

Global inequities in dietary calcium intake during pregnancy: a systematic review and meta-analysis

G Cormick,^{a,b} AP Betrán,^c IB Romero,^d CF Lombardo,^d AM Gülmezoglu,^c A Ciapponi,^a JM Belizán^a

^a Department of Mother and Child Health Research, Institute for Clinical Effectiveness and Health Policy (IECS-CONICET), Buenos Aires, Argentina ^b Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa ^c Department of Reproductive Health and Research, World Health Organization, HRP – UNDP, UNFPA, UNICEF, WHO, World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Geneva, Switzerland ^d Departamento de Salud, Universidad Nacional de la Matanza, San Justo, Argentina

Correspondence: G Cormick, Institute for Clinical Effectiveness and Health Policy (IECS), Emilio Ravignani 2024, Buenos Aires, Argentina. Email: gabmick@yahoo.co.uk

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Background Evidence shows that adequate calcium intake during pregnancy reduces the risk of hypertensive disorders of pregnancy. In most low- and middle-income countries (LMICs) the daily calcium intake is well below recommendations. Mapping calcium intake during pregnancy worldwide and identifying populations with low calcium intake will provide the evidence base for more targeted actions to improve calcium intake.

Objective To assess dietary calcium intake during pregnancy worldwide.

Search strategy MEDLINE and EMBASE (from July 2004 to November 2017).

Selection criteria Cross-sectional, cohort, and intervention studies reporting calcium intake during pregnancy.

Data collection and analysis Five reviewers working in pairs independently performed screening, extraction, and quality assessment. We reported summary measures of calcium intake and calculated the weighted arithmetic mean for high-income countries (HICs) and LMICs independently, and for geographic regions, among studies reporting country of recruitment, mean intake, and total number of participants. When available, inadequate intakes were reported.

Main results From 1880 citations 105 works met the inclusion criteria, providing data for 73 958 women in 37 countries. The mean calcium intake was 948.3 mg/day (95% CI 872.1–1024.4 mg/day) for HICs and 647.6 mg/day (95% CI 568.7–726.5 mg/day) for LMICs. Calcium intakes below 800 mg/day were reported in five (29%) countries from HICs and in 14 (82%) countries from LMICs.

Conclusion These results are consistent with a lack of improvement in calcium dietary intake during pregnancy and confirm the gap between HICs and LMICs, with alarmingly low intakes recorded for pregnant women in LMICs. From the public health perspective, in the absence of specific local data, calcium supplementation of pregnant women in these countries should be universal.

Keywords Calcium, dietary, high-income countries, hypertension, low- and middle-income countries, pre-eclampsia, pregnancy, systematic review.

Tweetable abstract Despite dietary recommendations, women in LMICs face pregnancy with diets low in calcium.

Linked article This article is commented on by GJ Hofmeyr, p. 457 in this issue. To view this mini commentary visit <https://doi.org/10.1111/1471-0528.15543>.

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Introduction

Hypertensive disorders of pregnancy cause around 46 000 maternal deaths and 1.5–2.0 million neonatal deaths annually.¹ Over 99% of these deaths occur in less developed countries.¹

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Although maternal mortality has decreased overall, the percentage of maternal deaths resulting from hypertension has remained stagnant, with 9.71% (36 497 deaths) in 1990 and 9.99% (29 275 deaths) in 2013.² Evidence has shown that calcium supplementation during pregnancy prevents the development of hypertensive disorders of pregnancy.³

Calcium is a mineral required for normal physiological functioning. Requirements increase in specific periods of

life, especially during pregnancy.⁴ There is no consensus regarding the recommended intake during pregnancy. Calcium recommendations for individuals over 19 years of age vary from 700 to 1000 mg, depending on the reference guidelines.^{5,6} Although most guidelines acknowledge the increased demand for calcium during pregnancy, some guidelines increase recommendations during pregnancy up to 1300 mg/day to achieve a positive balance, whereas others state that metabolic adaptations during pregnancy compensate for the increased demand for calcium.^{5,7–12}

