weight and infant mortality between ethnic populations in the Netherlands that are only partially understood. We suggest specific follow-up studies to better understand the causal pathways leading to these differences. In the meantime we recommend midwives and gynaecologists to be aware of these differences and to apply currently available strategies for the prevention, monitoring and management of adverse circumstances and conditions.

## References


1. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ. 1987;65(5):663-737.
2. Mohanty C, Prasad R, Srikanth Reddy A, Ghosh JK, Singh TB, Das BK. Maternal anthropometry as predictors of low birth weight. J Trop Pediatr. 2006 Feb;52(1):24-9.
3. Morrison J, Williams GM, Najman JM, Andersen MJ. The influence of paternal height and weight on birth-weight. Aust N Z J Obstet Gynaecol. 1991 May;31(2):114-6.
4. To WW, Cheung W, Kwok JS. Paternal height and weight as determinants of birth weight in a Chinese population. Am J Perinatol. 1998;15(9):545-8.
5. Wilcox MA, Newton CS, Johnson IR. Paternal influences on birthweight. Acta Obstet Gynecol Scand. 1995 Jan;74(1):15-8.
6. Smith GC, Shah I, White IR, Pell JP, Crossley JA, Dobbie R. Maternal and biochemical predictors of spontaneous preterm birth among nulliparous women: a systematic analysis in relation to the degree of prematurity. Int J Epidemiol. 2006 Oct;35(5):1169-77.
7. Kramer MS, Coates AL, Michoud MC, Dagenais S, Hamilton EF, Papageorgiou A. Maternal anthropometry and idiopathic preterm labor. Obstet Gynecol. 1995 Nov;86(5):744-8.
8. Harlow BL, Frigoletto FD, Cramer DW, Evans JK, LeFevre ML, Bain RP, et al. Determinants of preterm delivery in low-risk pregnancies. The RADIUS Study Group. J Clin Epidemiol. 1996 Apr;49(4):441-8.
9. Maternal anthropometry for prediction of pregnancy outcomes: memorandum from a USAID/WHO/PAHO/MotherCare meeting. Bull World Health Organ. 1991;69(5):523-32.
10. Statistics Netherlands. Migrants in the Netherlands, 2003. 2003.

