

Developing an Effective and Simple Digital Screening Tool to Identify Inadequate Calcium Intake in Pregnant Women: a prediction model in the Rotterdam Periconception cohort

Inez L. Vanwersch¹, Melek Rousian¹, Sam Schoenmakers¹, Sten Willemsen¹, Régine Steegers-Theunissen¹, and Lenie van Rossem¹

¹Erasmus MC Afdeling Verloskunde en Gynaecologie

June 2, 2023

Abstract

Objective To develop an evidence-based and simple screening tool to estimate calcium intake in pregnant women, suitable for use in daily clinical practice. **Design** Cross-sectional analysis within a cohort study **Population and setting** We extracted all data from the Rotterdam Periconceptional cohort (PREDICT study) conducted at the Erasmus MC, University Medical Centre in Rotterdam, the Netherlands, between November 2014 and December 2020. **Methods** Data was extracted from food frequency questionnaires. The estimated average requirement of 750 m/day was defined as the lower limit for an adequate calcium intake. We created a prediction model, using multivariable binary logistic regression with backward stepwise selection. We developed a simple screening tool based on the prediction model. **Main outcome measures** Probability of adequate calcium intake **Results** 694 participants are included, of which 201 (29%) had an adequate calcium intake. Total daily or weekly intakes of cheese, milk, and yogurt or curd were selected as predictors for the prediction model. The model had excellent discrimination (AUC 0.858), a good fit (Brier score 0.136, HL statistic $p=0.499$) and satisfactory calibration. The test accuracy measures were: sensitivity 80.9%, specificity 77.1%, PPV 89.7%, NPV 62.2%. A color coded digital screening tool was developed for use in clinical practice. **Conclusions** This evidence-based and simple screening tool is a reliable and efficient instrument to predict inadequate calcium intakes in pregnancy, which can easily be incorporated in daily clinical practice and existing pregnancy coaching platforms.

Developing an Effective and Simple Digital Screening Tool to Identify Inadequate Calcium Intake in Pregnant Women: a prediction model in the Rotterdam Periconception cohort

Inez L. Vanwersch MD¹, Melek Rousian MD PhD¹, Sam Schoenmakers MD PhD¹, Sten P. Willemsen PhD^{1,2}, Régine P.M. Steegers-Theunissen MD PhD¹, Lenie van Rossem PhD¹

¹ Department of Obstetrics and Gynecology, Erasmus MC, University Medical Center Rotterdam

² Department of Biostatistics, Erasmus MC, University Medical Center, Rotterdam, 3015GD, The Netherlands.

Address for correspondence:

Régine P.M. Steegers-Theunissen,

Dr. Molewaterplein 40,

3015 GA, Rotterdam, the Netherlands.

Phone: +31 612472643 (cell phone);

Fax: n.a.

Email: r.steegers@erasmusmc.nl

Running title: Developing a Screening Tool for Calcium Intake in Pregnancy

Word count of the abstract: 250

Word count main text: 2904

ABSTRACT

Objective

To develop an evidence-based and simple screening tool to estimate calcium intake in pregnant women, suitable for use in daily clinical practice.

Design

Cross-sectional analysis within a cohort study

Population and setting

We extracted all data from the Rotterdam Periconceptional cohort (PREDICT study) conducted at the Erasmus MC, University Medical Centre in Rotterdam, the Netherlands, between November 2014 and December 2020.

Methods

Data was extracted from food frequency questionnaires. The estimated average requirement of 750 m/day was defined as the lower limit for an adequate calcium intake. We created a prediction model, using multivariable binary logistic regression with backward stepwise selection. We developed a simple screening tool based on the prediction model.

Main outcome measures

Probability of adequate calcium intake

Results

694 participants are included, of which 201 (29%) had an adequate calcium intake. Total daily or weekly intakes of cheese, milk, and yogurt or curd were selected as predictors for the prediction model. The model had excellent discrimination (AUC 0.858), a good fit (Brier score 0.136, HL statistic $p=0.499$) and satisfactory calibration. The test accuracy measures were: sensitivity 80.9%, specificity 77.1%, PPV 89.7%, NPV 62.2%. A color coded digital screening tool was developed for use in clinical practice.

Conclusions

This evidence-based and simple screening tool is a reliable and efficient instrument to predict inadequate calcium intakes in pregnancy, which can easily be incorporated in daily clinical practice and existing pregnancy coaching platforms.

