Chapter 8

GENERAL DISCUSSION
Introduction

The aim of the present thesis was to elucidate the role of maternal nutrition in explaining ethnicity-related differences in fetal growth, as measured by birth weight at term (≥37.0 weeks’ gestation) and prevalence of small-for-gestational-age (SGA) births. The studies described were embedded in the Amsterdam Born Children and their Development (ABCD) study, a prospective community-based cohort study initiated in 2003 by the Municipal Health Service and the Academic Medical Center in Amsterdam. The major aim of the ABCD study is to gain more insight into the association between ethnicity and health, at birth as well as in later life. More specifically, the study aims to elucidate those factors that explain ethnicity-related health disparities, since ethnicity, rather than being a causal factor in itself, must be considered a “basket” factor that incorporates biological, social, and cultural components relevant to health and disease.\(^1\)

In the context of public health policy, Lin and Kelsey\(^1\) give the following arguments for the detailed analysis of ethnicity in relation to health and disease. Such an analysis:

1. provides leads about etiology;
2. helps to understand the roles of, and interactions between, genetic and environmental factors;
3. gives insight into the differences in biology (e.g., disease mechanisms) among ethnic groups;
4. assesses how the conceptualization of risk factors, symptoms, and disease may differ by ethnic/racial group, so that interventions may be better tailored to specific groups; and
5. identifies subgroups that may receive unequal preventive screening, or treatment, so that public health programs can be better targeted.

The ultimate goal of the ABCD study is to develop and improve public health programs, i.e., (4) and (5). However, to do this, research into (1), (2), and (3) is required.

In this thesis, we focused on the interrelation between ethnicity, nutrition, and birth weight for two nutrients/nutrient groups in particular: folate/folic acid and the n-3 and n-6 essential polyunsaturated fatty acids. We examined (a) the association between ethnicity and these nutrients (and determinants thereof); (b) the association between ethnicity and birth weight (focusing on explanatory factors other than nutrition); and (c) the role of these nutrients as determinants of birth weight. Data were collected by means of a questionnaire; in addition, a pragmatic approach to blood sampling was applied to measure the maternal nutrient status early in pregnancy. As the validity of these nutrient measurements in blood samples was assumed to depend on the validity of the sampling approach, this was also investigated. More specifically, the following research questions were addressed:
Validity of nutrient analyses:
1. Is a pragmatic approach to blood sampling suitable for valid measurement of nutrient status in a large-scale epidemiologic study? (Chapter 2)

Ethnicity and maternal nutrition:
2. (a) Does periconceptional use of folic acid supplements differ between women from ethnic minority groups and Dutch women; (b) are there ethnic-specific determinants that can explain ethnic differences in folic acid supplement use; and (c) how important is language proficiency as a determinant of use among women who were born in non-Dutch-speaking, non-Western countries? (Chapter 3)
3. (a) How do early pregnancy fatty acid concentrations among ethnic minority women compare to the early pregnancy fatty acid concentrations among Dutch women; and (b) to what extent can fish intake as a source of n-3 long-chain polyunsaturated fatty acids (LC-PUFAs) account for the ethnic variation in maternal n-3 and n-6 LC-PUFA concentrations? (Chapter 4)

Ethnicity and birth weight:
4. (a) How do the term birth weight distributions of ethnic minority women compare to the term birth weight distribution of Dutch women; and (b) to what extent can ethnic differences in birth weight be explained by conventional physiologic and environmental (but non-nutritional) risk factors? (Chapter 5)

Maternal nutrition and birth weight:
5. Is there a role for folate depletion in the association of short interpregnancy intervals with birth weight and SGA risk at term? (Chapter 6)
6. How does the maternal n-3 and n-6 fatty acid status relate to fetal growth as measured by infant birth weight and SGA risk at term? (Chapter 7)

In this chapter we will discuss our results, starting with a reflection on our findings and their implications for research, public health policy, and perinatal care. We will then discuss some general methodological issues and, finally, formulate our conclusions.