Previous studies show that in most low- and middle-income countries (LMICs) the daily calcium intake is well below recommendations; however, low intakes are also observed in particular age groups, such as adolescents in high-income countries (HICs).^{13–15} Current World Health Organization (WHO) guidelines recommend that in populations where the calcium intake is low, women should receive calcium supplementation after 20 weeks of gestation as part of antenatal care for the prevention of pre-eclampsia, particularly among those at higher risk of developing hypertension.¹⁶ In addition, results from a recent randomised trial suggest that the beneficial effects of calcium supplementation on the reduction of pre-eclampsia/eclampsia in women with low dietary calcium intake is greatest when supplementation is commenced before and continued throughout pregnancy.¹⁷ The mechanism by which calcium may have an effect on blood pressure is not well established; one hypothesis is that low calcium intakes increase the levels of parathyroid hormone and 1,25-dihydroxy vitamin D (DHVD), which are required to maintain specific calcium concentrations in extracellular fluids. Higher levels of parathyroid hormone and DHVD stimulate calcium influx into different cell types and increase intracellular calcium into the vascular smooth muscle cell, and consequently increased muscle reactivity, peripheral vascular resistance, and thus higher blood pressure.^{18,19}

In order to effectively implement the WHO recommendations and reduce the risk of hypertensive disorders of pregnancy in the most vulnerable women, it is essential to identify the specific populations or subpopulations at higher risk. This would allow the evidence-based prioritisation of calcium supplementation, and would inform the development of policies, strategies, and actions, including a population-specific quantity assessment of the additional calcium intake required. A systematic review was conducted and published in 2005 to assess calcium dietary intake in pregnant women globally, including studies published from 1991 to July 2004.¹³ We aimed to update the 2005 review and assess calcium intake during pregnancy worldwide from 2004 onwards. This update will map calcium intake during pregnancy worldwide and identify populations with

low calcium intake, which will provide the evidence base for more targeted actions in order to improve calcium intakes.

Methods

We followed the reporting recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group.^{20,21} The protocol of this review was published in PROSPERO (the international prospective register of systematic reviews).²² This systematic review did not include primary data collection, and there was no patient and public involvement in the development of the protocol for the review.

Criteria for considering studies for this review

The studies included in this review required the following criteria.

Type of study

The studies included were: cross-sectional, cohort or intervention studies reporting calcium intake at any time during pregnancy and using any methodology (e.g. 24-hour recall, food frequency questionnaires, weight records, food records). In the case of clinical trials, we included baseline data or data from the placebo arm. We excluded case reports and case-control studies. We only included studies reporting the country of recruitment.

Type of participants

The participants included pregnant women of any age, ethnic group, parity, education, and socio-economic status. We excluded studies reporting on women with specific conditions (e.g. women with systemic lupus, erythematosus lupus, rheumatoid arthritis, diabetes, bariatric surgery, twin pregnancies, and vegetarian diet); however, we included studies that only reported data for women who were obese or overweight.

Data collection period

We included all studies collecting data after July 2004, which is the date of the most recent data included in the previous systematic review.

Search strategy for the identification of studies

The search strategy was developed with the assistance of a librarian experienced in electronic search strategies for systematic reviews from the Institute of Clinical Effectiveness (IECS), and was tested by a second expert in search strategies from the WHO. We searched MEDLINE (from July 2004 to 7 November 2017) and EMBASE (from July 2004

to 7 November 2017) using a combination of medical subject headings, keyword terms, and word variants for pregnancy and calcium.

This review had no language restrictions. Appendix S1 presents the search strategy developed for this systematic review.

We checked the reference lists of systematic reviews and of primary studies selected for full-text evaluation for additional potentially relevant articles not identified by the electronic search. Authors of relevant papers were contacted regarding any further published or unpublished work. Authors of manuscripts reporting incomplete information were contacted to provide the missing information.

Process of study identification, selection, and data extraction

We used the software package COVIDENCE (Veritas Health Innovation Ltd, Melbourne, Victoria, Australia) for the selection of studies and data extraction. Five reviewers (GC, APB, CFL, IR, and EH) independently and in duplicate screened the titles and abstracts to select potentially relevant citations for full-text evaluation. Discrepancies were resolved through discussion and consensus. When citations were considered relevant or when information in the title or abstract was insufficient for decision on inclusion or exclusion criteria, the full text was retrieved and evaluated.

After full-text evaluation, three reviewers (GC, IR, and CFL) independently extracted data from the included studies using a template created in COVIDENCE. Data extracted from the studies included: study identification information (study title, authors, country, year); study characteristics (study design, data collection period); participants (sample size, study inclusion criteria, age of the women, country or United Nations region, gestational age at assessment); outcome (dietary assessment methodology, food chemical composition table used, daily calcium intake as mean or median in mg/day, percentage of inadequate intake as a percentage, and confidence interval and methodology for assessing inadequate intake).