Funding

The study was funded by the department of Obstetrics and Gynaecology of the Erasmus MC.

Keywords

Calcium, pregnant women, dietary intake, screening, prediction

INTRODUCTION

Managing adequate intakes of calcium during pregnancy is important in several physiological processes, and reduces the risk of perinatal adverse events such as hypertensive disorders and preterm birth. (1-3) The

recommended daily intake (RDI) of calcium is 1000 mg/day for all women of childbearing age. (1) Calcium demands increase substantially during pregnancy, but are met by an increased intestinal absorption, renal reabsorption and mobilization from the maternal skeleton, mediated mostly by an increase in PTH and IGF-I over the course of pregnancy. (4-6) However, these measures are insufficient to compensate for an inadequate intake. Adult women of childbearing age (18-50) have remarkably low intakes of calcium. 22.7-44.5% of women in the Netherlands consume less than the estimated average requirement (EAR) of 750 mg/day. (7) In the UK, 6-8% of women of childbearing age consume even less than the lower reference nutrient intake (LRNI) of 400mg/day. (8) Individuals habitually consuming less than the LRNI are almost certainly deficient of the nutrient concerned. (9) The EAR and recommended daily intake (RDI) are further explained in the supplement.

Calcium supplementation starting from the second or third trimester in women with chronically low intakes reduces risks of gestational hypertension and preeclampsia, with estimated risk reductions of 30% and 50%, respectively. (2, 3, 10) The WHO and Dutch guidelines for pregnancy consultation therefore recommend daily calcium supplementation starting from the 20th week of gestation in women with an inadequate intake. (11, 12) Due to tight regulation of serum calcium levels (2.10-2.55 mmol/L) (13)), there is poor association between dietary and total calcium serum levels. (5, 14) Hence, nutritional screening is the only appropriate method to assess calcium intake. During regular maternal outpatient clinic visits there is neither time nor expertise for elaborate dietary assessments. A simple screening tool for calcium intake could offer a solution, and contribute to better care and prevention through early detection and intervention in women at risk of having an inadequate intake, and with that the improvement of perinatal outcomes and maternal-fetal health. A digital screening tool could also contribute to improved self-management in periconceptional care, by enabling women to assess and improve their own calcium intake, and with that leading to greater health care efficiency and maternal and perinatal outcomes.

To our best knowledge, no studies have been conducted on the development of a calcium-specific FFQ or a prediction model to assess calcium intake in pregnancy. We hypothesize that intake of an adequate amount of calcium can accurately be predicted by a limited number of products.

Therefore, the aim of this study is to develop an effective and simple digital screening tool based on a prediction model for calcium intake in pregnancy, that is suitable for making accurate individual predictions with a minimal number of predictors and can be integrated in existing pregnancy health platforms (e.g. Smarter Pregnancy) to be used by both clinicians and women who are or are planning to become pregnant.

METHODS

Study design and population

Our study was conducted in the ongoing Rotterdam Periconceptional cohort (Predict study), a tertiary hospital based, prospective observational study that was set up in 2009 to investigate maternal and paternal periconceptional health and the impact on reproduction, pregnancy and neonatal outcomes. (15, 16) At study entry, pregnant couples fill out an extensive online questionnaire including a study-specific 196-item food frequency questionnaire (FFQ) for information about parental dietary patterns. Data collected from November 2014 up until December 2020 was available for analysis. During this period, a total of 2637 female participants were included in the Predict study, of which 1043 did not submit an FFQ. We calculated the outcome events per predictor variable (EPV) to estimate adequacy of the sample size. (17)

Eligibility criteria

The only inclusion criterion was availability of a completed FFQ. Participants with incomplete FFQs were omitted from any type of analysis. We used the Goldberg cutoff, based on individual basal metabolic rates (BMR) and physical activity levels (PAL), to identify participants with FFQs that were subject to significant underreporting of dietary intake. These records were excluded from analysis. (18)

Primary outcome

The FFQ output generates individual nutrition scores in mg or μg per day for each micronutrient, including calcium. We defined the EAR of 750 mg/day as the lower limit for an adequate calcium intake, since this intake value is most relevant to detect individuals at risk for deficiencies, while leaving a sizeable margin between the limit intake and dangerously low intakes. (1, 7, 19) The primary outcome was set as a dichotomous variable, with calcium intakes being either above (adequate) or below (inadequate) the limit of 750 mg/day.