Ethnic disparities in birth weight: constitution is important

In Chapter 5, we observed that for the 1st and 2nd generations of all ethnic minority groups the crude birth weight distributions (standardized for gestational age only) were shifted to a lower birth weight (−21 g to −255 g) compared with the Dutch group. Ethnic minority groups
included all of the main ethnic groups in Amsterdam (Surinamese, Antillean, Ghanaian, Turkish, Moroccan) as well as an “other non-Dutch” group. Rather than environmental determinants (most importantly maternal smoking, body mass index (BMI), and work-related stress), constitutional factors (infant sex, maternal parity, age, and height) largely explained these disparities; after adjustment for the latter group of determinants, the birth weights of Turkish, Moroccan, and other non-Dutch newborns were similar to the birth weights of Dutch newborns. The minimal role of modifiable environmental determinants implicates that for these groups the potential for preventive actions – though still important on the individual level – is small.

Although constitutional rather than environmental factors were also responsible for a reduction in the birth weight disparities observed for the groups primarily of African origin (Surinamese, Antilleans, and Ghanaians), these newborns remained significantly smaller than the Dutch newborns (−98 g to −159 g). Explanations for these persisting disparities may include not only nutrition (see next paragraph), but also other unmeasured environmental determinants, constitutional/genetic factors, or their interaction. In this context, a potential pathway worth investigating is the vascular reactivity pathway. Women of African origin have shown higher rates of chronic and pregnancy-induced hypertension. A genetic predisposition to increased vascular reactivity, in combination with a higher exposure to environmental stress factors (e.g., racism, socioeconomic deprivation), could affect uteroplacental blood flow, and hence, fetal growth. Further research is also required to determine the consequences of the birth weight disparities. At the moment, we do not know if and how the lower birth weights of Surinamese, Antillean and Ghanaian newborns affect their short- or longer-term health. The ABCD study, however, provides a unique opportunity to investigate the longer-term consequences by follow-up measurements in childhood and beyond. With regard to short-term effects, preliminary analysis of weight-specific rates of mortality and morbidity of births registered in the Netherlands Perinatal Registry (PRN) suggests that the smaller size of Surinamese infants at birth is indeed related to more adverse outcomes (G.J. Bonsel, personal communication, 2008).

**Role of maternal nutrition in ethnic birth weight disparities**

The observed associations of maternal nutrition with both ethnicity (Chapters 3 and 4) and birth weight (Chapters 6 and 7) suggest that maternal nutrition could still – at least in part – explain the observed ethnic disparities in birth weight. This suggestion also emerges from **Table 8.1**, which illustrates the role of the maternal fatty acid profile in explaining the birth weight differences between ethnic groups; note, however, that the changes (model 2 vs. model 1) are modest. Further studies to explore the impact of other nutritional components would be worthwhile, but, as our studies show, these too should take into account the complex nature of
the interrelation between ethnicity, nutrition, and birth weight. More specifically, they should consider (1) the nonlinearity of the association between nutrition and birth weight; (2) the intercorrelations between nutrients; and (3) the indirect relationship between nutrient intake and nutrient status in maternal blood.

Table 8.1 Differences in birth weight (standardized for gestational age, in grams) between the ethnic groups, adjusted for constitutional and environmental non-nutritional determinants (model 1) and fatty acid profile (model 2)\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>B</td>
<td>95% CI</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch (reference)</td>
<td>2237</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Surinamese</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st generation</td>
<td>146</td>
<td>−140.9</td>
<td>−214.6, −67.2</td>
<td>−112.8</td>
</tr>
<tr>
<td>2nd generation</td>
<td>91</td>
<td>−169.0</td>
<td>−260.0, −77.9</td>
<td>−150.3</td>
</tr>
<tr>
<td>Antillean</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st generation</td>
<td>41</td>
<td>−104.4</td>
<td>−233.1, 24.3</td>
<td>−88.2</td>
</tr>
<tr>
<td>2nd generation</td>
<td>15</td>
<td>−65.9</td>
<td>−274.6, 142.9</td>
<td>−64.7</td>
</tr>
<tr>
<td>Turkish</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st generation</td>
<td>120</td>
<td>35.5</td>
<td>−47.0, 118.0</td>
<td>75.9</td>
</tr>
<tr>
<td>2nd generation</td>
<td>34</td>
<td>108.0</td>
<td>−35.9, 251.8</td>
<td>149.4</td>
</tr>
<tr>
<td>Moroccan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st generation</td>
<td>182</td>
<td>−20.9</td>
<td>−90.7, 48.9</td>
<td>−2.8</td>
</tr>
<tr>
<td>2nd generation</td>
<td>42</td>
<td>−34.1</td>
<td>−163.6, 95.3</td>
<td>−13.0</td>
</tr>
<tr>
<td>Ghanaian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st + 2nd generation</td>
<td>37</td>
<td>−106.8</td>
<td>−244.7, 31.1</td>
<td>−118.9</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st generation</td>
<td>554</td>
<td>28.8</td>
<td>−13.3, 70.9</td>
<td>38.2</td>
</tr>
<tr>
<td>2nd generation</td>
<td>167</td>
<td>0.2</td>
<td>−64.4, 64.9</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Fatty acids – cumulative exposure score\textsuperscript{c}