Risk of bias assessment

Three reviewers (GC, IR, and FL) independently assessed the quality of each included study, discrepancies were discussed, and if consensus was not reached a third reviewer was consulted (AC). We assessed the quality of the data in each included study using an adapted version of the Newcastle–Ottawa Scale (NOS) for non-randomised studies in meta-analyses, Robins (Risk Of Bias in Non-randomized Studies – of Interventions), and the Scottish Intercollegiate Guidelines Network (SIGN).^{23,24} We

evaluated the risk of bias by assessing the eligibility criteria, sample size, representativeness (whether a sampling methodology was used appropriately to produce an estimate representative of the target population or if a convenience sample or special group was selected), response rate, data collection tool, clarity of the questions/statements and definition of the outcome, clarity of the objective, ethical considerations, and consistency between research question and data reported (Appendix S2).²⁵ We present the evaluation results for each question for each included study. The potential risk of bias was characterised as follows: eligibility criteria (low risk, defined eligibility; high risk, not defined); sample size (low risk, 100 subjects or more; high risk, <100 or not explained); data collection tool (low risk, described with references; moderate risk, described without references; high risk, not described); definition of the outcome (low risk, well defined; high risk, improperly defined); clarity of results data (low risk, reported with numerators and denominators; high risk, not clearly reported), and representativeness (low risk, representative; moderate risk, not described or somehow representative; high risk, selected group).²⁶ Study quality was characterised as follows: the clarity of the objective was assessed as clear, not clear, or not described; ethical consideration was defined as reporting committee approval and informed consent (either of these or none); consistency of results and conclusion were scored as yes or no; and the response rate was scored as $\geq 70\%$ or $< 70\%$.

Strategy for analysis and data synthesis

We reported summary measures of calcium intake for each included study. For studies reporting mean intake, standard deviation (SD), and total number of participants we calculated the standard error of the mean (SE). If we found similar values of means and medians reported in some studies we would assume a normal distribution. Following the Cochrane Handbook recommendations, for studies with a sample size of more than 100 and reporting the median and the interquartile, we calculated the adjusted SD by subtracting the interquartile and dividing it by 1.35, the suggested width of one standard deviation.²⁴ We then performed meta-analyses by World Bank Classification of country income, country, United Nations region, and trimester of gestational age using STATS DIRECT.²⁷ We present the random-effects model results of the meta-analysis. Stratum weights were calculated as the inverse of the variance for the mean. The pooled estimate was calculated as a weighted mean (sum of weights for each stratum divided by the sum of the weights). The inconsistency of results across studies was summarised as the I^2 statistic, which is the percentage of variation across studies resulting from heterogeneity rather than chance. We tested group