Predictors

We searched the FFQs for frequently consumed sources of calcium, using the Dutch Nutrient Database (NEVO) (20) as a reference for information on nutritional values, and the Dutch National Food Consumption survey (7) for information on frequently consumed sources of calcium by women of reproductive age. Food categories that are listed as a main dietary source of calcium (e.g., cheese, milk) were included as potential predictors, along with subcategories that had higher calcium contents than the total category average (e.g., low fat cheese contains more calcium than the average kind of cheese,). Predictors were included in statistical analysis when the calcium content for each product serving was at least 10% of the RDI (100 of 1000mg/day).

Statistical analysis

Model development

A prediction model was developed using multivariable binary logistic regression with backward stepwise selection, excluding variables with p-values > 0.10 . We excluded predictors with less than 0.010 contribution to total model performance, expressed in area under the ROC curve (AUC). Categories were only replaced by calcium richer subcategories when substitution led to an increase in AUC. We used the final regression output to calculate individual probabilities of having an adequate calcium intake.

Model discrimination was assessed using the AUC. We used the Hosmer and Lemeshow test and Brier score as measures for goodness of fit. Internal validity was assessed through a bootstrapping procedure using 5 bootstrap samples, resulting in optimism corrected estimates of model performance, which are presented in the results section. Model calibration was assessed by a calibration plot, comparing the predicted probabilities of having an adequate calcium intake with the actual proportion of participants with an adequate intake.

Screening tool

The optimal cut off value for the model positivity criterion was determined by comparison of test classification measures (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)) at different cut off values. We prioritized PPV and specificity over NPV and sensitivity, in order to minimize the number of women that are erroneously classified as having an adequate intake. A positive test result indicated an adequate calcium intake.

Finally, we combined the probability scores resulting from the prediction model into a risk assessment table with corresponding predictors and their intake frequency ranges. Risk scores were color coded for high (red), medium (orange) and low (green) probabilities of having an inadequate calcium intake.

RESULTS

Case selection

1594 Participants completed their FFQs, 595 participants were excluded due to significant underreporting of caloric intake according to the Goldberg cutoff, 268 participants were excluded because of missing data, and 37 first trimester FFQs were detected as duplicates due to participants' prior participation in the preconceptional study, leaving a total of 694 FFQs for analysis (Figure 1).

General participant characteristics

Participant characteristics are displayed in Table 1. The mean age was 32.8 (± 4.37) years, the mean BMI was 24.1 (± 3.98) and the mean daily caloric intake 2127 (± 531) kCal. Most participants were of Dutch ethnicity

(n=453). 278 (40.1%) participants had calcium intakes at or above the RDI of 1000 mg/day. Twenty-nine percent of participants consumed less than the EAR, and 5% of participants consumed less than 500 mg/day. Participants who were excluded due to significant underreporting of caloric intake reported an average daily caloric intake of 1256 kCal (± 339). The group of excluded participants was on average 0.8 years younger ($p=0.004$), had a higher mean BMI by 2.8 points ($p<0.001$) than the included participants, and had a smaller proportion of higher educated participants (56% vs. 63%; $p=0.023$).

Predictors

Examination of the FFQ and NEVO resulted in the following food categories and subcategories as potential predictors: cheese; low or medium fat cheeses; yogurt or curd; milk; soy milk, drinks or dessert; meat substitutes; dairy drinks; fish; smoked, steamed or canned fish; vegetables; green leafy vegetables; nuts and seeds. Table 2 displays the calcium contents of each potential predictor per 100g and per serving, and the percentage of RDI attribution per serving in descending order. Additionally, it contains the portion of Predict participants consuming each (sub)category and the distribution of consumed quantities amongst participants.

Prediction model

The backward stepwise selection process selected three predictors ($p<0.10$) for calcium intake: cheese; milk; yogurt and curd. The EPV was satisfactory at 29 (232 cases, 7 degrees of freedom). Table 3 presents the full logistic prediction model. The regression coefficient corresponds with the odds of having an adequate calcium intake for a person who's consumption matches any other category, compared to the reference category. To calculate the predicted probability of having an adequate calcium intake, the beta coefficients are entered in the formula stated in the footnote of table 3.