<table>
<thead>
<tr>
<th>Exposure Score</th>
<th>0–1</th>
<th>2–3</th>
<th>4–5</th>
<th>≥6</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1707</td>
<td>1181</td>
<td>511</td>
<td>267</td>
</tr>
<tr>
<td>B</td>
<td>0.0</td>
<td>−31.8</td>
<td>−57.3</td>
<td>−133.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>−62.7, −0.9</td>
<td>−102.0, −12.7</td>
<td>−195.0, −72.8</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Linear regression analysis, B (95% CI) is the unstandardized regression coefficient with 95% confidence interval, representing the difference in the birth weight in the specific ethnic group and that in the Dutch reference group. Model 1: adjusted for infant sex, parity, maternal age, height, education, cohabitant status, BMI, smoking, alcohol consumption, depression, and work stress (see Chapter 5). Model 2: as model 1, plus additional adjustment for maternal fatty acid profile.

\textsuperscript{b} The maternal fatty acid profile is defined by the cumulative exposure score. The exposure score is based on the univariate associations of the individual fatty acids with birth weight (see Chapter 7). For each fatty acid positively associated with birth weight (i.e., 18:3n-3, 20:4n-3, 20:5n-3, 22:6n-3, and 20:3n-6), the lowest quintile was scored as 1 (exposed); for each fatty acid negatively associated with birth weight (i.e., 18:2n-6, 20:4n-6, 22:4n-6, 22:5n-6, and 18:1n-9t), the highest quintile was scored as 1. After summation, scores were combined into 4 categories (0–1, 2–3, 4–5, and ≥6), and the latter category was defined as the most adverse profile.
Nonlinear association

As shown in Chapters 6 and 7, the association between a specific nutritional factor and birth weight is likely to be nonlinear. As also noted by others, it is more probable that a relationship between (a) a nutrient and (b) functions dependent on that nutrient will plateau at levels above need. For example, Figure 6.1 in Chapter 6 illustrates that the positive effect of the use of supplements containing folic acid on fetal growth (as reflected by a higher mean birth weight and lower SGA risk in comparison to nonusers) is present at short (typically defined as <6 months) intervals only, i.e., among the women most at risk of folate depletion. This positive effect of folic acid supplement use is further illustrated in Table 8.2, which shows the mean birth weight and SGA prevalence according to supplement use in intervals <6 months compared to intervals of 18 to 23 months.

Similarly, in Chapter 7 we observed that the specific associations of the n-3 and n-6 fatty acids with birth weight were present at the extremes only. Low concentrations of n-3 eicosatetraenoic acid (20:4n-3), eicosapentaenoic acid (EPA, 20:5n-3) and docosapentaenoic acid (DPA, 22:5n-3) as well as the n-6 LC-PUFA dihomo-γ-linolenic acid (DGLA, 20:3n-6) and high concentrations of the n-6 LC-PUFA arachidonic acid (AA, 20:4n-6) affected fetal growth, with an estimated 50 to 60 g decrease in birth weight and 40% to 50% increase in SGA risk at the extremes (lower/upper quintile) when compared to average concentrations (middle quintile). Thus, when investigating the role of nutritional factors in ethnic birth weight disparities, the nonlinearity of the associations should be considered, since simple linear correlation statistics will not be sufficient in that case and can be misleading.