11. Verkerk PH, Zaadstra BM, Reerink JD, Herngreen WP, Verloove-Vanhorick SP. Social class, ethnicity and other risk factors for small for gestational age and preterm delivery in The Netherlands. Eur J Obstet Gynecol Reprod Biol. 1994 Feb;53(2):129-34.
12. Kramer MS, Goulet L, Lydon J, Seguin L, McNamara H, Dassa C, et al. Socio-economic disparities in preterm birth: causal pathways and mechanisms. Paediatr Perinat Epidemiol. 2001 Jul;15 Suppl 2:104-23.
13. Kramer MS, Seguin L, Lydon J, Goulet L. Socio-economic disparities in pregnancy outcome: why do the poor fare so poorly? Paediatr Perinat Epidemiol. 2000 Jul;14(3):194-210.
14. Raatikainen K, Heiskanen N, Heinonen S. Marriage still protects pregnancy. BJOG. 2005 Oct;112(10): 1411-6.
15. Wen SW, Goldenberg RL, Cutter GR, Hoffman HJ, Cliver SP. Intrauterine growth retardation and preterm delivery: prenatal risk factors in an indigent population. Am J Obstet Gynecol. 1990 Jan;162(1): 213-8.
16. Fraser AM, Brockert JE, Ward RH. Association of young maternal age with adverse reproductive outcomes. N Engl J Med. 1995 Apr 27;332(17):1113-7.
17. Lee KS, Corpuz M. Teenage pregnancy: trend and impact on rates of low birth weight and fetal, maternal, and neonatal mortality in the United States. Clin Perinatol. 1988 Dec;15(4):929-42.
18. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005 Feb 26-Mar 4;365(9461):785-99.
19. Ernst M, Moolchan ET, Robinson ML. Behavioral and neural consequences of prenatal exposure to nicotine. J Am Acad Child Adolesc Psychiatry. 2001 Jun;40(6):630-41.
20. Jaakkola JJ, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. Am J Public Health. 2004 Jan;94(1):136-40.
21. Kleinman JC, Pierre MB, Jr., Madans JH, Land GH, Schramm WF. The effects of maternal smoking on fetal and infant mortality. Am J Epidemiol. 1988 Feb;127(2):274-82.
22. Wakschlag LS, Leventhal BL, Pine DS, Pickett KE, Carter AS. Elucidating early mechanisms of developmental psychopathology: the case of prenatal smoking and disruptive behavior. Child Dev. 2006 Jul-Aug;77(4):893-906.
23. Hofhuis W, de Jongste JC, Merkus PJFM. Adverse health effects of prenatal and postnatal tobacco smoke exposure on children. Arch Dis Child. 2003 December 1, 2003;88(12):1086-90.
24. Bromiker R, Glam-Baruch M, Gofin R, Hammerman C, Amitai Y. Association of parental consanguinity with congenital malformations among Arab newborns in Jerusalem. Clin Genet. 2004 Jul;66(1): 63-6.
25. Zlotogora J. What is the birth defect risk associated with consanguineous marriages? Am J Med Genet. 2002 Apr 15;109(1):70-1.
26. Grant JC, Bittles AH. The comparative role of consanguinity in infant and childhood mortality in Pakistan. Ann Hum Genet. 1997 Mar;61(Pt 2):143-9.
27. Hussain R, Bittles AH, Sullivan S. Consanguinity and early mortality in the Muslim populations of India and Pakistan. Am J Hum Biol. 2001 Nov-Dec;13(6):777-87.
28. Stoltenberg C, Magnus P, Lie RT, Daltveit AK, Irgens LM. Influence of consanguinity and maternal education on risk of stillbirth and infant death in Norway, 1967-1993. Am J Epidemiol. 1998 Sep 1; 148(5):452-9.
29. Tuncbilek E, Koc I. Consanguineous marriage in Turkey and its impact on fertility and mortality. Ann Hum Genet. 1994 Oct;58(Pt 4):321-9.
30. Khoury MJ, Cohen BH, Chase GA, Diamond EL. An epidemiologic approach to the evaluation of the effect of inbreeding on prereproductive mortality. Am J Epidemiol. 1987 Feb;125(2):251-62.
31. Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, et al. The Generation R Study: Design and cohort profile. Eur J Epidemiol. 2006;21(6):475-84.
32. Singh-Manoux A. Commentary: Modelling multiple pathways to explain social inequalities in health and mortality. Int J Epidemiol. 2005 Jun;34(3):638-9.

