Maternal homocysteine and small-for-gestational-age offspring: systematic review and meta-analysis\textsuperscript{1,2}

Marije Hogeveen, Henk J Blom, and Martin den Heijer

ABSTRACT

Background: Growth retardation in utero leading to small-for-gestational-age (SGA) newborns is associated with increased neonatal morbidity and mortality and with lifelong consequences such as poor cognitive function and cardiovascular diseases. Maternal total homocysteine (tHcy) concentrations have been linked to a wide range of adverse pregnancy outcomes and could possibly influence birth weight.

Objective: We performed a systematic review of and meta-analysis on the association of maternal tHcy and birth weight.

Design: A literature search of English, German, and French publications with the use of the PubMed database (January 1966–July 2010) found 78 abstracts. Search terms were as follows: homocysteine AND (birth weight OR small for gestational age OR intrauterine growth retardation). Studies were eligible if information on maternal tHcy and birth weight and the possible association between maternal tHcy and birth weight was available. Effect size estimates were converted to ORs as estimates of the RR of a woman to deliver SGA offspring when maternal tHcy exceeded the 90th percentile.

Results: The search yielded 19 studies for analysis, consisting of 21,326 individuals. Pooled analysis resulted in a crude OR of 1.25 (95% CI: 1.09, 1.44). When this estimate was expressed as a linear effect, it corresponded to a decrease in birth weight of 31 g (95% CI: −13, −51 g) for a 1-SD increase in maternal tHcy.

Conclusions: Higher maternal tHcy concentrations are associated with a small increased risk for SGA offspring. The small estimated birth weight difference might be of little clinical relevance for the individual newborn; however, it could be of greater importance at a population level. Am J Clin Nutr 2012;95:130–6.

INTRODUCTION

Growth retardation is a global major public health problem and 1 of the 4 leading causes of perinatal death in the Netherlands (1). It poses newborn infants at increased risk of morbidity and mortality in the neonatal phase and at increased risk of long-term cognitive and motor impairment (2). Consequences of being born SGA\textsuperscript{3} can be lifelong: SGA is associated with increased risk of reduced stature, poor cognitive function, coronary heart disease, stroke, hypertension, and type 2 diabetes (3–5). The fetal origins of chronic disease model suggests that nutrition during fetal life changes gene expression and thereby responses to later environment in such a way that the pace and pathway of early growth appear to be a risk factor for chronic disease in adulthood (6). Although birth weight is the end result of many different paths of fetal growth, it nevertheless provides a basis for estimating risks of development of disease later in life.

Homocysteine is a sulfur-containing amino acid formed from methionine in several steps. It can be remethylated to methionine by using 5-methyltetrahydrofolate and methylcobalamin as the methyl donor and cofactor, respectively. Increased maternal tHcy concentrations (defined as varying from >15 µmol tHcy/L or as the highest quartile, 80th, 90th, or 95th percentile of the reference populations) have a plausible causal link to neural tube defects (7–9). It has been postulated that increased maternal tHcy concentrations could be associated with congenital heart defects (10, 11) and a wide range of adverse pregnancy outcomes, including recurrent early pregnancy loss (12, 13), abruptio placentae (14, 15), preeclampsia (14, 16), and fetal loss (17, 18). These adverse pregnancy outcomes are all possibly related to maternal vascular compromise. If maternal tHcy were causally related to vascular compromise, it could be anticipated that birth weight may be influenced. Studies regarding the possible association between maternal tHcy and birth weight performed until now have yielded conflicting conclusions. Sample size, different cutoffs for birth weight, confounders, and timing of maternal blood sampling may contribute to these inconsistent outcomes (14, 17–50).

Because of the increased short- and long-term risks of infants who are born SGA, the determination of possibly treatable risk factors is of utmost importance. If maternal tHcy were negatively associated with birth weight, folic acid intervention trials that lower tHcy concentrations could be the next step. Our aim was to perform a systematic review and meta-analysis focusing on the question of whether maternal tHcy concentrations are related to the offspring’s birth weight. We estimated the RR of SGA off-

\textsuperscript{1} From the Department of Pediatrics (MH) and the Departments of Epidemiology and Biostatistics and Endocrinology (MdH), Radboud University, Nijmegen Medical Center, Nijmegen, Netherlands, and the Metabolic Unit, Department of Clinical Chemistry (HJB) and the section of Endocrinology, Department of Internal Medicine (MdH), VU Medical Center, Amsterdam, Netherlands.