Table 8.2  Birth weight and small-for-gestational-age (SGA) prevalence for term births among nonusers, late users, and early users of folic acid supplements: comparison between mothers with interpregnancy intervals of <6 months and mothers with interpregnancy intervals of 18 to 23 months

<table>
<thead>
<tr>
<th>Interval</th>
<th>Nonusers</th>
<th>Late users</th>
<th>Early users</th>
<th>Nonusers</th>
<th>Late users</th>
<th>Early users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Birth weight (g)</td>
<td>SGA (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>45</td>
<td>3281 ± 404(^a)</td>
<td>35.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>3510 ± 491</td>
<td>20.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>3636 ± 543</td>
<td>8.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–23 months</td>
<td>96</td>
<td>3633 ± 605</td>
<td>13.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>137</td>
<td>3704 ± 500</td>
<td>11.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>174</td>
<td>3637 ± 453</td>
<td>10.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Mean ± SD (all such values).

Nutrient intercorrelations

Aside from the "single nutrients" such as folate (nutrients with an established role in pregnancy at levels not normally obtainable from foods), the required physiologic amounts of the nutrients essential to fetal growth are generally obtained from the pregnant woman's diet. However, diet represents a complex set of exposures that can be strongly intercorrelated,
an issue which studies of single nutrients in isolation – though important first steps in establishing nutritional effects – do not take into account. In this thesis, the importance of intercorrelations between nutrients was demonstrated in Chapter 7, in which we examined not only the individual associations of the maternal n-3, n-6, and \textit{trans} fatty acids with birth weight, but also the role of the overall maternal fatty acid profile. This measure, defined by the combination of the individual fatty acid concentrations, was specifically developed to consider the metabolic interrelations between these fatty acids. The analysis showed that infants born to the 7\% of mothers with the most adverse profile were 125 g lighter and twice as likely to be SGA, an effect comparable to that of smoking. These results, in conjunction with the emerging evidence on the importance of a healthy diet (which would indicate an adequate overall nutrient status), stress the importance of more detailed research into the significance of nutrient intercorrelations for fetal growth, as has also been argued by others. In this context, additional research is recommended to investigate in particular the synergy between folate and the n-3 LC-PUFAs that has recently been suggested by some studies, but contradicted by others. Since nutrient status was extensively measured in the ABCD study (in addition to folate and the n-3 and n-6 fatty acids, we measured the minerals iron, zinc, magnesium, and calcium, and the vitamins A, D, and B1), future studies are also planned to examine these nutrients, their interrelations, and their associations with ethnicity and birth weight.

\textit{Indirect relationship between nutrient intake and status}

Much of our knowledge of the role of maternal nutrition in fetal growth has been derived from observational studies and intervention trials in which low or high maternal intakes have been associated with adverse or favorable pregnancy outcomes. However, the final supply of nutrients to the placenta not only depends on the mother’s intake, but also on her intermediary metabolism and endocrine status, her partitioning of nutrients among storage, use, and circulation, and cardiovascular adaptations that enhance uterine blood flow. Consequently, what is measured at the intake level may not necessarily correspond to what is measured at a more physiologic level, i.e., in maternal blood. This discrepancy was especially demonstrated in Chapter 4, in which we described the interethnic differences in maternal n-3 and n-6 fatty acid concentrations and examined the role of fish and fish oil consumption as an explanation for the observed differences in concentrations of EPA and docosahexaenoic acid (DHA, 22:6n-3), as well as DGLA and AA. Compared to Dutch women, Surinamese, Antillean, Turkish, and Moroccan women had generally lower concentrations of n-3 fatty acids but higher concentrations of n-6 fatty acids, with the exception of DGLA. Ghanaian women, in contrast, had higher concentrations of the n-3 fatty acids EPA, DPA, and DHA, but generally lower concentrations of n-6 fatty acids. Interestingly, while differences were most pronounced in the groups who reported the lowest and highest fish intake (Turkish and Ghanaian, respectively), the explanatory strength of this factor was only minor. Thus,
rather than intake variation, the observed differences assumingly reflect metabolic variation between ethnic groups.