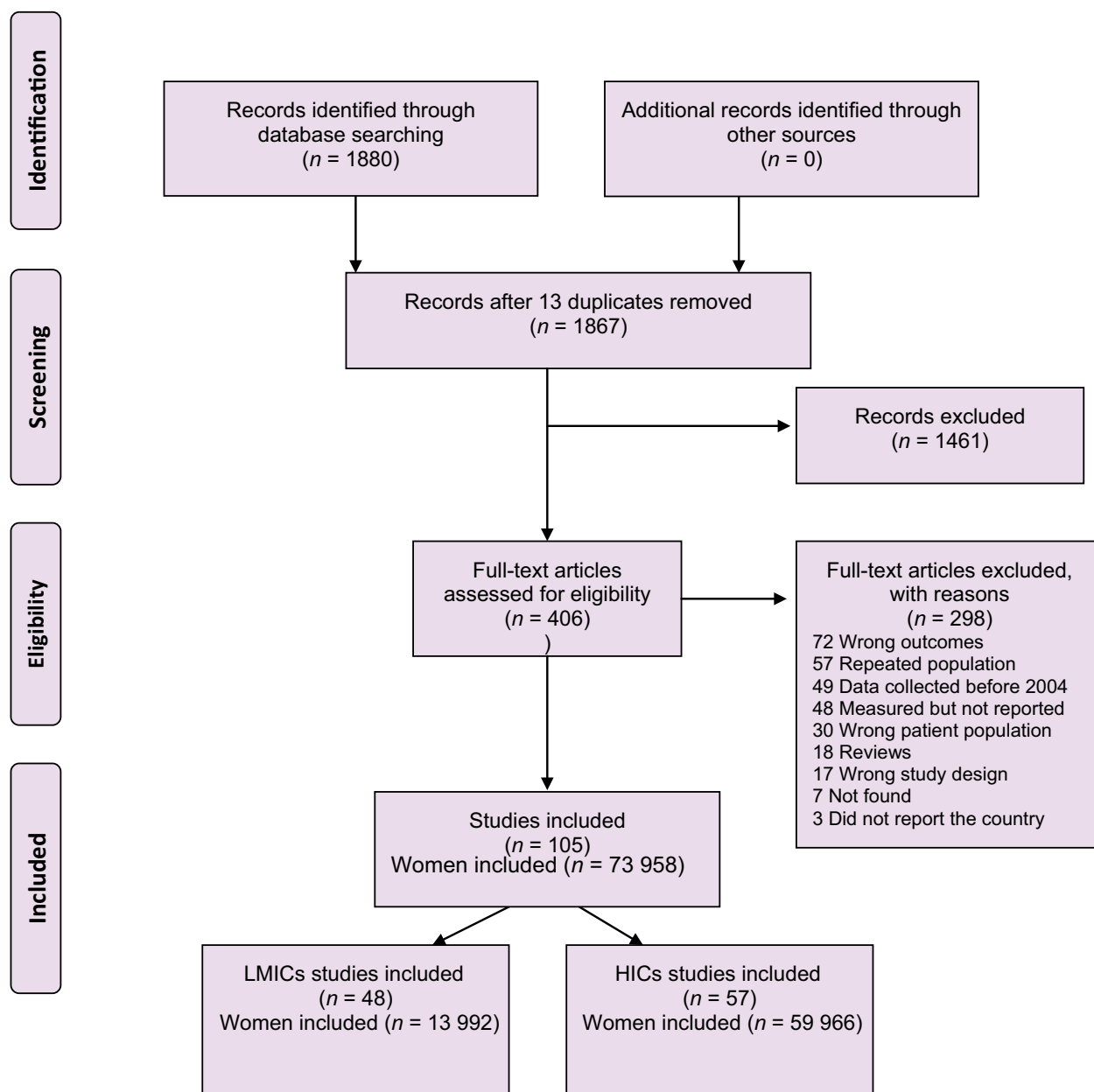


Figure 1. Study selection process for systematic review. PRISMA 2009 flow diagram.

differences between HIC and LMIC using The Cochrane Manager Reviewer (REVMAN 5).²⁸

As recommended by the Institute of Medicine (IOM), we used the Estimated Average Requirement (EAR) of 800 mg of calcium/day as the cut-off point to assess the adequacy of calcium intake in populations.²⁹

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Results

The search strategy retrieved a total of 1880 articles, 1867 of which were screened after excluding 13 duplicates. A total of 406 were selected for full-text evaluation and finally 105 articles were included in the review (Figure 1).^{30–128} The summary of characteristics of the included studies are shown in Table 1.

This review included 73 958 women from 37 countries, of which 19 are HICs (Table S1) and 18 are LMICs (Table S2). Fifty-seven studies were from HICs, although

they represented 81.1% of the women included in the review (59 966). Forty-eight studies were from LMICs representing 18.9% of the women (13 992). Regions were unevenly represented: 47 studies in Western Europe (55 646 women), 37 studies in the Asia Pacific Group (12 638 women), 11 studies in Latin America (3009 women), six studies in Africa (1902 women), and only four studies in Eastern Europe (763 women). Around two-thirds of the studies in LMICs were conducted in four countries: India (10 studies, 2137 women), Iran (seven studies, 1949 women), Brazil (eight studies, 2514 women), and China (seven studies, 2763 women). Half of the studies in high-income countries were conducted in four countries: USA (15 studies, 3795 women), Ireland (six studies, 2522 women), Australia (five studies, 1058 women), and Greece (four studies, 817 women).

We wrote to the corresponding authors of 22 studies; six authors replied. We included five of those six studies, as authors of four studies confirmed the data collection dates,^{34,40,104,129} and one study confirmed the total number of included subjects.⁶⁶ The sixth study was excluded as the data collection date was before 2004.¹⁰⁹

The characteristics informing the risk of bias assessment are summarised in Figure S1 and Table S3. Most studies clearly defined their objective (91, 86.7%) and the eligibility criteria (70, 66.7%), had a sample of at least 100 individuals or a sample size calculation (66, 62.9%), used a data collection tool defined with references to the sources (43, 41.0%), or without references (57, 54.3%), had a well-defined outcome (87, 82.9%), presented the results clearly (77, 73.3%), and demonstrated consistency between the research question and outcome reporting (83, 79.0%). On the other hand, only 33 (31.4%) had a representative sample of the population included in the study. The summary of risk of bias is presented in Figure S2.