\textsuperscript{2} Address correspondence to M Hogeveen, Radboud University, Nijmegen Medical Center, PO Box 9101, 6500 HB Nijmegen, Netherlands. E-mail: m.hogeveen@ckz.umcn.nl.

\textsuperscript{3} Abbreviations used: GA, gestational age; SGA, small for gestational age; tHcy, total homocysteine.

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METHODS

Search strategy and selection criteria

Eligible studies were identified by searching the electronic literature [PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/)] for relevant publications between January 1966 and July 2010 with the use of the following search terms: homocysteine AND (birth weight OR small for gestational age OR intrauterine growth retardation). We (MH and MdH) performed a hand-search of bibliographies of all relevant studies on this topic. The population was defined as women who gave birth or who were pregnant at or after the time of inclusion. Effect size estimates could exist of the following: 1) comparison of maternal tHcy between appropriate-for-gestational-age and SGA, 2) a correlation between maternal tHcy and birth weight, 3) determination of the risk of SGA above a cutoff for maternal tHcy, or 4) regression analysis with maternal tHcy as the possible determinant and birth weight as the dependent factor. The authors of the included studies used SGA as well as low birth weight (<2500 g), tertiles or quartiles of birth weight, intrauterine growth retardation, or increase in estimated fetal birth weight in their analyses. We defined our primary outcome as SGA offspring.

Study eligibility criteria

Studies were eligible for this meta-analysis if 1) the study contained data on women who had been or who were pregnant at the time of inclusion or who were included preconceptionally; 2) information on birth weight could be extracted, whether as continuous variable, or dichotomized; 3) information on maternal tHcy was available, whether as continuous variable or dichotomized; and 4) an analysis regarding the possible association between maternal tHcy and birth weight was performed. Eligibility assessment of 78 abstracts was performed in an unblinded manner independently by 2 investigators (MH and MdH), on the basis of title and abstract content. There were no disagreements between the reviewers (Figure 1).

Report eligibility criteria

The search was restricted to human studies in English, French, or German published between January 1966 and July 2010.

Data collection

A standard data extraction form was developed and used on the possible relevant articles. All data from eligible articles were abstracted by one review author (MH) by using the data extraction form, and extracted data were checked by a second review author (MdH). Information was sought in each individual study on the following: 1) general study information, including title, first author, journal, year of publication; 2) characteristics of participants (including number of participants, maternal age, parity, use of vitamin supplements, smoking, maternal tHcy, threshold of maternal tHcy, timing of maternal sample); 3) outcome measures (birth weight, newborn sex, GA); 4) statistical analyses and definitions, including definition of SGA, type of analyses, results, and adjustments.

Summary measures

Because birth weight is strongly associated with GA, the use of a birth weight <2500 g will result in a heterogeneous group of premature and term newborns. We chose to use SGA, which is defined as birth weight below the (sex-specific) 10th percentile for GA. The primary outcome measure was the OR as an estimate of the RR of a woman to deliver SGA offspring when maternal tHcy exceeded the 90th percentile.

Statistical analysis

The 19 studies that contained effect size estimates differed in the kinds of effect size estimates. Some studies showed mean differences in tHcy between mothers of children with normal birth weight and mothers of children born SGA (17, 20, 21, 26, 28–31). Other studies provided ORs as estimates of RR of having a child born SGA (14, 21, 23–25, 27, 32, 35), whereas a third group of articles showed regression coefficients or correlation coefficients between maternal tHcy and birth weight (19, 22, 24, 27, 28, 33–35).

To convert these effect sizes to ORs, we extended the method used for dichotomous outcome studies (51, 52). This method assumes a linear relation between maternal tHcy and birth weight.