33. Andrews WW, Goldenberg RL, Mercer B, Iams J, Meis P, Moawad A, et al. The Preterm Prediction Study: association of second-trimester genitourinary chlamydia infection with subsequent spontaneous preterm birth. Am J Obstet Gynecol. 2000 Sep;183(3):662-8.
34. Fiscella K. Racial disparities in preterm births. The role of urogenital infections. Public Health Rep. 1996 Mar-Apr;111(2):104-13.
35. Hillier SL, Nugent RP, Eschenbach DA, Krohn MA, Gibbs RS, Martin DH, et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group. N Engl J Med. 1995 Dec 28;333(26):1737-42.
36. Ugwumadu AH. Bacterial vaginosis in pregnancy. Curr Opin Obstet Gynecol. 2002 Apr;14(2):115-8.
37. Balcazar H, Cole G, Hartner J. Mexican-Americans' use of prenatal care and its relationship to maternal risk factors and pregnancy outcome. Am J Prev Med. 1992 Jan-Feb;8(1):1-7.
38. Balcazar H, Hartner J, Cole G. The effects of prenatal care utilization and maternal risk factors on pregnancy outcome between Mexican Americans and non-Hispanic whites. J Natl Med Assoc. 1993 Mar;85(3):195-202.
39. Krueger PM, Scholl TO. Adequacy of prenatal care and pregnancy outcome. J Am Osteopath Assoc. 2000 Aug;100(8):485-92.
40. Orvos H, Hoffmann I, Frank I, Katona M, Pal A, Kovacs L. The perinatal outcome of pregnancy without prenatal care. A retrospective study in Szeged, Hungary. Eur J Obstet Gynecol Reprod Biol. 2002 Jan 10;100(2):171-3.
41. Schulpen TW, van Steenbergen JE, van Driel HF. Influences of ethnicity on perinatal and child mortality in the Netherlands. Arch Dis Child. 2001 Mar;84(3):222-6.
42. van der Wal MF, Uitenbroek DG, van Buuren S. Birth weight of infants in Amsterdam according to ethnic origin [In Dutch]. Tijdschrift voor Gezondheidswetenschappen. 2000;78:15-20.
43. van Enk A, Buitendijk SE, van der Pal KM, van Enk WJ, Schulpen TW. Perinatal death in ethnic minorities in The Netherlands. J Epidemiol Community Health. 1998 Nov;52(11):735-9.
44. Schulpen TW. Mortality differences between migrant and native Dutch children in the Netherlands [In Dutch]. Utrecht: Centre for migration and child health; 1996.
45. Differences in infant mortality between blacks and whites--United States, 1980-1991. MMWR Morb Mortal Wkly Rep. 1994 Apr 29;43(16):288-9.
46. From the Centers for Disease Control. Infant mortality and low birth weight among black infants--United States, 1980-2000. JAMA. 2002 Aug 21;288(7):825-6.
47. Infant mortality and low birth weight among black and white infants--United States, 1980-2000. MMWR Morb Mortal Wkly Rep. 2002 Jul 12;51(27):589-92.
48. Racial and ethnic disparities in infant mortality rates--60 largest U.S. cities, 1995-1998. MMWR Morb Mortal Wkly Rep. 2002 Apr 19;51(15):329-32, 43.
49. Aveyard P, Cheng KK, Manaseki S, Gardosi J. The risk of preterm delivery in women from different ethnic groups. BJOG. 2002 Aug;109(8):894-9.
50. Schieve LA, Handler A. Preterm delivery and perinatal death among black and white infants in a Chicago-area perinatal registry. Obstet Gynecol. 1996 Sep;88(3):356-63.
51. Shiono PH, Klebanoff MA. Ethnic differences in preterm and very preterm delivery. Am J Public Health. 1986 Nov;76(11):1317-21.
52. Lumley J, Oliver SS, Chamberlain C, Oakley L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev. 2004(4):CD001055.
53. Dornelas EA, Magnavita J, Beazoglou T, Fischer EH, Oncken C, Lando H, et al. Efficacy and cost-effectiveness of a clinic-based counseling intervention tested in an ethnically diverse sample of pregnant smokers. Patient Educ Couns. 2006 Dec;64(1-3):342-9.
54. McBride CM, Curry SJ, Lando HA, Pirie PL, Grothaus LC, Nelson JC. Prevention of relapse in women who quit smoking during pregnancy. Am J Public Health. 1999 May;89(5):706-11.
55. Solomon L, Quinn V. Spontaneous quitting: self-initiated smoking cessation in early pregnancy. Nicotine Tob Res. 2004 Apr;6 Suppl 2:S203-16.

56. Scholl TO, Hediger ML, Belsky DH. Prenatal care and maternal health during adolescent pregnancy: a review and meta-analysis. J Adolesc Health. 1994 Sep;15(6):444-56.
57. Rogers MM, Peoples-Sheps MD, Suchindran C. Impact of a social support program on teenage prenatal care use and pregnancy outcomes. J Adolesc Health. 1996 Aug;19(2):132-40.
58. Teebi AS, El-Shanti HI. Consanguinity: implications for practice, research, and policy. Lancet. 2006 Mar 25;367(9515):970-1.