The AUC was 0.858 (Figure 2), indicating excellent discrimination. The Hosmer and Lemeshow test ($p=0.499$) and Brier score (0.136) both indicated a good fit of the model. Figure 3 displays the calibration plot, with a null line representing predictions that perfectly match the observed incidence. The size of the dots represents the number of participants within the corresponding intake group. The model was very well calibrated, with most predictions bordering the null line. Predictions that did not match the observed incidence were generally found in midrange intake groups with small numbers of participants.

Screening tool

Figure S1 illustrates the shift in test classification measures at varying cut-off probabilities for the test positivity criterion. The optimal combination of sensitivity and specificity was at a cut-off point of 0.700. Application of the cut-off to the study population resulted in the following classification measures: sensitivity 80.9%, specificity 77.1%, PPV 96.8%, NPV 62.2% (Table 4). We created a graphically designed screening tool with color coded risk scores based on the prediction model (Figure 4). Green cells indicate low probabilities of having an inadequate calcium intake, orange cells indicate medium high probabilities, red cells indicate high probabilities. User instructions are enclosed with the screening tool.

DISCUSSION

Main findings

Our prediction model accurately detects inadequate intakes of calcium in a tertiary hospital based cohort of women in the periconceptional period. The model has low error rates, with a high sensitivity and specificity. The screening tool based on this model enables clinicians to make a quick estimate of the adequacy of calcium intake in pregnancy. The prediction model has yet to be externally validated.

Strengths and limitations

The main strength of this study is the availability of a very large set of validated FFQ data. (21) Furthermore, to our knowledge, this study is the first to develop a nutrient specific screening tool with a minimal number of predictors that is applicable on an individual level while maintaining predictive accuracy. Finally, as this

tool was developed in line with clinical needs, it is an evidence-based tool that should be relatively easy to implement in practice.

A limitation of this study is the use of dietary surveys, which could be prone to bias (22). Dietary surveys are primarily subject to underreporting (23, 24). We minimized the effects of underreporting by eliminating FFQs with unrealistically low dietary intakes. Additionally, the Predict study is a tertiary hospital based cohort, and disease or medication related side effects can influence dietary habits, and with that calcium intake or uptake. Since calcium is absorbed in the small intestine, certain gastrointestinal (inflammatory) diseases or intestinal surgery can severely restrict calcium uptake. (25) However, the tool assesses dietary calcium intake, rather than uptake. Intake levels are unlikely to be affected by a reduced uptake. Therefore, there is no reason to suspect that this would influence the tool's generalizability. We cannot think of any other indication for tertiary pregnancy care where calcium intake would be severely compromised, and therefore, we think our results apply to each pregnant woman, irrespective of underlying comorbidities or risks.

Interpretation

Results in the context of what is known

In previous research, screening tools for general nutritional health and nutrition related health factors have been developed. (26-28) For example, Huijgen et. al. (26) have developed a simple tool to assess an inadequate habitual diet in clinical practice, which has been incorporated in the e-coaching program Smarter Pregnancy. (29) Furthermore, micronutrient specific FFQs and checklists have been developed for a number of micronutrients. (30-32) To our knowledge, this study is the first to develop a calcium-specific screening method.

Clinical implications

The screening tool has an explicit focus on dairy products for calcium intake, which are the most important sources of calcium in a Western-style diet, but not in plant based or non-Western-style diets. The tool could therefore underestimate calcium intake in women with non-Western dietary habits or a plant based diet. However, the average dietary calcium intake in Asian, African and South American countries generally ranges between 400-700 mg/day, and women with a plant based diet have shown to consistently have calcium intakes below the RDI and EAR. (33, 34) This indicates that non-dairy sources of calcium on its own are probably not sufficient to meet calcium requirements. The classification of these diets as having an inadequate calcium intakes might therefore be an appropriate outcome of the tool. However, the FFQ does not account for calcium fortified foods and drinks or supplements. Hence, calcium intake is likely to be underestimated in women who rely on fortified products or supplements to meet dietary requirements.