This assumption is met as shown in the generalized additive model curves presented in our previous article (35). Testing for departure from linearity by using the NLCHECK routine in STATA (Stata...
Corporation) (53) yielded a P value of 0.97. Under this assumption of linearity, we simulated a data set of 1,000,000 observations with a normal distribution and a correlation coefficient between −0.99 and 0.99 for each possible value at 2 decimals of precision. From these simulated data sets, we calculated standardized mean differences at a certain cutoff for birth weight (most studies used the 10th percentile, but other studies used the 5th or 33rd percentile). Furthermore, we calculated ORs for these cutoffs of birth weight and different cutoffs of tHcy (67th, 75th, 90th percentile). Because some ORs in published articles were provided for a top compared with bottom quartile, we calculated these top compared with bottom quartile ORs as well. So, for each possible correlation coefficient, we calculated standardized mean differences (also known as Cohen’s d) and ORs at certain cutoffs. The results of these calculations are shown in Supplemental Tables S1–S5 available under “Supplemental data” in the online issue). From these tables, one can easily convert an effect size that is expressed as a standardized mean difference or an OR into a correlation coefficient and vice-versa.

Studies that presented mean tHcy in cases and controls did not always provide estimates of SD; however, they did provide P values for t tests. In that case, the standardized mean difference was calculated from the t statistic and the number of cases and controls (54). The same principle was applied to the studies that provided regression coefficients without an SD but with a P value. In that case, we calculated the correlation coefficient from the P value and the number of subjects. If a P value was expressed as P < 0.01 or P ≤ 0.001, we took it as P = 0.01 or P = 0.001, respectively, which occurred in only 2 studies (20, 22). The method described above allowed us to provide reliable effect size estimates of ORs for infants being born SGA when maternal tHcy was >90th percentile. From these ORs and the number of cases and controls we could easily calculate the 2 × 2 table that underlies the ORs and subsequently calculate the SEs and 95% CIs by using the Woolf’s method (55).

With the use of these ORs, we performed a pooled analysis on the log-transformed ORs with the inverse of the SE as weight and by using a fixed-effects model. The METAN routine of STATA statistical software (version 11.0; Stata Corporation) was used for this analysis. We repeated the analysis after exclusion of studies that used maternal blood sampled months or years after delivery (14, 25).

RESULTS

The PubMed search yielded 78 titles after applying the limits of human studies and English, French, or German language. After the reading of all abstracts, the 33 studies whose full text was retrieved for detailed assessment showed 2 further studies through a hand search of bibliographies (22, 23). From these 35 studies, 16 were excluded (Figure 1). Six studies were excluded because they were performed in a population of women with preeclampsia only (36–38, 40, 41, 47), 2 because they studied associations between polymorphisms and pregnancy outcome (39, 43), 2 because no maternal tHcy concentrations were described (42, 48) and one because no information on birth weight could be retrieved (45). One study turned out to be a review (44), one study did not describe a control group (18), and 3 studies did not describe a relation between maternal tHcy and birth weight (46, 49, 50).

Our final analysis included 19 studies, which consisted of 21,326 individuals (14, 17, 19–35). These studies analyzed the association between maternal tHcy and birth weight through comparison of mean values between cases and controls (n = 8) (17, 20, 21, 26, 28–31), by calculating ORs or RRs of having SGA infants with increased maternal tHcy (n = 8) (14, 21, 23–25, 27, 32, 35), through the use of linear regression analysis to study maternal tHcy as a determinant for birth weight (n = 8) (19, 22, 24, 27, 28, 33–35), or by using a combination of the methods listed previously. Extensive description of the characteristics of all included studies is described in Tables 1–3.