Usually, in large epidemiologic (cohort) studies a food frequency questionnaire (FFQ) is preferred over other assessments of the maternal diet or nutrient status, being a convenient and inexpensive method to measure hundreds or even thousands of people. However, as our results show, the use of biomarkers can be a valuable addition to gain a better understanding of the physiologic aspects of nutrition and their relevance to health and disease as well as any related ethnic disparities. That a valid measurement of biomarkers does not necessarily require central collection and immediate processing, as is generally assumed, was demonstrated in Chapter 2. Here we observed that a pragmatic approach to blood collection (i.e., a decentralized collection with samples sent by mail or courier to a central laboratory) still allowed for a valid analysis of the biomarkers of interest: most markers showed limited variance within a 96-h storage period, and although for folate, linoleic acid, and adrenic acid significant changes (≥10%) over time were observed, these changes did not significantly affect measures of 28h-validity (intraclass correlation coefficients ≥ 0.9, n = 50 bootstrap Spearman rank correlation coefficients ≥ 0.8).

Arguably, in some cases the FFQ approach may still be preferred over biomarker measurements, depending also on the relative validity of the questionnaire. Studies that validated self-reported folic acid supplement use by comparison with biomarker measurements have reported strong and significant linear associations between folate concentrations and folic acid intake, suggesting that when women report taking more folic acid, and for a longer period of time, their serum and red blood cell levels increase correspondingly. Since similar observations were done within the ABCD study (where serum folate concentrations among users was generally twice that of concentrations among nonusers) and we aimed for groups of a sufficient size for analysis, we preferred to include supplement use rather than blood measurements of folate in Chapter 6.

**Improving maternal nutrition**

When considering the implications of our results for public health policy and perinatal care, a distinction must be made between the n-3 and n-6 essential polyunsaturated fatty acids and folate.

As noted before, folate is a nutrient that already has an established effect in pregnancy already, at intake levels unattainable by diet alone. An adequate folate status in pregnancy is undisputedly important for preventing neural tube defects, and may be relevant for preventing not only lower birth weight, but also other pregnancy complications such as preeclampsia, preterm
birth, stillbirth, and abortion.\textsuperscript{25} Public health programs to promote the intake of folic acid supplements (ensuring an adequate status) have been implemented since the 1990s,\textsuperscript{25,26} but have met with limited success among ethnic minority groups.\textsuperscript{25,28} In our study (Chapter 3) we also observed folic acid supplement use to be significantly lower among women born in non-Dutch-speaking, non-Western countries (<41\%) than among women born in the Netherlands (86\%) or in another Western country (78\%). While the use of folic acid supplements was primarily determined by knowledge about folic acid, the key factor for this knowledge, in both the Western and non-Western groups, was language proficiency.

Perhaps the best alternative to the current supplementation policy in the Netherlands would be a fortification policy. However, fortification has been debated, on the one hand with regard to the short and longer term benefits and risks, on the other hand with regard to “the right of personal integrity”.\textsuperscript{29} Although this debate recently received a new impetus,\textsuperscript{30} it seems unlikely that fortification will be implemented in the near future, and other approaches to enhance folic acid intake among ethnic minority groups should be considered. From a more general perspective, the language education recently made mandatory by the Dutch government for all new immigrants is a promising approach, particularly if it integrates information about prenatal health and health care. Alternatively, the ethnic health advisors appointed some years ago in maternal and child health centers throughout Amsterdam, can help target the groups most at risk. Within their own cultural context and in their own language, these advisors can educate women about folic acid use as well as family planning, the latter being an important strategy to avoid folate depletion associated with short interpregnancy intervals.

At this stage, no evidence-based intervention strategies exist to improve the maternal n-3 and n-6 essential fatty acid status, although in the general population the use of fish oil supplements as a source of the n-3 LC-PUFAs seems to have increased over the past few years. While overall our results suggest that research into the effects of either a dietary or pharmacological adaptation of the maternal n-3 and n-6 fatty acid intake would be worthwhile, some circumspection is necessary. Dietary change in a multi-ethnic society could be difficult to achieve, because it requires an intensive measure (e.g., dietary counseling)\textsuperscript{31} that must take account of existing cultural patterns and trends and recognize the heterogeneity between as well as within ethnic groups.\textsuperscript{32} In terms of feasibility, perhaps more can be expected from a pharmacological adaptation, i.e., via supplementation. Still, for both strategies, the expectations of intervention effects should not be exaggerated, given the dynamics of fatty acid metabolism (see Chapter 4). Monitoring of the effect should thus include measurement of nutrient status before and after the intervention.
Methodological considerations

As does any epidemiologic study, the ABCD study has its methodological strengths and limitations. The methodological considerations directly relevant to the specific studies have been discussed in the Discussion sections of the previous chapters. In this section, we will address some issues of general importance: (1) the definition of ethnicity, (2) selective nonresponse, and the strengths and limitations of (3) exposure and (4) outcome measurements.

