Is birth weight a risk factor for ischemic heart disease in later life?1−3

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ABSTRACT

Background: An inverse association between birth weight and ischemic heart disease (IHD) has been seen in observational studies.

Objective: We wanted to determine the strength and consistency of the association between birth weight and subsequent IHD.

Design: We conducted a systematic review of observational studies.

Results: Seventeen published studies of birth weight and subsequent IHD were identified that included a total of 144 794 singletons. Relative risk estimates for the association between birth weight and IHD were available from 16 of these studies. Additional data from 2 unpublished studies of 3801 persons were also included. In total, the analyses included data from 18 studies on 4210 nonfatal and 3308 fatal IHD events in 147 009 persons. The mean weighted estimate for the association between birth weight and the combined outcome of nonfatal and fatal IHD was 0.84 (95% CI: 0.81, 0.88) per kilogram of birth weight (P < 0.0001). No significant heterogeneity was observed between estimates in different studies (P = 0.09), nor was there evidence of publication bias (P = 0.3, Begg test). Neither restricting the analysis to fatal IHD events nor adjusting for socio-economic status had any appreciable effect on the findings.

Conclusions: These findings are consistent with a 1 kg higher birth weight being associated with a 10–20% lower risk of subsequent IHD. However, even if causal, interventions to increase birth weight are unlikely to reduce the incidence of IHD materially. Further studies are needed to determine whether the observed association reflects a stronger underlying association with a related exposure or is due (at least in part) to residual confounding.

KEY WORDS Birth weight, ischemic heart disease, follow-up studies

INTRODUCTION

The “fetal origins” hypothesis of adult disease postulates that fetal undernutrition is associated with an increased susceptibility to the development of ischemic heart disease (IHD) and allied disorders in later life (1). It was suggested that low birth weight might explain a significant proportion of IHD mortality (2) and, furthermore, that strategies to increase early fetal growth could substantially reduce the number of subsequent deaths from IHD (3). Some published studies have suggested that a 1 kg higher birth weight is associated with about one-quarter lower risk of IHD, independent from the effects of confounding (particularly by social factors operating throughout the life course) (4). Recently, the World Health Organization described low birth weight as a newly emerging risk factor for cardiovascular disease (5).

Coinciding with the discovery of study populations with more detailed birth records, other measures of size at birth [such as ponderal index (in kg/m3), birth length, and head circumference] were postulated to be better predictors of IHD risk than birth weight (6, 7). Individual published studies of the relation between size at birth and subsequent IHD have often had limited statistical power to assess an association reliably and explored the impact of confounding to differing degrees. Moreover, the extent of publication bias in reports on these associations has not been formally examined. Hence, there is a need for a systematic review of the evidence that relates birth size and IHD. A similar approach was used to examine associations reported between impaired fetal growth and a range of intermediary cardiovascular outcomes, including elevated blood pressure (8) and elevated blood total cholesterol (9, 10), which are considered to be among the possible mechanisms by which the intrauterine environment might “program” subsequent IHD risk (3, 11). Reviews of such associations among birth weight, blood pressure, and blood lipids indicate that their strength may have been overestimated as a result of publication bias and unduly selective emphasis on particular results (8, 9). The present systematic review of the association between size at birth and IHD incidence aims to determine the likely relevance of impaired fetal growth for the subsequent development of cardiovascular disease.