Most studies had a cross-sectional (52, 49.5%) or cohort (28, 26.7%) design (Table 1). Sample size ranged from nine to 32 653 pregnant women. The results of some studies were presented by population subgroups, mainly by age of the pregnant women and gestational age (Tables S1 and S2). Sixty-one studies (58.1%) only included adult women, although they represented 82.7% of the women included in this review; 33 (31.4%) studies included both adults and adolescents. Three (2.9%) studies only reported adolescent pregnancies, representing 0.7% of the women in the review (529). Dietary assessment was performed during the third trimester in 24 studies (22.9%) or at any trimester in 31 studies (29.5%). The methodology most frequently used was 24-hour recall in 41 (39.0%) studies and food frequency questionnaire (FFQ) in 31 (29.5%) studies (Table 1). Although 31 (29.5%) studies reported the percentage of inadequate intakes, only 22 (20.9%) reported the cut-off

Table 1. General characteristics of the 105 included studies with 73 958 women

Study characteristic	Number of studies	%	Number of women	%
Country income level				
High income	57	54.3	59 966	81.1
Upper middle income	27	25.7	8582	11.6
Lower middle income	19	18.1	4851	6.6
Low income	2	1.9	559	0.8
Country region				
Western Europe and others	47	44.8	55 646	75.2
Asia Pacific	37	35.2	12 638	17.1
Latin America and Caribbean	11	10.5	3009	4.1
Africa	6	5.7	1902	2.6
Eastern Europe	4	3.8	763	1.0
Study design				
Cross-sectional	52	49.5	16 540	22.4
Cohort	28	26.7	53 014	71.7
Randomised controlled trial	14	13.3	2936	4.0
Quasi-experimental	3	2.9	300	0.4
Case-control	1	1.0	40	0.1
N/A	7	6.7	1128	1.5
Population				
Adult women only	61	58.1	61 161	82.7
Adolescents only	3	2.9	529	0.7
Adults and adolescents	33	31.4	10 932	14.8
N/A	8	7.6	1336	1.8
Sample size				
<100	39	37.1	1951	2.6
100-1000	56	53.3	18 222	24.6
>1000	10	9.5	53 785	72.7
Time of dietary assessment				
Trimester 1	15	14.3	4608	6.2
Trimester 2	13	12.4	44 909	60.7
Trimester 3	24	22.9	8239	11.1
All	31	29.5	11 467	15.5
Each trimester reported	7	6.7	1796	2.4
N/A	15	14.3	2939	4.0
Data collection methodology				
24-h recall	41	39.0	20 427	27.6
FFQ	31	29.5	44 861	60.7
Food records	16	15.2	3300	4.5
Diet history	4	3.8	2990	4.0
Other	7	6.7	1616	2.2
N/A	6	5.7	764	1.0

point used, which are different, thus making it difficult to compare studies. Only three studies fully reported the methodology used to obtain the inadequate intake values.^{21,51,63}

Included in the meta-analysis were 91 studies that reported mean intakes with standard deviation, standard

error, or confidence interval, or median values with confidence intervals. Figures 2 and 3 show the mean calcium intakes and approximate 95% CIs for each of the 91 studies included in the meta-analyses: 50 studies with 58 subgroups for HICs and 41 studies with 44 subgroups for LMICs, respectively. The mean calcium intake was 948.3 mg/day (95% CI 872.1–1024.4 mg/day) for HICs and 647.6 mg/day (95% CI 568.7–726.5 mg/day) for LMICs. There was a statistically significant difference between LMICs and HICs ($P < 0.00001$), $I^2 = 96.4\%$. The meta-analysis by UN regions showed 621.7 mg/day (95% CI 400.4–843.0 mg/day) for Latin America (ten studies), 566.0 mg/day (95% CI 408.1–723.9 mg/day) for Africa (five studies), 652.7 mg/day (95% CI 583.8–721.6 mg/day) for Asia Pacific (32 studies), and 988.5 mg/day (95% CI 920.8–10756.1 mg/day) for Western Europe and others group (43 studies); only one study reported on the calcium intake for Eastern Europe, with 1235 mg/day (95% CI 1102.0–1367.9 mg/day; Figure S3).

Figure S4 shows the mean and 95% CI calcium intake for each trimester in LMICs and HICs separately. The first trimester showed a mean calcium intake of 656.9 mg/day (95% CI 578.9–735.0 mg/day) in LMICs (eight countries) and 923.0 mg/day (95% CI 734.4–1111.7 mg/day) in HICs (11 countries); the second trimester showed a mean calcium intake of 565.9 mg/day (95% CI 358.9–772.9 mg/day) in LMICs (four countries) and 928.9 mg/day (95% CI 871.4–986.5 mg/day) in HICs (13 countries); and the third trimester showed a mean calcium intake of 826.6 mg/day (95% CI 739.8–913.4 mg/day) in LMICs (15 countries) and 931.5 mg/day (95% CI 756.2–1106.8 mg/day) in HICs (12 countries).