Defining ethnicity

In epidemiologic and public health research, the concept of ethnicity continues to be a source of debate. As a multidimensional concept, ethnicity is not well-defined, and often encompasses different classifications, depending on the context in which the definition is made. Broadly, three dimensions of ethnicity may be distinguished, all three of which appear relevant to perinatal health: (1) race/genetic constitution; (2) sociocultural orientation; and (3) migrant status. These dimensions are often approached from a cross-sectional perspective, whereas all three are to some extent dynamic, through genetic admixture, acculturation, and adaptation to a host country. Measurement is often a challenge, both in terms of classification (which categories make up the classification?) and identification (on what basis do you identify a person as belonging to a certain category?). For example, whereas the classification of race is often based on geographical origin (or ancestry), identification usually relies on records of one's physical appearance (e.g., skin color) by the researcher or care provider, which is a subjective and imprecise measure. With respect to sociocultural orientation, it is interesting to note that the concept itself includes several dimensions and may consequently be measured very differently depending on the underlying research question. Among the measurement strategies most relevant, those incorporating country of birth may be considered most stable; both cultural characteristics and self-identification can be quite fluid and change over time. Also the concept of migrant status may encompass several dimensions that could be difficult to capture, such as the reason for migration, the experience of migration itself, and orientation towards return migration.

In the ABCD study, we aimed to capture all three dimensions; in our view, the classification most suitable for this was country of birth. As a measure of geographical origin it reflects the genetic heritage, as well as the social heritage of culture and traditions that are inherent to the concept of ethnicity. In addition, by including maternal country of birth, this approach also allowed for the distinction between women who themselves immigrated (1st generation) and women who are the children of immigrants (2nd generation). Useful as the classification based on country of birth may be, it should be kept in mind that this measure does not capture heterogeneity in history, culture, language, or dietary preferences within ethnic groups, as exists, for example, among the Creole and Hindustani populations of Surinam. However, to the extent that information was available that allowed us to distinguish between these groups,
the Surinamese-Creole and Surinamese-Hindustani people did not differ from each other in outcomes (see Chapter 5). Moreover, it can be assumed that in the Amsterdam population, the Surinamese-Creole group largely outnumbers the Surinamese-Hindustani group.38

Selective nonresponse

The overall response rate of the ABCD study was 67%, which agrees with the response rates observed in other large-scale community-based pregnancy cohorts, such as the Generation R study in the Netherlands (61%)39 and the Southampton Women's Survey (75%)40 and ALSPAC study (85%) in the UK.41 During data collection, two supportive measures were taken to enhance enrolment of foreign-born women in particular: we (1) provided a Turkish, Arabic, or English translation to women born in Turkey, Morocco, or another non-Dutch-speaking country, respectively, and (2) offered oral administration to women who were illiterate or had reading difficulties. Overall, these measures resulted in an adequate response among foreign-born women, although response remained lower than among Dutch-born women: 42% to 64% vs. 77% for the questionnaire, 31 to 55% vs. 59% for the biomarker study. To investigate the degree of selection bias resulting from this selective ethnic nonresponse, a nonresponse analysis by anonymous linkage with the PRN was conducted. The results confirmed the selective ethnic nonresponse with lower participation rates among women from non-Western ethnic origin, but indicated that selection bias was minimal: the association between ethnicity and low birth weight was similar in both the response and nonresponse group.42 This suggests that, with our study population, conclusions about the associations between ethnicity, birth weight determinants, and birth weight can validly be drawn.

Exposure measurement

The measurement of nutrient status in conjunction with the questionnaire allowed us to capture a large set of risk factors relevant to fetal growth, but we are aware that this advantage may have been counterbalanced by the questionnaire's self-reporting nature. However, given the prospective design of the study, and the assurance of confidentiality provided to all women involved, we expect any information bias to be minimal. All exposures/risk factors were, by design, measured as early in pregnancy as possible, and it could be argued that our results are influenced by changes in exposures occurring in late pregnancy. However, our focus on early pregnancy was chosen on the basis of the existing evidence that the trajectory of fetal growth and development is set at this early stage43 and under the assumption that any changes in risk factors are most likely attenuations (e.g., women with the most stressful working conditions taking earlier leave).44 Nevertheless, as variability in nutrient status in particular cannot be excluded, future research into the late effects of nutrients is recommended.