### TABLE 1

Study characteristics of the 8 studies on the association between maternal tHcy concentrations and birth weight that compared mean values (of the 19 total studies for analysis)

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Year</th>
<th>n</th>
<th>tHcy</th>
<th>n</th>
<th>tHcy</th>
<th>P value</th>
<th>Definition of SGA</th>
<th>Maternal tHcy determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke (17)</td>
<td>1992</td>
<td>37</td>
<td>7.7 ± 2.3</td>
<td>35</td>
<td>7.9 ± 2.3</td>
<td>NM</td>
<td>10th percentile&lt;sup&gt;6&lt;/sup&gt;</td>
<td>48–72 h AD</td>
</tr>
<tr>
<td>Hogg (20)</td>
<td>2000</td>
<td>22</td>
<td>5.7 ± 1.9</td>
<td>402</td>
<td>5.3 ± 1.8</td>
<td>0.35</td>
<td>10th percentile&lt;sup&gt;6&lt;/sup&gt;</td>
<td>37 wk GA</td>
</tr>
<tr>
<td>D’Anna (26)</td>
<td>2004</td>
<td>36</td>
<td>5.85 ± 1.0</td>
<td>36</td>
<td>5.6 ± 1.11</td>
<td>0.20</td>
<td>10th percentile&lt;sup&gt;6&lt;/sup&gt;</td>
<td>16 wk GA</td>
</tr>
<tr>
<td>Yajnik (28)</td>
<td>2005</td>
<td>30</td>
<td>7.2 (5.4, 9.8)</td>
<td>50</td>
<td>5.5 (4.4, 6.7)</td>
<td>&lt;0.01</td>
<td>10th percentile&lt;sup&gt;6&lt;/sup&gt;</td>
<td>At delivery</td>
</tr>
<tr>
<td>Lindblad (29)</td>
<td>2005</td>
<td>46</td>
<td>12 (4, 23)</td>
<td>82</td>
<td>9.6 (5, 23)</td>
<td>0.02</td>
<td>&lt;11%&lt;sup&gt;6&lt;/sup&gt; EFBW&lt;sup&gt;6&lt;/sup&gt;</td>
<td>At delivery</td>
</tr>
<tr>
<td>Onalan (30)</td>
<td>2006</td>
<td>41</td>
<td>6 (2.3, 16)</td>
<td>324</td>
<td>5 (1.8, 25.3)</td>
<td>&lt;0.001</td>
<td>5th percentile&lt;sup&gt;6&lt;/sup&gt;</td>
<td>15–19 wk GA</td>
</tr>
<tr>
<td>Martin (31)</td>
<td>2007</td>
<td>30</td>
<td>9.7 ± 0.6</td>
<td>52</td>
<td>9.1 ± 0.4</td>
<td>0.4</td>
<td>2.5 percentile&lt;sup&gt;6&lt;/sup&gt;</td>
<td>4 d AD</td>
</tr>
<tr>
<td>Ronnenberg (21)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2002</td>
<td>65</td>
<td>8.2 (7.6, 8.8)</td>
<td>358</td>
<td>8.1 (7.8, 8.5)</td>
<td>NM</td>
<td>10th percentile&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Preconception</td>
</tr>
</tbody>
</table>

<sup>1</sup> Data from 8 individual studies comparing mean values included in our review and meta-analysis are shown. AD, after delivery; EFBW, estimated fetal birth weight; GA, gestational age; NM, not mentioned; SGA, small for gestational age; tHcy, total homocysteine.
<sup>2</sup> Values are means ± SDs.
<sup>3</sup> Sex-specific percentile for GA.
<sup>4</sup> Values are geometric means; interquartile ranges in parentheses.
<sup>5</sup> Values are medians; ranges in parentheses.
<sup>6</sup> Lack of increase (↑) in EFBW in 2 wk (<11% compared with standard curves).
<sup>7</sup> Percentile for GA.
<sup>8</sup> Values are means ± SEs.
<sup>9</sup> Values are geometric means; 95% CIs in parentheses.
TABLE 2
Study characteristics of the 8 studies on the association between maternal tHcy concentrations and BW that presented ORs (of the 19 total studies for analysis)