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SUBJECTS AND METHODS

We followed a modified version of the MOOSE guidelines for the conduct of meta-analyses of observational studies (12). These guidelines provide a standard protocol for the search and identification of eligible studies (both published and unpublished), data extraction, data analysis, and assessment of between-study heterogeneity. Studies published between 1966 and October 2005 were identified through EMBASE and MEDLINE with the use of a search strategy that combined text word and MESH heading of birth weight (birth weight, intrauterine growth retardation, fetal growth retardation) and of IHD (coronary heart disease, ischemic heart disease, cardiovascular disease). References in reports of identified studies were also scanned to identify any other relevant studies. Investigators of disease. References in reports of identified studies were also scanned to identify any other relevant studies. Investigators of large studies in adults (n > 500 persons) that were previously included in published reviews of the associations of size at birth with blood pressure (8) and with blood cholesterol (9) were invited to contribute data to the present study. However, inclusion of such data can introduce bias because those studies might be an unrepresentative sample of all unpublished studies; hence, sensitivity analyses were conducted both before and after excluding data from any unpublished studies. Studies were excluded if the population consisted entirely of abnormal subgroups (such as very low birth weight infants or preterm infants). Studies were included if they had reported quantitative or qualitative estimates of the association between IHD outcomes and some measure of size at birth (eg, weight, length, head circumference). IHD mortality was defined as death attributed to codes 410 to 414.9 from the International Classification of Disease version 9. Nonfatal IHD events were defined as any of the following: nonfatal myocardial infarction (MI; classified as nonfatal if the patient was alive 28 days after the event occurred), coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), hospitalization because of unstable angina pectoris, or angina pectoris according to the Rose (World Health Organization) questionnaire. Because low birth weight was reported to be inversely associated with the risks of both fatal and nonfatal cardiovascular disease, the analyses were based chiefly on the combined outcome of fatal and nonfatal IHD to maximize the statistical power. Analyses were conducted separately for singletons and for twins because of reports of differential effects of their fetal growth on risks of subsequent disease (13, 14).

The principal investigators of all identified studies were asked to provide Cox proportional hazard ratios (HRs) or, when this was not possible, logistic odds ratios (and SEs) for the association of birth weight with IHD incidence (fatal and nonfatal), IHD mortality, or IHD prevalence, adjusted for age and sex. In the analyses, we used estimates for incidence when available, but otherwise we used the estimates for mortality or, when not available, for prevalence. Additional information on the effect of adjustment for some measure of socioeconomic position was also sought. When information on the same cohort was published more than once, data involving the longest period of follow-up were used. Some studies had reported results adjusted for current body size (ie, at the time of the IHD event), which may have an impact on the associations of birth weight with IHD (15, 16), so analyses were sought with and without adjustment for body mass index (BMI; in kg/m²). Investigators were also asked to repeat the analyses with the use of ponderal index at birth as the exposure variable when this was available. In addition, because it was reported that the association between birth weight and IHD becomes positive at higher birth weights (perhaps because women who develop gestational diabetes are more likely to give birth to macrosomic infants who are at increased risk of developing diabetest in later life) (17), investigators were asked to repeat the analyses after exclusion of persons weighing ≥4 kg at birth (normal birth weights are in the range of 3–4 kg).

The contribution of each of the studies was “weighted” according to an estimate of its “statistical size” derived from the inverse of the variance of the regression coefficient (ie, regression coefficients with smaller variances, which typically involved larger numbers of people, were given greater weight). These weighted regression coefficients were combined by means of a fixed-effects approach, which reflects only the random error within each study and does not make assumptions about the representativeness of the available studies (18, 19). HRs were predominantly used in the analysis. Odds ratios and risk ratios were used when HRs were not available and were considered appropriate because the incidence of IHD was <10–15% in most of the populations studied. Analyses were performed with the use of SPSS 10 (SPSS Inc, Chicago, IL) and STATA (Stata Corporation, College Station, TX). Publication bias was assessed with the use of the Begg and the Egger tests. The Begg test uses an adjusted rank correlation method to examine the association between the effect estimates and their variances (20), whereas the Egger test uses a linear regression approach, in which the standard normal deviate is regressed against precision. This latter method is equivalent to a weighted regression of treatment effect on its SE (with weights inversely proportional to the variance of the effect size) (21). The greater the value of the intercept, the greater the evidence for “small study effects” (ie, a greater likelihood for smaller studies to show larger sizes of effect) (22).