Our prediction model has a relatively low negative predictive value, especially compared to other test accuracy measures. In the selection of the optimal cut of probability we prioritized positive predictive value and specificity over negative predictive value and sensitivity, based on a benefit-risk assessment of an increased calcium intake in pregnancy through both supplementation or dietary intervention. Increasing calcium intake in pregnant women with inadequate intakes has explicit beneficial effects on bones, nerves and cardiovascular health, and gives a risk reduction of pre-eclampsia (RR 0.51) and gestational hypertension (RR 0.70). (10) The tolerable upper intake level of calcium is 2500 mg/day (35), which is nearly impossible to reach through dietary intake alone. All interventions that focus on dietary counselling to improve calcium intake are therefore considered safe. In contrast, the possible risks of calcium supplementation are not completely clear, though harmful effects such as cardiovascular event, carcinoma, and kidney stones are only reported in older patients, and with doses of >1000 mg/day. (36) Lower dosages have proven to be sufficient for the prevention of both preeclampsia and gestational hypertension. (3, 10) In summary, calcium supplementation appears to be harmless for the target population, especially when using low to moderate dosages. Based on these considerations, we prefer a tool that improperly classifies women as having an inadequate calcium intake over a tool that erroneously classifies women as having an adequate calcium intake.

Current guidelines recommend calcium supplementation starting from the 20th week of gestation in women

with an inadequate calcium intake. The 20 week limit has been established because no effect of supplementation in earlier stages of pregnancy has been scientifically proven. The presented screening tool is developed to primarily facilitate the implementation of current guidelines. For this purpose, it can be used to assess calcium intake at around 20 weeks of gestation. However, the tool's ability to predict calcium intake levels is not limited to this gestational age. Although there is no scientific evidence, beneficial effects of an adequate calcium intake on embryonic growth and placentation cannot be precluded. Moreover, though current guidelines for pregnant women recommend the use of calcium supplements, we want to encourage clinicians to aim for dietary advises or interventions first. Calcium intake can very well be increased through dietary intake alone, which is not only safer, but can also be part of an overall healthier diet. While supplementation tackles isolated micronutrients, dietary improvements can tackle a range of macro- and micronutrients and improve general fitness and health. When aiming for dietary improvements, it is presumably rewarding to start interventions periconceptionally, providing women with the needed time frame to make adjustments in their diet and lifestyle. For this purpose, the screening tool can also be used during preconceptional hospital or midwife visits, at the general practitioner's office or at outpatient clinics for lifestyle care. (37) By using an early intervention strategy focused on diet and lifestyle, risks of supplementation are diminished, general health is improved and possible beneficial effects even in the early stages of pregnancy can be achieved.

Research implications

This screening tool could be the foundation for a multicenter pragmatic trial to evaluate its efficacy in real life routine practice conditions. Moreover, further research could be aimed at the external validation of the developed screening tool.

CONCLUSION

This study has demonstrated the possibility of accurately estimating calcium intake based on a limited number of food items. The simplified digital screening tool presented in this study is an efficient and reliable instrument to accurately estimate calcium intake in pregnant women practicing a Western-style diet. It can be used in clinical practice to detect women at risk of having an inadequate calcium intake and as such contribute to better periconceptional and pregnancy care for mother and offspring.

ACKNOWLEDGEMENTS

Disclosure statement: The author(s) report(s) no conflict of interest

CONTRIBUTION TO AUTHORSHIP

I.V. and L.R. conceived the presented idea. I.V. conducted theoretical studies and performed the analyses for the development of the screening tool. S.W. assisted with and verified the statistical analysis. L.R. and R.S. supervised the project. I.V., M.R., S.S., R.S., and L.R. contributed to the interpretation of the results and implications of the screening tool in clinical practice. I.V. took the lead in writing the manuscript. All authors discussed the results and contributed to the final manuscript.

FUNDING

The study was funded by the department of Obstetrics and Gynaecology of the Erasmus MC.

REFERENCES

1. van Goudoever J, Bonsel G, Corpeleijn E, Gubbels J, Kieft J, Kremers S, et al. Voedingsaanbevelingen voor zwangere vrouwen. In: Aan: de minister van Volksgezondheid WeS, de minister voor Medische Zorg en de staatssecretaris van Volksgezondheid, Welzijn en Sport, editor. Den Haag2021.
2. Hacker AN, Fung EB, King JC. Role of calcium during pregnancy: maternal and fetal needs. *Nutr Rev.* 2012;70(7):397-409.
3. Woo Kinshell ML, Sarr C, Sandhu A, Bone JN, Vidler M, Moore SE, et al. Calcium for pre-eclampsia prevention: A systematic review and network meta-analysis to guide personalised antenatal care. *BJOG.*

2022.