# Summary

## Introduction

The perinatal and infant mortality in the Netherlands is higher among several large non-Dutch populations (Moroccan, Turkish, Surinamese and Antillean) compared to the Dutch native population. Previous research indicated that the increased perinatal mortality in blacks and Hindustani might be attributed for large part to an increased risk of low birth weight and/or (very) preterm birth. However, these previous studies were not able to sufficiently distinguish between ethnic populations and were not able to take into account several important determinants of perinatal and infant mortality, such as maternal height, maternal smoking, consanguinity, and an individual measure of socio-economic status. Additionally, these previous studies were unable to examine the magnitude of the ethnic differences in birth weight and gestational age. Finally, these studies did not examine the determinants of low birth weight and preterm birth in specific populations and therefore could not identify determinants that might be eligible for prevention strategies.

The studies in this thesis are undertaken to improve the understanding of ethnic differences in perinatal and infant mortality. Ethnic differences in infant mortality are interpreted as being part of ethnic inequalities in fetal growth, birth weight and gestational age and/or as being caused by specific determinants of fetal growth, birth weight and gestational age.

In this thesis we address the following research questions:

1) What is the magnitude of ethnic differences in total and cause-specific infant mortality?
2) What is the magnitude of ethnic differences in fetal growth, birth weight and/or gestational age?
3) What is the role of specific determinants in explaining ethnic differences in fetal growth, birth weight, gestational age?

## Ethnic differences in infant mortality

Studies on ethnic differences in infant mortality are presented in part 1 of this thesis. *Chapter 2* describes the study of ethnic differences in total and cause-specific infant mortality in the Netherlands. We observed that the Moroccan, Turkish, Surinamese and Antillean populations in the Netherlands have a higher infant mortality than the Dutch native population. Ethnic inequalities as a result of socio-economic position and demographic factors, such as marital status and maternal age, partially explain the ethnic differences in infant mortality. We found that infants of the Moroccan and Turkish

populations have an increased risk of dying from congenital anomalies compared to the infants of the Dutch population. Infants of the Surinamese and Antillean populations have an increased risk of dying from perinatal causes compared to the infants of the Dutch population.

The association of generational status and age at immigration of the mother with infant mortality was examined in *chapter 3*. We observed that the infant mortality rate in Turkish mothers rose with lower age at immigration and was highest for the Dutch-born Turkish mothers. In contrast, we observed that infant mortality in Surinamese mothers declined with lower age at immigration and was lowest for the Dutch-born Surinamese mothers. We hypothesize that these associations might be determined by both acculturation processes and by selection upon migration.

## Determinants of fetal growth, birth weight and gestational age

Studies on determinants of fetal growth, birth weight and gestational age are presented in part 2 of this thesis. Ethnic differences in prenatal growth and the association of fetal growth with fetal and maternal characteristics were examined in *chapter 4*. We found that there are ethnic differences in fetal growth, which to a large extent are associated with maternal weight, height, age and parity. We observed differences in fetal size for Turkish, Surinamese-creole, Surinamese-hindustani and Capeverdean women. For the Turkish group the differences could be totally explained by differences in the maternal and fetal characteristics. For Surinamese-creole, Surinamese-hindustani and Capeverdean women up to one third of the differences was explained by maternal and fetal characteristics.

In *chapter 5* we examined whether ethnic differences in birth weight can be explained by determinants of birth weight. We found that the mean birth weight was lower in the offspring of all non-Dutch women (except in Moroccans) compared with the mean birth weight in offspring of Dutch women. Differences in gestational age, maternal and paternal height largely explained the lower birth weight in the Turkish, Surineamese-creole and Antillean populations. Differences in birth weight between the Dutch and the Surinamese-hindustani and Capeverdean populations could only be partly explained by several biomedical, socio-demographic and life-style related determinants. Our findings confirm significant differences in birth weight between ethnic populations that can only be partly understood from established determinants of birth weight. The part that is understood points to the importance of determinants that cannot easily be modified.

Consanguinity, which is relatively common in the Turkish and Moroccan populations in the Netherlands, has been shown to be a risk factor for perinatal and infant mortality. In *chapter 6* we examined the effect of consanguinity on fetal growth and

birth weight in the Turkish and Moroccan populations. We found that in these populations consanguinity is associated with a higher mean birth weight and an accelerated fetal growth and fetal abdominal circumference growth. We hypothesize that these findings may be related to specific selection factors, or to genetic, immunological and social factors linked to consanguinity.