Tables S1 and S2 show daily calcium intakes of each included study for HICs and LMICs, respectively. Calcium intake in HICs ranged from 283 to 2228 mg/day, whereas in LMICs the intake ranged from 210 to 1631 mg/day. Within the HICs there were two studies with extreme values compared with the other studies in that region. Mannion et al. interviewed 264 women who agreed to participate out of 1000 who were attending a prenatal course in Alberta, Canada.⁹⁶ They calculated calcium intake using an FFQ via telephone and included the use of calcium supplements and antacids with calcium. They acknowledge the difficulty of the methodology used to estimate antacid intake and state that a 500-mg/day dose was used when information was missing. Karras et al. report very low calcium intake in northern Greece; however, the data are published in abstract format and do not provide details of the sample nor methodology used.⁷⁸

Considering an estimated average requirement of 800 mg/day, which is the suggested value to estimate the prevalence of nutrient inadequacy at a population level, five (27.8%)

countries from HICs report calcium intakes below this value at least in one subgroup, whereas from LMICs 15 (88.2%) countries reported calcium intakes below this value (Figure S5).^{29,130}

Table S4 shows the 39 subgroups of 30 studies (12 HICs and 18 LMICs) that reported percentages of inadequate intakes and the cut-off point used. The proportion of the population below the estimated average intake ranged from above 90% in Israel, Ethiopia, Kenya, and Indonesia, to below 10% in Greece and Canada.

Discussion

Main findings

This systematic review shows that about 27.8% (five out of 18) of the countries from HICs have a calcium intake below the 800-mg/day recommended for this during pregnancy, whereas in LMICs the vast majority are below these values (88.2% of included countries from LMICs). The differences in mean calcium intake between LMICs and HICs is around 300 mg/day, and this difference remains throughout all trimesters of pregnancy, although they lessen in the third trimester.

Our results corroborate the results of the previous review, which included studies from 1991 to 2004, where calcium intake was below 600 mg/day in LMICs and above 1000 mg/day in HICs.¹³ The data gathered in our review is consistent with a lack of improvement in the dietary intake of calcium in pregnant women, and confirms the gap between higher and lower income countries.

Strengths and limitations

The strengths of this review include the broad search strategy to capture the largest number of publications with data from July 2004 and the great number of articles included (a two-fold increase in the number of articles included compared with the previous review), showing the growing scientific and epidemiological interest in this issue. We tried to reduce bias by screening and extracting the information in duplicate using a data-extraction form specifically designed for this review.

Our review has several limitations. None of the studies were nationally representative and thus the dietary intake estimates reported cannot be extrapolated to the entire country. About two-thirds of the studies were not representative of their included population, even if not nationally representative, or their assessment about the representativeness was uncertain. In addition, the variability in the methodology used to collect the data on micronutrient intake limits the comparability. We found very few studies reporting inadequate intakes, with also diverse methodologies and cut-off points. Data were available only from a limited number of countries (18 HICs and 19 LMICs), and