RESULTS

Availability of data

Sixteen published reports on 17 studies involving 7518 cases of nonfatal and fatal IHD in 144 794 persons had previously commented on the association of birth weight in singleton births with IHD in later life (Table 1) (4, 6, 7, 23–35). Additional data for the present analyses were provided by the investigators from 13 of these studies. For 3 of the remaining 4 published studies, it was possible to use published relative risks (4, 35); for the fourth study, involving ≈300 cardiovascular events in 1500 men, no quantitative estimate was available so the study had to be excluded (6). Unpublished data were also available from 2 studies with information on 387 IHD events in 3801 persons (36, 37) (see Acknowledgments). In total, therefore, these combined analyses included data from 18 studies on 4:210 nonfatal and 3308 fatal IHD events in 147 009 persons. Only 1 study of birth weight and IHD among twin pairs was identified, which involved a nested case-control study of acute MI among 132 twins (38). All but 1 of these studies were from higher-income countries, namely mainland Europe (11 studies), the United Kingdom (7 studies), and the United States (1 study), with the remaining study from India.
<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Year of report</th>
<th>Country</th>
<th>Study size</th>
<th>Data on BW</th>
<th>IHD events</th>
<th>Age range</th>
<th>Published association</th>
<th>Adjustment factors in published report</th>
<th>Unpublished age and sex-adjusted relative risks (95% CI) for meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmond (23)</td>
<td>1993</td>
<td>UK</td>
<td>16 652 M&amp;F</td>
<td>Birth records</td>
<td>941</td>
<td>21–81</td>
<td>M: inverse (P &lt; 0.005) F: inverse (NS)</td>
<td>None</td>
<td>ND 0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Barker (6)</td>
<td>1993</td>
<td>UK</td>
<td>1586 M</td>
<td>Birth records</td>
<td>316*</td>
<td>27–83</td>
<td>Inverse (P = 0.06)</td>
<td>None</td>
<td>ND 0.91 (0.74, 1.10)</td>
</tr>
<tr>
<td>Stein (7)</td>
<td>1996</td>
<td>India</td>
<td>517 M&amp;F</td>
<td>Birth records</td>
<td>52</td>
<td>39–59</td>
<td>No significant association (P = 0.20)</td>
<td>Age 7</td>
<td>ND 0.78 (0.64, 0.94)</td>
</tr>
<tr>
<td>Eriksson (35)</td>
<td>2000</td>
<td>Holland</td>
<td>736 M&amp;F</td>
<td>Birth records</td>
<td>24</td>
<td>50</td>
<td>Inverse (P = 0.13)</td>
<td>Sex</td>
<td>0.37 (0.14, 0.98)</td>
</tr>
<tr>
<td>Eriksson (28)</td>
<td>1999</td>
<td>Finland</td>
<td>3447 F</td>
<td>Birth records</td>
<td>279</td>
<td>38–71</td>
<td>Inverse (P = 0.007)</td>
<td>Gestational age, placental weight</td>
<td>ND 1.00 (0.61, 1.63)</td>
</tr>
<tr>
<td>Lawlor (34)</td>
<td>2004</td>
<td>UK</td>
<td>1394 F</td>
<td>Birth records</td>
<td>199</td>
<td>60–79</td>
<td>I-SD increase in BW OR: 0.84 (0.72–0.97)</td>
<td>Age, maternal survival status, childhood SES</td>
<td>ND 0.80 (0.68, 0.94)</td>
</tr>
<tr>
<td>Eriksson (35)</td>
<td>2004</td>
<td>Sweden</td>
<td>1319 M</td>
<td>Birth records</td>
<td>735</td>
<td>56–85</td>
<td>RR IHD per 1-kg increase BW: 0.91 (95% CI: 0.74, 1.12)</td>
<td>Gestational age</td>
<td>ND 0.92 (0.75, 1.13)</td>
</tr>
<tr>
<td>Lawlor (36)</td>
<td>2005</td>
<td>UK</td>
<td>10 803 M&amp;F</td>
<td>Birth records</td>
<td>296</td>
<td>11–49</td>
<td>HR 1-kg increase in BW: 0.62 (95% CI: 0.50, 0.78)</td>
<td>Age, gestational age, childhood: SES, BMI, and height: maternal: hypertension, age, and parity</td>
<td>NA</td>
</tr>
<tr>
<td>Martin (37)</td>
<td>Unpub</td>
<td>UK</td>
<td>639 M&amp;F</td>
<td>Self-report</td>
<td>25</td>
<td>71</td>
<td>Unpublished</td>
<td>Unpublished</td>
<td>ND 0.65 (0.30, 1.39)</td>
</tr>
<tr>
<td>Wadsworth (38)</td>
<td>Unpub</td>
<td>UK</td>
<td>3157 M&amp;F</td>
<td>Self-report</td>
<td>362</td>
<td>53</td>
<td>Unpublished</td>
<td>Unpublished</td>
<td>0.82 (0.65, 1.04)</td>
</tr>
</tbody>
</table>