Maternal smoking during pregnancy is an important modifiable risk factor for unfavourable pregnancy outcomes. Patterns and correlates of maternal smoking during pregnancy could differ according to ethnic background and these differences might have consequences for intervention strategies. In *chapter 7* we examined the patterns of smoking during pregnancy and the associations of socio-economic demographic and lifestyle correlates with smoking during pregnancy. We observed that smoking rate were highest in the Turkish group and lowest in the Moroccan group. Turkish and Moroccan women were less likely to stop smoking before pregnancy and more likely to continue smoking during pregnancy compared to Dutch women. Lower education was associated with smoking during pregnancy only in the Dutch group. No significant association of education was seen in the non-Dutch groups. Partner smoking, maternal alcohol use and single motherhood were important predictors of smoking during pregnancy across ethnic groups.

In *chapter 8* we examined whether ethnic differences in gestational duration, preterm and very preterm delivery may be explained by biological, socio-demographic, lifestyle and medical determinants. Compared to Dutch women, we observed that gestational duration is longer in Moroccan women and shorter in Antillean, Surinamese-creole and Surinamese-hindustani women. The odds ratios for preterm delivery were increased in the Antillean and Surinamese-hindustani populations compared to the Dutch population. The increased odds ratios in these populations were largely explained by maternal height. Moroccan women had a decreased odds ratio for preterm delivery compared to Dutch women. Surinamese-creole women had an increased risk of delivering very preterm compared to Dutch women, which was only partly explained by the explanatory determinants. These findings suggest that ethnic differences in gestational duration and preterm delivery are determined for a large part by biological factors and are less amenable to modification. Ethnic differences in very preterm delivery could not be completely explained.

## General discussion

*Chapter 9* provides a general discussion in which way our findings can help improve the understanding of the differences in perinatal and infant mortality between the non-Dutch and Dutch populations. From our findings we can conclude that the Turkish,

Moroccan, Antillean and Surinamese populations in the Netherlands have an increased risk of infant mortality, that seems to be mediated by birth weight and gestational age in the Surinamese-creole, Surinamese-hindustani, Antillean and Capeverdean populations, while the increased risk of infant mortality in the Turkish and Moroccan populations seems to be mediated by different causal pathways. The most important determinants in explaining the differences in fetal growth and birth weight between the Surinamese-creole, Surinamese-hindustani, Antillean and Capeverdean populations and the Dutch population are maternal and paternal height, educational level of the mother, maternal age and marital status. Important determinants of explaining differences in (very) preterm birth between these populations and the Dutch population are maternal height, marital status and pre-eclampsia. In the Turkish and Moroccan populations we found that smoking during pregnancy and consanguinity are determinants that might be of importance in the explanation of the increased risk of perinatal and infant mortality in these populations.

We discuss relevant methodological issues that might have influenced our findings. Furthermore we argue about unstudied determinants that might contribute to a fuller understanding of the increased risk of infant mortality. Finally, some implications for policy are considered and a few directions for future research are outlined.

# Samenvatting

## Introductie

De perinatale en zuigelingensterfte is in de belangrijkste allochtone bevolkingsgroepen (Surinamers, Antillianen, Turken en Marokkanen) hoger dan onder de 'autochtone' Nederlandse bevolking. Eerder onderzoek suggereert dat de verhoogde perinatale sterfte in de 'zwarte' en hindoestaanse bevolkingsgroepen voor een groot deel wordt verklaard door een verhoogd risico op laag geboortegewicht en/of vroeggeboorte. Deze voorgaande onderzoeken waren echter niet in staat voldoende onderscheid te maken tussen de verschillende etnische bevolkingsgroepen en hielden geen rekening met enkele belangrijke risicofactoren voor perinatale en zuigelingensterfte, zoals maternale lengte, roken van de moeder, consanguiniteit en een op individueel niveau gemeten maat voor sociaal-economische status. De voorgaande studies waren ook niet in staat om de grootte van de etnische verschillen in geboortegewicht en zwangerschapsduur te bestuderen. Tenslotte onderzochten voorgaande studies niet de risicofactoren van laag geboortegewicht en vroeggeboorte in specifieke bevolkingsgroepen en waren daardoor niet in staat risicofactoren te identificeren die in aanmerking komen voor de ontwikkeling van preventie strategieën.