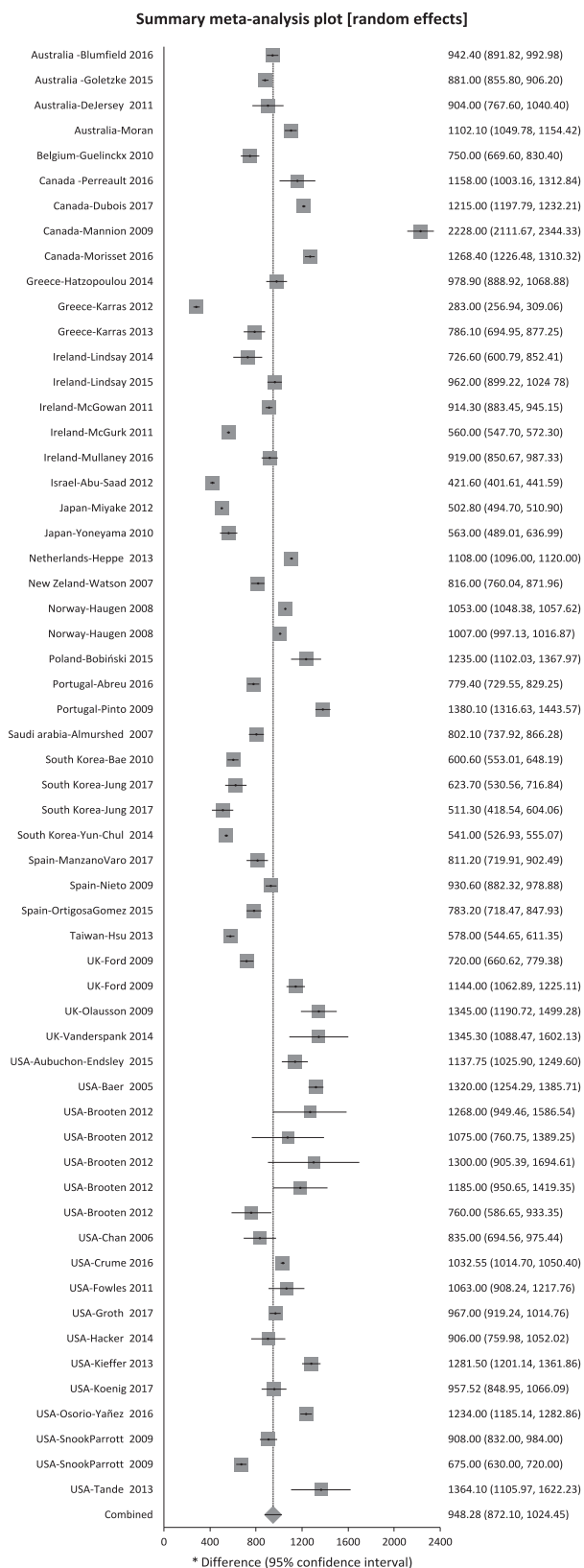


Figure 2. Mean calcium intake and approximate 95% CIs in studies from high-income countries.

information and estimates from the most deprived populations and from many LICs is lacking.

Interpretation

Taking in consideration that LMICs have a mean intake of around 600 mg, an increase in the population mean intake of around 400–500 mg/day of calcium intake may help to attain values close to current calcium intake recommendations for pregnancy. We observed considerable variability, however, and thus setting-specific in-depth analysis and action is warranted.

The attainment of calcium recommendations before and during pregnancy would involve a substantial reduction in the incidence of pregnancy hypertension, as pre-eclampsia is one of the three major causes of maternal mortality globally.^{1,132}

Strategies to increase calcium intake at the population level in populations with low calcium intake would be of relevance. This is in line with the observation that originated the hypothesis about the relationship between calcium intake and pregnancy hypertension, such as the association of population calcium intake and prevalence of pre-eclampsia/eclampsia.¹³¹

There are three broad approaches to improve dietary intake: one is behavioral interventions that, although ideal, rely on personal habits and ability; the second is supplementation that targets individuals; and the third is fortification, which aims to improve the dietary intake of the whole population.¹³²

Recommendations to improve dietary calcium by increasing the consumption of calcium-rich foods and taking calcium supplements have been around for many years; however, data from this systematic review show a current low intake and almost no change from the previous similar review in LMICs.⁶ Supplementation strategies are difficult to achieve in LMICs as women in these countries do not always attend antenatal care early in pregnancy.¹³³ Additionally, depending on the dose, complete adherence to supplementation is difficult to achieve, even if women come for Antenatal care, because of the texture of the calcium tablets or some minor side effects. Logistic and cost are also barriers in some low-resource settings.

There are several successful food fortification strategies that have been used in both HICs and LMICs, such as fortification with iron, iodine, vitamin A, vitamin B complex, folic acid, zinc, vitamin D, and vitamin B12. These have contributed to improvements in health and the lowering of the incidence of goiter, beriberi, pellagra, anaemia, and neural tube defects.^{134–136} In order to carefully develop this strategy and decide the vehicle to fortify, and the amount of calcium required, however, more detailed information is needed regarding the dietary intakes of calcium that are representative of populations from LMICs so as not to cause harm through excessive intake in any population group. Any food fortification strategy should be preceded with intake simulations to ensure that none of the