7 ND, no data on outcome; NA, data not available for current analyses; BW, birth weight; HR, hazard ratio; OR, odds ratio; RR, relative risk; Unpub, unpublished data made available; SES, socioeconomic status; UK, United Kingdom; US, United States.
8 Data on BW is method of data collection for birth weight either through self-report or through birth records.
9 IHD events are combined fatal and nonfatal outcomes.
10 Age range is the age at which the participants were followed, or, in the case of Lawlor et al (34), the age at the time of the cross-sectional survey.
11 Odds ratio; 95% CI in parentheses.
12 Study reported that the inverse association remained after adjustment for age, fibrinogen, cholesterol, systolic blood pressure, BMI, smoking, and parental and current social class and marital status.
13 Study reported that additional adjustment for adult cigarette smoking, parental occupation, breastfeeding, hypertension, hypercholesterolemia, and diabetes made no material difference to the age-adjusted estimate.
Association of birth weight with IHD incidence, mortality, and prevalence

All of the identified studies showed an inverse association between birth weight and IHD. In 8 studies that examined the relation of birth weight with incident IHD (fatal and nonfatal), the overall age- and sex-adjusted relative risk was 0.86 (95% CI: 0.81, 0.91) per 1 kg higher birth weight; in 14 studies that examined the relation with fatal IHD, the adjusted relative risk was 0.84 (95% CI: 0.80, 0.88); and in 6 studies that examined the relation with prevalent IHD, the adjusted relative risk was 0.83 (95% CI: 0.76, 0.91). Combining the results from all available studies, the overall age- and sex-adjusted relative risk of IHD was 0.84 (95% CI: 0.81, 0.88) per 1 kg higher birth weight (P < 0.0001), which was unaltered after exclusion of data from 2 unpublished studies (HR: 0.84; 95% CI: 0.81, 0.88). The observed results in these 18 individual studies were not statistically significant from each other (heterogeneity; P = 0.09; Figure 1). Pooled estimates by tertiles of SE size did not indicate publication bias (data not presented), and the Begg and the Egger tests for sensitivity for detecting small study effects, particularly in relatively small meta-analyses, the potential for publication bias remains (39). In the 8 studies that were able to adjust for BMI, the weighted estimate remained largely unaltered: 0.86 (95% CI: 0.80, 0.92) unadjusted compared with 0.83 (95% CI: 0.77, 0.89) adjusted. After exclusion of persons who weighed >4 kg at birth from 11 studies, the age- and sex-adjusted relative risk was slightly strengthened from 0.87 (95% CI: 0.82, 0.91) to 0.84 (95% CI: 0.79, 0.90) and was little altered by adjustment for BMI (0.81; 95% CI: 0.76, 0.87).

Impact of adjustment for potential confounders

In the published reports, the level of adjustment for potential confounders of the association between birth weight and IHD varied substantially across the studies (Table 1). Socioeconomic position is inversely related to birth weight, is positively associated with cardiovascular risk factors (such as smoking, physical activity, and diet) and so may confound associations of birth weight with IHD (40, 41). In the current analyses, associations in 15 of the studies with information on 116 994 persons (81% of information from all studies) could be adjusted for some measure of social class, either at birth or in adult life. Such adjustment did not alter the overall age- and sex-adjusted association between birth weight and subsequent IHD among these studies: 0.85 (95% CI: 0.81, 0.90) unadjusted compared with 0.85 (95% CI: 0.81, 0.90) adjusted.

Because twins experience similar environments in childhood and adolescence, studies within twin pairs may be less prone to confounding than are studies that involve singleton births (42). Only one study among 132 twin pairs was published on the association with IHD risk, and it reported that a 1 kg higher birth weight was associated with an odds ratio for acute MI of 0.61 (95% CI: 0.37, 1.00) when twinship was not taken into consideration. However, when twinship was taken into consideration, no difference was observed in mean birth weight between the twin who had experienced MI and the twin who had not (2548 and 2534 g, respectively; P = 0.73). Significant associations...
were not observed with other measures of fetal development: birth length ($P = 0.91$), ponderal index ($P = 0.32$), or head circumference ($P = 0.92$) (38).