Doel van de onderzoeken in dit proefschrift is een bijdrage te leveren aan het verbeteren van de kennis van etnische verschillen in perinatale en zuigelingensterfte. Etnische verschillen in zuigelingensterfte worden gezien als onderdeel van etnische verschillen in foetale groei, geboortegewicht en zwangerschapsduur en/of te worden veroorzaakt door specifieke risicofactoren van foetale groei, geboortegewicht en zwangerschapsduur.

In dit proefschrift hadden we de volgende onderzoeksvragen:

1) Wat is de grootte van de etnische verschillen in totale en oorzaak-specifieke zuigelingensterfte?
2) Wat is de grootte van de etnische verschillen in foetale groei, geboortegewicht en zwangerschapsduur?
3) Wat is de rol van specifieke risicofactoren in de verklaring van de etnische verschillen in foetale groei, geboortegewicht en zwangerschapsduur?

## Etnische verschillen in zuigelingensterfte

De onderzoeken naar etnische verschillen in zuigelingensterfte worden gepresenteerd in deel 1 van dit proefschrift. *Hoofdstuk 2* beschrijft het onderzoek naar etnische verschillen in totale en oorzaak-specifieke zuigelingensterfte in Nederland. We vonden dat de Marokkaanse, Turkse, Surinaamse en Antilliaanse bevolkingsgroepen in Nederland een

hogere zuigelingensterfte hebben vergeleken met de Nederlandse bevolkingsgroep. Etnische verschillen als gevolg van sociaal-economische positie en demografische factoren, zoals burgerlijke status en leeftijd van de moeder, verklaren deels de gevonden verschillen in zuigelingenstefte. Verder bleek dat zuigelingen in de Marokkaanse en Turkse bevolkingsgroepen een hoger risico hebben om te overlijden ten gevolge van aangeboren afwijkingen vergeleken met de Nederlandse bevolkingsgroep. Zuigelingen in de Surinaamse en Antilliaanse bevolkingsgroepen hebben een verhoogd risico om te overlijden ten gevolge van perinatale oorzaken vergeleken met de Nederlandse bevolkingsgroep.

De associatie van generatie en leeftijd van immigratie van de moeder met zuigelingensterfte werd onderzocht in *hoofdstuk 3*. We vonden dat de zuigelingensterfte bij de Turkse moeders steeg met een lagere leeftijd van immigratie en het hoogste was in de groep met de in Nederland geboren Turkse moeders. In tegenstelling hiermee, vonden wij dat de zuigelingensterfte bij de Surinaamse moeders afnam met een lagere leeftijd van immigratie en het laagst was in de groep met in Nederland geboren Surinaamse moeders.



## Risicofactoren van foetale groei, geboortegewicht en zwangerschapsduur

Studies naar de risicofactoren van foetale groei, geboortegewicht en zwangerschapsduur worden beschreven in deel 2 van dit proefschrift. Etnische verschillen in prenatale groei en de associatie van foetale groei met foetale en maternale risicofactoren werd bestudeerd in *hoofdstuk 4*. We vonden dat er etnische verschillen zijn in foetale groei, die in sterke mate geassocieerd zijn met gewicht, lengte, leeftijd en pariteit van de moeder. We observeerden verschillen in foetale groei in de groepen van Turkse, Surinaamse-creoolse, Surinaams-hindoestaanse en Kaapverdiaanse vrouwen vergeleken met de groep Nederlandse vrouwen. De verschillen in de Turkse groep werden verklaard door verschillen in foetale en maternale karakteristieken. In de Surinaamse-creoolse, Surinaams-hindoestaanse en Kaapverdiaanse groepen werd ongeveer 1/3 van de verschillen verklaard door foetale en maternale factoren.