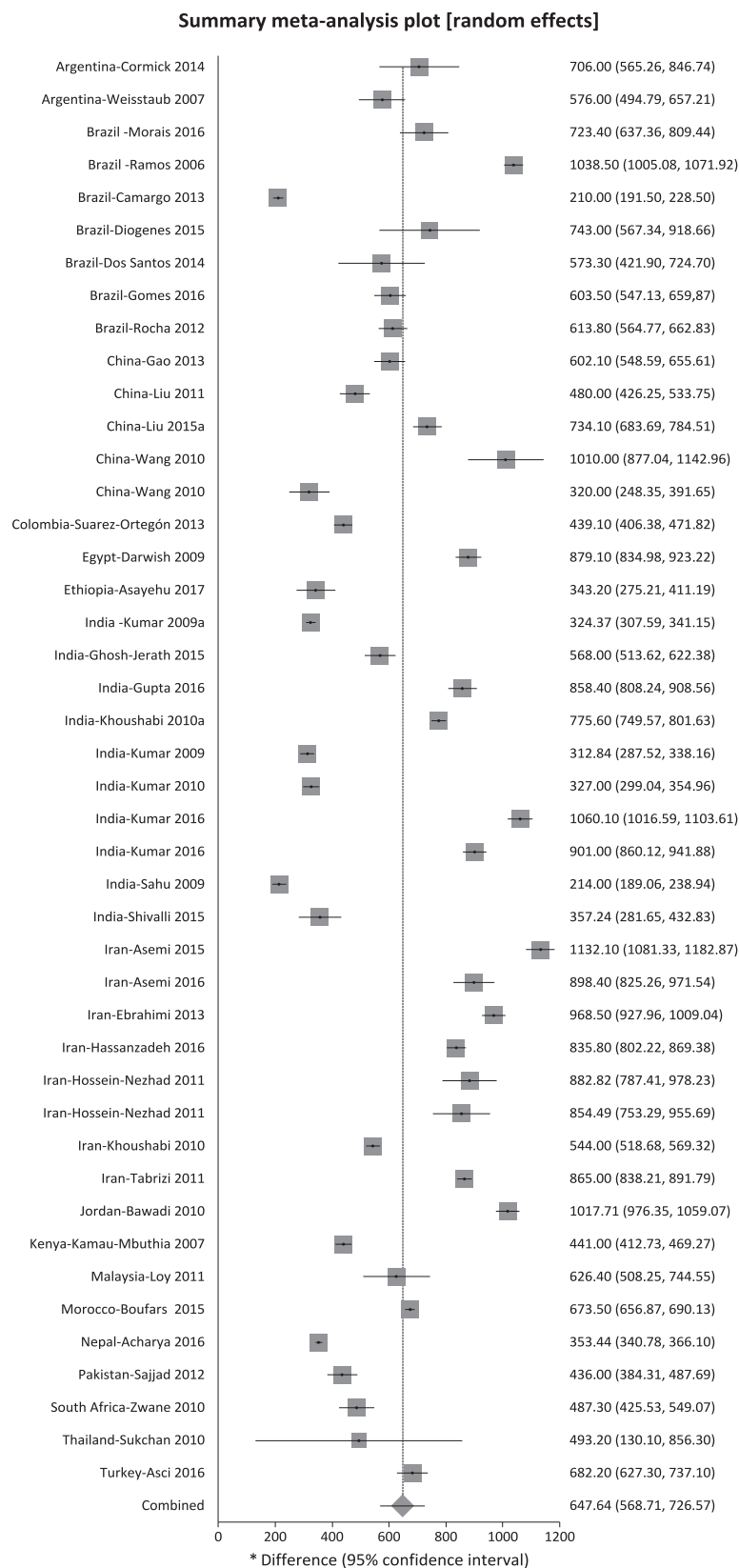


Figure 3. Mean calcium intake and approximate 95% CIs in studies from low- and middle-income countries.

population groups exceeds the upper limit of intake recommendations. This review shows that a strategy to increase calcium intake by around 400–500 mg/day in populations of low calcium intake would take these populations closer to the recommendations, decreasing the gap between HICs.

Conclusion

This study confirms the gap between HICs and LMICs with alarming low calcium intakes in pregnant women in LMICs. From the public health perspective, in the absence of specific local data, calcium supplementation of pregnant women in these countries should be universal.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information..

Contribution to authorship

APB and AMG conceived the idea. GC, APB, IR, and CFL carried out data extraction. GC, APB, AC and JB carried out the analysis. All authors carried out the interpretation of the data, revised the article critically for intellectual content, and approved the final draft for publication.

Details of ethics approval

Not required for this review.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Risk of bias graph: author's judgment about each risk of bias item.

Figure S2. Risk of bias summary.

Figure S3. Means and 95% CIs for regions according to United Nations classification.

Figure S4. Means and 95% CIs for trimester in low- and middle-income countries and in high-income countries.

Figure S5. Means and 95% CIs for 35 included countries.

Table S1. Reported daily calcium intakes from HICs.

Table S2. Reported daily calcium intakes from LMICs.

Table S3. Summary of risk of bias.

Table S4. Studies reporting percentage of the population with inadequate intakes as percentages below the estimated average intake (EAR) order.

Appendix S1. Search strategy.

Appendix S2. Risk of bias and quality assessment prompts for the included studies. ■

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