**Associations among other indexes of size at birth with later IHD**

It has been suggested that, compared with birth weight, other measures of size at birth (e.g., ponderal index, birth length, or head circumference) may reflect distinct temporal patterns of fetal undernutrition that are more predictive of future IHD risk (27, 43). Seven of the 18 studies, involving 32,114 persons (22% of total studied), provided information on the association between ponderal index and IHD risk. An increase of the ponderal index by a value of 5 (equivalent to a 2 SD difference, analogous to 1 kg higher birth weight) was associated with an overall age- and sex-adjusted relative risk for IHD of 0.90 (95% CI: 0.82, 1.00); this estimate was not materially altered by adjustment for BMI or socioeconomic position (data not shown).

**Sex differences in the relations of size at birth to subsequent IHD risk**

Some studies had reported that sex differences may exist in the associations between body size at birth and the risk of subsequent IHD. For example, a low ponderal index at birth (perhaps reflecting fetal undernutrition during the third trimester) was associated with higher IHD risk for men but not for women (27, 31). Conversely, a short birth length (which was suggested might reflect fetal undernutrition in early gestation) was associated with higher IHD risk for women but not for men (27). As a consequence, it was hypothesized that lower rates of IHD in adult life among women may originate in their different rates of growth in utero (4). Comparison of the weighted estimates from the 11 single-sex studies did not, however, indicate any significant sex difference between the relative risks for IHD associated with birth weight in men (0.85; 95% CI: 0.79, 0.91) than in women (0.84; 95% CI: 0.78, 0.90). In the 3 studies of men with information on ponderal index, a weak inverse association between ponderal index and IHD (0.95; 95% CI: 0.93, 0.97) was observed, whereas in the 2 studies of women with such information no evidence of an association (1.02; 95% CI: 0.98, 1.06) was observed.

**DISCUSSION**

The findings from this systematic overview, including data on >7500 IHD events among 147,000 persons, indicate that there is an inverse association between size at birth and the subsequent development of IHD, with a 10–20% lower risk observed per 1 kg higher birth weight. No evidence suggested that the association between birth weight and IHD differed between men and women; no evidence suggested that ponderal index, which may reflect different patterns of fetal growth (44), was more strongly associated with IHD risk in later life.

It was previously suggested that the inverse association of size at birth with subsequent IHD risk may partly reflect confounding by socioeconomic position (45, 46). In the current review, adjustment for some measure of social class (either current or at the time of birth) had little impact on the strength of the association between birth weight and subsequent IHD risk. However, residual confounding remains possible because such measures may not fully capture all aspects of socioeconomic status and other relevant factors, including adult cigarette smoking, diet, and physical activity (47). Moreover, information on other potentially important early life confounders, such as maternal smoking and maternal hypertension [which are both associated with low birth weight and were shown to predict smoking (48), higher blood pressure (49, 50), and obesity in offspring (51)] were not routinely collected in the original reports. It remains uncertain, therefore, what role (if any) such factors might have in the generation of an association between size at birth and subsequent IHD. Because twins share similar early life environments, the impact of confounding on the results from studies between twin pairs is likely to be less than in studies of singletons. In the one small twin study that reported on the association between size at birth and subsequent IHD, no apparent association was observed of birth weight with MI when within-twin comparisons were made (although that study was too small to rule out 10–20% differences in IHD risk per kilogram of birth weight) (38). Furthermore, despite twins being an average of nearly 1 kg lighter than singletons at birth (52), large registries have not found twins to be at higher risk than singletons of death from IHD or other causes (14, 53) [although an explanation proposed for this observation is that twins might experience a different form of growth retardation from singletons (14)].