In *hoofdstuk 5* onderzochten wij of etnische verschillen in geboortegewicht verklaard kunnen worden door risicofactoren voor laag geboortegewicht. We vonden dat het gemiddeld geboortegewicht lager was bij de kinderen van alle onderzochte niet-Nederlandse bevolkingsgroepen (behalve de Marokkaanse bevolkingsgroep) vergeleken met het gemiddeld geboortegewicht van de kinderen in de Nederlandse bevolkingsgroep. Verschillen in zwangerschapsduur, maternale en paternale lengte verklaarden voor een groot deel het lagere geboortegewicht in de Turkse, Surinaams-creoolse en Antilliaanse bevolkingsgroep. Verschillen in geboortegewicht tussen de Nederlanse en Surinaams-

hindoestaanse en Kaapverdiaanse bevolkingsgroep werden deels verklaard door de verschillende biomedische, socio-demografische en leefstijl gerelateerde risicofactoren. Onze bevindingen bevestigen dat er significante verschillen zijn in geboortegewicht tussen etnische bevolkingsgroepen die deels verklaard kunnen worden door bekende risicofactoren van laag geboortegewicht. Het deel dat kan worden verklaard laat zien dat enkele risicofactoren van belang zijn die niet makkelijk beïnvloedbaar zijn.

Consanguiniteit, dat relatief frequent voorkomt in de Turkse en Marokkaanse bevolkingsgroepen in Nederland, is een bekende risicofactor voor perinatale en zuigelingensterfte. In *hoofdstuk 6* onderzochten we het effect van consanguiniteit op foetale groei en geboortegewicht in de Turkse en Marokkaanse bevolkingsgroepen. We vonden dat in deze bevolkingsgroepen consanguiniteit is geassocieerd met een hoger gemiddeld geboortegewicht en een versnelde foetale groei en foetale abdominale groei. We formuleren enkele hypotheses dat deze bevindingen gerelateerd zijn aan specifieke selectie-factoren, of aan genetische, immunologische en sociale factoren verbonden aan consanguiniteit.

Roken van de moeder tijdens de zwangerschap is een belangrijke beïnvloedbare risicofactor voor ongunstige zwangerschapsuitkomsten. De patronen en risicofactoren voor roken van de moeder tijdens de zwangerschap kunnen verschillend zijn tussen etnische bevolkingsgroepen en deze verschillen hebben mogelijk consequenties voor interventie strategieën. In *hoofdstuk 7* onderzochten we de patronen van roken tijdens de zwangerschap en de associaties met sociaal-demografische en leefstijl factoren. We vonden dat roken het meest frequent werd gezien in de Turkse groep en het minst in de Marokkaanse groep. Turkse en Marokkaanse vrouwen stopten minder frequent met roken voor de zwangerschap en continueerden vaker het roken tijdens de zwangerschap vergeleken met de Nederlandse vrouwen. Een lage opleiding was geassocieerd met roken tijdens de zwangerschap alleen in de Nederlandse groep. Geen significante associatie van opleiding met roken werd gezien in de niet-Nederlandse groepen. Het roken van de partner, alcohol gebruik van de moeder en alleenstaand moederschap waren belangrijke voorspellers van roken tijdens de zwangerschap in alle etnische groepen.

In *hoofdstuk 8* onderzochten we of de etnische verschillen in zwangerschapsduur, vroeggeboorte en extreme vroeggeboorte verklaard kunnen worden door biologische, socio-demografische, leefstijl en medische risicofactoren. Vergeleken met Nederlandse vrouwen vonden we dat de zwangerschapsduur langer is bij Marokkaanse vrouwen en korter bij de Antilliaanse, Surinaamse-creoolse en Surinaams-hindoestaanse vrouwen. Het risico op vroeggeboorte was verhoogd in de Antilliaanse en Surinaams-hindoestaanse bevolkingsgroepen. Het verhoogd risico in deze groepen werd grotendeels verklaard door lengte van de moeder. Marokkaanse vrouwen hadden een verlaagd risico op vroeggeboorte vergeleken met de Nederlandse vrouwen. De Surinaams-creoolse