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Year</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR (95% CI)</th>
<th>Threshold tHcy</th>
<th>Threshold BW</th>
<th>Maternal tHcy determination</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ronnenberg (21)</td>
<td>2002</td>
<td>65</td>
<td>358</td>
<td>1 (0.4, 2.2)</td>
<td>&gt;12.4 (\mu)mol/L</td>
<td>&lt;10th percentile</td>
<td>Preconception</td>
<td>Batch GA, sex, BMI, smoking, maternal age</td>
</tr>
<tr>
<td>Murphy (27)</td>
<td>2004</td>
<td>91</td>
<td>358</td>
<td>1.2 (0.39, 3.72)</td>
<td>&gt;67th percentile</td>
<td>&lt;3rd percentile</td>
<td>32 wk GA</td>
<td>GA, sex, BMI, smoking, maternal age</td>
</tr>
<tr>
<td>Hogeveen (35)</td>
<td>2010</td>
<td>366</td>
<td></td>
<td>1.17 (0.70, 1.95)</td>
<td>&gt;75th percentile</td>
<td>&lt;25th percentile</td>
<td>30–34 wk GA</td>
<td>—</td>
</tr>
<tr>
<td>Vollset (14)</td>
<td>2000</td>
<td>1727</td>
<td>12,688</td>
<td>1.21 (1.02, 1.43)</td>
<td>&gt;75th vs &lt;25th percentile</td>
<td>&lt;10th percentile</td>
<td>Years AD</td>
<td>Parity, year of birth, maternal age, smoking</td>
</tr>
<tr>
<td>Steegers (25)</td>
<td>2004</td>
<td>144</td>
<td>176</td>
<td>1.90 (1.30, 3.60)</td>
<td>&gt;15 (\mu)mol/L</td>
<td>&lt;10th percentile</td>
<td>6 wk AD</td>
<td>—</td>
</tr>
<tr>
<td>Dodds (32)</td>
<td>2007</td>
<td>129</td>
<td>1707</td>
<td>1.60 (1.00, 2.60)</td>
<td>&gt;90th percentile</td>
<td>&lt;10th percentile</td>
<td>&lt;20 wk GA</td>
<td>—</td>
</tr>
<tr>
<td>Infante-Rivard (24)</td>
<td>2003</td>
<td>483</td>
<td>468</td>
<td>0.55 (0.39, 0.81)</td>
<td>Increase in tHcy</td>
<td>&lt;10th percentile</td>
<td>&lt;48 h AD</td>
<td>Race, time interval</td>
</tr>
<tr>
<td>Murakami (23)</td>
<td>2001</td>
<td>35</td>
<td>714</td>
<td>0.78 (0.10, 5.91)</td>
<td>&gt;97.5 percentile</td>
<td>&lt;10th percentile</td>
<td>6–12 wk GA</td>
<td>—</td>
</tr>
</tbody>
</table>

1 Data from 8 individual studies describing ORs included in our review and meta-analysis are shown. AD, after delivery; BW, birth weight; GA, gestational age; tHcy, total homocysteine.
2 90th percentile.
3 Percentile for GA.
4 Overall population.
5 Sex-specific percentile for GA.
6 Values are means; 95% CIs in parentheses.
7 \(5 \mu\)mol/L.

Pooled analysis showed an overall OR of 1.25 (95% CI: 1.09, 1.44) for being SGA when maternal tHcy concentrations were >90th percentile (Figure 2). After exclusion of the 2 studies that sampled maternal blood months or even years after pregnancy, pooled analysis showed an overall OR of 1.45 (95% CI: 1.14, 1.85) (14, 25).

DISCUSSION

Summary of key findings

Our meta-analysis of 19 eligible studies on maternal tHcy in relation to birth weight showed a 25% increased risk of SGA when maternal tHcy concentrations were >90th percentile. To express this effect size estimate as a linear effect, this OR of 1.25 (95% CI: 1.09, 1.44) can be converted to a regression coefficient (see Supplemental table S3 under “Supplemental data in the online issue”), which implies that for a 1-SD increase in maternal tHcy, birth weight will decrease ~0.062 SD (95% CI: ~0.025, ~0.10 SD). By using an SD for a birth weight of 505 g (on the basis of the data in the literature studied for this review) and for maternal tHcy of 1.9 \(\mu\)mol/L, it can be estimated that a 1.9-\(\mu\)mol/L increase in maternal tHcy would result in a decrease in birth weight of 31 g (95% CI: ~13, ~51 g). We assume that this is of relatively little influence for an individual newborn. However, if maternal tHcy is causally related to SGA offspring and could be modified in a way that fewer newborns would be born SGA, eg, by the use of folic acid, this could be of importance on a population level, because being born SGA is 1 of the 4 main causes of perinatal death in the Netherlands.