Arguably, the definition of early pregnancy can be arbitrary. All participants in the ABCD study were approached during their first antenatal visit to their obstetric care provider; and variation in the timing of this appointment unavoidably introduced variation in timing of
the questionnaire (and biomarker measurements), with the largest delays observed for women of ethnic minority background. Still, the majority of women (90%) filled out their questionnaires in the first half of pregnancy (≤20th week), and 60% before the 16th week, which in our view justifies the reference to early pregnancy for all women. It should be noted that the timing and nature of the questionnaire may have also resulted in a suboptimal measurement of medical factors like chronic or gestational hypertension and diabetes, which are particularly relevant to placental function and hence to nutrient supply to the fetus. With the recent linkage of ABCD records to information from the PRN, more reliable information has become available, which can be included in future analyses.

**Outcome measurement**

In this thesis we used term birth weight (as a continuous measure) and SGA (dichotomized) as indicators of fetal growth. Ideally, the assessment of the determinants of fetal growth would start from the expected trajectory for each infant throughout the course of pregnancy, and quantify the deviation in actual growth relative to the expected pattern. However, for most studies, including ours, birth weight is often the only feasible measure. To the extent that the trajectory of fetal growth has been measured in a pregnancy cohort, analyses have not yet provided new information on the determinants of growth or explanations of ethnic disparities. It should be noted that for the classification of SGA, an accurate assessment of not only birth weight but also gestational age is necessary. In the ABCD study, information on birth weight and gestational age as recorded by the obstetric care providers was obtained via the Youth Health Care department of the Municipal Health Service. Since in the Netherlands a routine ultrasound measurement is offered to all pregnant women starting obstetric care and is accepted by the majority of women (>90%), we believe accurate pregnancy dating was ascertained.

**In conclusion**

In this thesis, we aimed to elucidate the role of maternal nutrition in explaining ethnic disparities in birth weight. From the studies described, the following three conclusions can be drawn.

First, whereas nutritional factors were shown to be relevant to fetal growth, their role in explaining ethnic disparities in birth weight appears to be modest. Although preventing inadequate maternal nutrition is important at an individual level, caution is advised with regard to expectations of intervention effects at the population level. With respect to the n-3 and n-6 essential polyunsaturated fatty acids, interventions aimed at improving the maternal
profile of these fatty acids still require further study, which should take into account the
dynamics of fatty acid metabolism. Improving the maternal periconceptional folate status, still
of undisputed importance for preventing neural tube defects, may in a multi-ethnic society
best be achieved by fortification, but this option is still being debated in the Netherlands.
Promising alternative strategies are the employment of ethnic health advisors in maternal and
child health care centers and language courses for immigrants: both measures allow for the
dissemination of linguistically appropriate, comprehensive information about folic acid use
as well as family planning, the latter being an important measure to prevent folate depletion
in a subsequent pregnancy.

Second, when examining ethnic disparities in health and disease, three concepts of ethnicity
are relevant: (1) race/genetic constitution; (2) sociocultural orientation; and (3) migrant status.
Which concepts to consider depends on their relative importance to the health problem and
research question at stake. For example, research into the role of nutrition in explaining ethnic
disparities in perinatal health requires an understanding of the dietary (sociocultural) as well
as metabolic (genetic) aspects of nutrition. The same is true when deciding on a public health
strategy. Some problems (e.g., lower birth weight) may require a more tailored intervention
restricted to specific subgroups (women of African descent), whereas other problems (folic
acid supplement use) may benefit best from a universal measure (language education for all
immigrants).

Third, it can be assumed that the observed ethnic disparities, both in birth weight
and the determinants thereof, are also relevant to ethnic disparities in later life (the “fetal
origins of disease” hypothesis). In time, the ABCD study will provide more insight into the
consequences of an adverse fetal environment to health and disease in childhood, and into
the extent to which ethnic health differences are indeed explained by ethnic differences in the
fetal environment. As such, the study will form a basis for developing and implementing early
life interventions.
References


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