vrouwen hadden een verhoogd risico op extreme vroeggeboorte vergeleken met de Nederlandse vrouwen, welke slechts deels verklaard kon worden door de onderzochte risicofactoren. Deze bevindingen suggereren dat de etnische verschillen in zwangerschapsduur en vroeggeboorte voor een groot deel worden verklaard door biologische factoren en dat deze niet goed beïnvloedbaar zijn. De etnische verschillen in extreme vroeggeboorte konden niet worden verklaard door de onderzochte risicofactoren.

## Discussie

*Hoofdstuk 9* geeft een algemene discussie over de manier waarop onze bevindingen bij kunnen dragen aan een beter begrip van de verschillen in perinatale en zuigelingensterfte tussen de niet-Nederlandse en Nederlandse bevolkingsgroepen. Uit onze bevindingen concluderen we dat de Turkse, Marokkaanse, Antilliaanse en Surinaamse bevolkingsgroepen in Nederland een verhoogd risico hebben op zuigelingensterfte, dat gemedieerd wordt door geboortegewicht en zwangerschapsduur in de Surinaamse-creoolse, Surinaamse-hindoestaanse, Antilliaanse en Kaapverdiaanse groepen, terwijl de verhoogde zuigelingesterfte in de Turkse en Marokkaanse bevolkingsgroepen langs een andere weg tot stand lijkt te komen. De belangrijkste risicofactoren die de verschillen in foetale groei en geboortegewicht verklaren tussen de Surinaamse-creoolse, Surinaamse-hindoestaanse, Antilliaanse en Kaapverdiaanse groepen en de Nederlandse groep zijn maternale en paternale lengte, opleidingsniveau van de moeder, leeftijd van de moeder en burgerlijke staat. Belangrijke risicofactoren die verschillen in (extreme) vroeggeboorte verklaren tussen deze bevolkingsgroepen en de Nederlandse groep zijn maternale lengte, burgerlijk staat en pre-eclampsie. In de Turkse en Marokkaanse bevolkingsgroepen vonden we dat roken tijdens de zwangerschap en consanguiniteit risicofactoren zijn die mogelijk van belang zijn bij de verklaring van het verhoogde risico op perinatale en zuigelingesterfte in deze populaties.

We bediscussiëren relevante methodologische problemen die onze resultaten mogelijk hebben beïnvloed. Verder bespreken we enkel niet-bestudeerde risicofactoren die bij kunnen dragen aan completer begrip van de verhoogde risico's op zuigelingensterfte. Tenslotte bespreken we enkele aanbevelingen voor beleid en doen we enkele aanbeveling voor toekomstig onderzoek.

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## About the author

Ernst-Jan Troe werd op 5 augustus 1972 geboren in Voorburg. In 1991 behaalde hij het Gymnasium B diploma aan het Sint Maartenscollege in Voorburg. In hetzelfde jaar startte hij met de studie Geneeskunde aan de Universiteit Leiden. In 2000 deed hij zijn artsexamen en aansluitend werkte hij tot maart 2002 als AGNIO kindergeneeskunde in het Groene Hart Ziekenhuis in Gouda. Vanaf maart 2002 werkte hij als arts-onderzoeker bij het instituut Maatschappelijke Gezondheidszorg aan het onderzoek beschreven in dit proefschrift. In 2005 voltooide hij de opleiding tot Master of Science in Epidemiology aan the Netherlands Institute for Health Sciences (Nihes) in Rotterdam. Vanaf maart 2004 combineerde hij zijn promotieonderzoek met de opleiding tot huisarts aan het Leids Universitair Medisch Centrum (LUMC). In juni 2008 verwacht hij de huisartsopleiding te voltooien.

Ernst-Jan is getrouwd met Roos Uittenbogaart en zij hebben 2 kinderen, Tijn en Gijs.