Previously, it was suggested that blood pressure, blood cholesterol, and other known causal risk factors might be links by which intrauterine environment programs later IHD risk (1). In such circumstances, associations of the putative risk factor (e.g., birth weight) with the values of such causal intermediates (e.g., blood pressure or cholesterol) might be expected to translate into somewhat weaker associations of the risk factor with IHD risk. As recent reviews have shown, however, no strong associations were observed between birth weight and either blood pressure or blood total cholesterol concentration (8–10). Even so, associations with other important cardiovascular intermediates (such as type 2 diabetes) and the possibility that an association between birth weight and subsequent IHD risk might operate through other, as yet unknown, mechanisms cannot be precluded. Alternatively, birth weight may be acting as a surrogate marker of a stronger in utero exposure or genetic trait (54), which influences lifetime risk. If true, then the current estimate of a 10–20% lower risk of IHD per kilogram higher birth weight would be lower than the underlying relation between any true causal factor and the risk of IHD. It is also possible that the association between birth weight and subsequent IHD is particularly strong in subgroups of the population with unfavorable profiles of adult risk factors [e.g., it was suggested that low birth weight may interact with later obesity in its effects on IHD risk (55)]. A further limitation of this current review is the lack of information on gestational age in most of the studies; thus, we were unable to differentiate between low birth weight caused by undernutrition and that caused by prematurity. Moreover, because these data are almost entirely derived from high-income study populations, it is not possible to generalize these findings to those from lower- and middle-income countries that are more likely to experience nutritional mismatch between the pre- and postnatal environments (56). An overview of individual participant data would permit more detailed examination of interactions between birth weight and other exposures in later life. It would also allow the opportunity to examine more fully the impact of confounding throughout the life course (e.g., in infancy, adolescence, adulthood) on the association between size at birth and subsequent IHD and potentially...
provide insight into prenatal exposures that may be more relevant to future health outcomes than birth weight per se.

Despite 2 decades of research, it remains unclear which exposures in early life (if any) might underlie the reported links between fetal growth and later IHD. Maternal undernutrition has been implicated (1, 54), but evidence from studies of exposure to famine (which is less likely to be affected by socioeconomic confounding) does not provide compelling support for suboptimal maternal and fetal nutrition being associated with increased cardiovascular risk in adult life. For example, studies of adults conceived or born during the Dutch hunger winter did not find that maternal undernutrition in mid-late gestation was associated with increased incidence of heart disease (28). Similarly, a follow-up study of adults conceived or born during the Leningrad Siege study found no evidence of excess mortality from heart disease (57). By contrast, exposure to starvation during puberty was recently reported from the Leningrad Siege study to be associated with increased risk of IHD (58). In another study of birth cohorts born during a severe famine in Finland, famine exposure throughout fetal life and early childhood was not associated with increased all-cause mortality in adulthood, and the investigators concluded that “it seems unlikely that nourishment before birth and during infancy per se is crucial to adult health” (59). Increased fetal glucocorticoid exposure was also suggested to mediate the epidemiologic association between low birth weight and subsequent cardiovascular disease, possibly by altering hormonal axes that influence growth and development (54). However, 2 randomized controlled trials found no evidence of any differences in levels of cardiovascular risk factor among adult offspring exposed to antenatal glucocorticoid treatments compared with those who were not (60, 61).

It was suggested that low birth weight is an important risk factor for cardiovascular disease, particularly in lower- and middle-income countries (5). Even if 1 kg higher birth weight really is causally associated with 10–20% lower relative risk of IHD, then the direct relevance to public health would still be rather small (although the biological implications would not necessarily be small) (62). For assuming that nutritional interventions in pregnancy could increase birth weight by as much as 100 g (with comparable changes in any other relevant size-related factors), which is the most that can be achieved through current nutritional interventions (63), then this association might be small) (62). For assuming that nutritional interventions in pregnancy could increase birth weight by as much as 100 g (with comparable changes in any other relevant size-related factors), which is the most that can be achieved through current nutritional interventions (63), then this association might underlie the reported links between low birth weight and subsequent cardiovascular disease—possibly by altering hormonal axes that influence growth and development (54). However, 2 randomized controlled trials found no evidence of any differences in levels of cardiovascular risk factor among adult offspring exposed to antenatal glucocorticoid treatments compared with those who were not (60, 61).

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The authors’ responsibilities were as follows—RH had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors contributed to interpreting these analyses and drafting the manuscript. None of the authors had a conflict of interest in relation to this study.

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