Novelty of findings

The discovery of possibly treatable determinants of SGA is clinically relevant not only for newborns but also for the risk of common diseases occurring later in life. Results of studies regarding the association between maternal tHcy and birth weight performed so far have yielded different conclusions. With the use of an innovative statistical technique we were able to convert all of the different effect sizes into ORs, which allowed us to compare and pool the results.

TABLE 3
Study characteristics of the 8 studies on the association between maternal tHcy concentrations and body weight that used regression analysis (of the 19 total studies for analysis)

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Year</th>
<th>n</th>
<th>Effect size</th>
<th>Unit Hcy</th>
<th>Maternal tHcy determination</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malinow (19)</td>
<td>1998</td>
<td>35</td>
<td>(r = -0.36, P = 0.036)</td>
<td>1 (\mu)mol/L</td>
<td>Labor</td>
<td>—</td>
</tr>
<tr>
<td>Infante (24)</td>
<td>2003</td>
<td>483</td>
<td>(\beta = 1.275 (39.8, 215.5))</td>
<td>Hcy (\uparrow) 5 (\mu)mol/L</td>
<td>(&lt;48) h AD</td>
<td>GA, sex, race, time interval</td>
</tr>
<tr>
<td>Hogeveen (35)</td>
<td>2010</td>
<td>366</td>
<td>(\beta = -0.56 (-108, -4.5))</td>
<td>Hcy (\uparrow) 1 SD</td>
<td>30–34 wk GA</td>
<td>Birth weight standardized for GA</td>
</tr>
<tr>
<td>Takimoto (33)</td>
<td>2007</td>
<td>82</td>
<td>(\beta = -151, P &lt; 0.01)</td>
<td>1 (\mu)mol/L</td>
<td>34–36 wk GA</td>
<td>Maternal age, BMI, parity</td>
</tr>
<tr>
<td>Yajnik (28)</td>
<td>2005</td>
<td>80</td>
<td>(\beta = -280.3, P = 0.027)</td>
<td>1 (\mu)mol/L</td>
<td>At delivery</td>
<td>Maternal height, weight, GA, sex</td>
</tr>
<tr>
<td>Murphy (27)</td>
<td>2004</td>
<td>91</td>
<td>(\beta = -0.66 (93.1))</td>
<td>1 (\mu)mol/L</td>
<td>32 wk GA</td>
<td>GA, sex, BMI, smoking, maternal age</td>
</tr>
<tr>
<td>Watanabe (34)</td>
<td>2008</td>
<td>187</td>
<td>(\beta = -10.8, P = 0.86)</td>
<td>1 (\mu)mol/L</td>
<td>32 wk GA</td>
<td>Maternal age, sex, parity</td>
</tr>
<tr>
<td>Pagan (22)</td>
<td>2002</td>
<td>285</td>
<td>(\beta = 7.2, P = 0.679)</td>
<td>1 (\mu)mol/L</td>
<td>30 wk GA</td>
<td>GA, sex, BMI, smoking, race</td>
</tr>
</tbody>
</table>

1 Data from the 8 individual studies that used regression analysis included in our review and meta-analysis are shown. AD, after delivery; GA, gestational age; tHcy, total homocysteine; \(\uparrow\), increase.
Interpretation, strength, and limitations in the context of the totality of evidence

As anticipated, the included studies used different methods for effect size estimation, such as mean differences, calculation of ORs, or regression analysis. Furthermore, they used different definitions of hyperhomocysteinemia and SGA. After conversion of all effect sizes to ORs for maternal tHcy concentrations exceeding the 90th percentile and SGA offspring, we were able to perform a pooled analysis. This conversion of effects estimates is reliable only under the assumption of a linear effect. This was tested in our own study but was not addressed in other studies (35). The rounding of the different effect size estimates published could result in a distortion of the estimates of SD. However, this will introduce random errors. The adjustments for known and strong confounders such as GA (14, 20–32, 35), newborn sex (14, 20, 22, 24–29, 31, 32, 34), parity (14, 33), and smoking (14, 22, 27) were performed in some but not all studies. In studies describing both adjusted and unadjusted effect size estimates, the strength of association decreased after adjustments in 4 studies (25, 28, 35). The association remained the same in the study by Ronnenberg et al (21) and increased in the study by Infante-Rivard et al (24). Some of the well-known determinants of birth weight, such as smoking and GA, have an association with tHcy. In our previous study, the association between maternal tHcy and birth weight disappeared after introducing smoking into the statistical model (35). We are not able to adjust all of the data for the same possible confounders, but the examples mentioned above show that adjustments could attenuate the pooled effect size estimate.

Taken together, there are many sources of uncertainty that imply that the precision of the pooled estimated effect size might be less than reflected by the CIs.

tHcy concentrations are influenced by B vitamin status, especially by folate and hence by folic acid supplementation or fortification. In only one of the countries in which the studies were performed folic acid fortification had been introduced very recently (1998 in Canada) (24). In 8 studies, information on supplementation was described, varying from using a non–folate-deficient study population on the basis of serum folate concentrations (28, 33), using a percentage of women with low folate at a certain GA (22), to describing the percentage of women receiving folic acid supplementation (14, 19, 32, 34, 35). Folate status can possibly influence the association between maternal tHcy and SGA: a possible association could differ according to low or high folate status (56, 57). Theoretically, an observed association between tHcy and SGA could be a reflection of an association between folate and SGA. Positive associations between folic acid intake and birth weight and reduced risk of being SGA have been observed by several authors, as summarized by Timmermans et al (58), although no information on tHcy is available. Recent observational studies showed 37–68 g higher birth weight in women who received periconceptional folic acid supplementation (58, 59). This birth weight difference is comparable to the difference in our meta-analysis. Furthermore, folic acid started preconceptionally resulted in a decreased risk of being SGA (OR: 0.40; 95% CI: 0.22, 0.72) in analyses adjusted for maternal age, height and weight, GA, parity, newborn sex,
ethnicity, educational level, and smoking) (58). Several randomized controlled trials and observational studies observed similar associations between folic acid supplementation or maternal folate status and SGA rate (60–64). In contrast, other studies did not observe such an association (35, 59, 65, 66). To summarize, studies on the effect of folic acid or maternal folate status in relation to SGA or offspring’s birth weight yielded different conclusions.

In several studies, the timing of maternal blood sampling varied from preconceptional (21), during pregnancy (20, 22, 23, 26, 27, 30, 32–35), and peripartum (19, 24, 26, 28, 31) to different time intervals after delivery (14, 25). The timing of maternal samples can influence observed maternal tHcy. Maternal tHcy concentrations in pregnancy tend to decrease at first, reach a trough between 20 and 32 wk, and increase again at or shortly after delivery to preconceptional concentrations (27, 67–69).

In this meta-analysis we observed a slight increase in estimated effect size after exclusion of the studies that sampled maternal blood months or even years after delivery. We did not observe an association between effect size and timing of maternal sampling during pregnancy (data not shown).

Conclusions

On the basis of this review and a meta-analysis of 19 eligible studies we conclude that there is only a small increased risk of infants being SGA with increased maternal tHcy concentrations. One may debate whether such a small increase in risk will be of clinical relevance for the individual newborn. However, at the population level, if it were possible to decrease the total number of SGA newborns by lowering maternal tHcy, decreased perinatal death rate and improved general population health could result.

The authors’ responsibilities were as follows—MH, MdH, and HJB: designed the research (project conception, development of overall research plan, and study oversight); MH and MdH: conducted the research (hands-on conduct of the experiments and data collection); MdH: analyzed the data and performed statistical analysis; MH: wrote the manuscript and had primary responsibility for final content; and HJB and MdH: critically revised the manuscript. All authors read and approved the manuscript. There were no conflicts of interest.

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