4. Hovdenak N, Haram K. Influence of mineral and vitamin supplements on pregnancy outcome. *Eur J Obstet Gynecol Reprod Biol.* 2012;164(2):127-32.
5. Kovacs CS. Calcium and bone metabolism disorders during pregnancy and lactation. *Endocrinol Metab Clin North Am.* 2011;40(4):795-826.
6. Vargas Zapata CL, Donangelo CM, Woodhouse LR, Abrams SA, Spencer EM, King JC. Calcium homeostasis during pregnancy and lactation in Brazilian women with low calcium intakes: a longitudinal study. *Am J Clin Nutr.* 2004;80(2):417-22.
7. van Rossem C, Buurma-Rethans E, Dinissen C, Beukers M, Brants H, Dekkers A, et al. The diet of the Dutch, results of the Dutch National Food Consumption Survey 2012-2016. Bilthoven: National Institute for Public Health and the Environment, RIVM; 2020. Contract No.: 2020-0083.
8. HE T. Dietary calcium and health. *British Nutrition Foundation Nutrition Bulletin.* 2005;30:237-77.
9. Health Do. Dietary Reference Values: a Guide. London: Crown; 1991.
10. Sun X, Li H, He X, Li M, Yan P, Xun Y, et al. The association between calcium supplement and preeclampsia and gestational hypertension: a systematic review and meta-analysis of randomized trials. *Hypertens Pregnancy.* 2019;38(2):129-39.
11. WHO recommendation Calcium supplementation during pregnancy for the prevention of pre-eclampsia and its complications. Geneva: World Health Organization; 2018.
12. Bax CJ KS, Duvekot, de Boer MA, Lely AT, Hajenius PJ, Ganzevoort JW, van der Heijden OWH, van der Molen FM, van der Horst MC, Doppenberg AMM, Mooij A, VandenAuweele KLHE. Richtlijn Hypertensieve aandoeningen in de zwangerschap, Module Calciumsuppletie tijdens de zwangerschap. NVOG; 2020.
13. Hooijkaas H MK, Smeets LC, Souverein JHM, Taks GHM, red. Handboek Medische Laboratoriumdiagnostiek. Houten: Prelum Uitgevers; 2013.
14. Darwish AM, Mohamad SN, Gamal Al-Din HR, Elsayed YA, Ahmad SI. Prevalence and predictors of deficient dietary calcium intake during the third trimester of pregnancy: the experience of a developing country. *J Obstet Gynaecol Res.* 2009;35(1):106-12.
15. Steegers-Theunissen RP, Verheijden-Paulissen JJ, van Uitert EM, Wildhagen MF, Exalto N, Koning AH, et al. Cohort Profile: The Rotterdam Periconceptional Cohort (Predict Study). *Int J Epidemiol.* 2016;45(2):374-81.
16. Rousian M, Schoenmakers S, Eggink AJ, Gootjes DV, Koning AHJ, Koster MPH, et al. Cohort Profile Update: the Rotterdam Periconceptional Cohort and embryonic and fetal measurements using 3D ultrasound and virtual reality techniques. *Int J Epidemiol.* 2021;50(5):1426-71.
17. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol.* 1996;49(12):1373-9.
18. Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake: basal metabolic rate. A practical guide to its calculation, use and limitations. *Int J Obes Relat Metab Disord.* 2000;24(9):1119-30.
19. Institute of Medicine FN, Board. Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients. 1998.
20. NEVO online version [Internet]. RIVM, service department from the Ministry of Health, Welfare and Sports. 2019. Available from: <https://nevo-online.rivm.nl/>.

21. Verkleij-Hagoort AC, de Vries JH, Stegers MP, Lindemans J, Ursem NT, Steegers-Theunissen RP. Validation of the assessment of folate and vitamin B12 intake in women of reproductive age: the method of triads. *Eur J Clin Nutr.* 2007;61(5):610-5.
22. Kipnis V, Midthune D, Freedman L, Bingham S, Day NE, Riboli E, et al. Bias in dietary-report instruments and its implications for nutritional epidemiology. *Public Health Nutr.* 2002;5(6A):915-23.
23. Poslusna K, Ruprich J, de Vries JH, Jakubikova M, van't Veer P. Misreporting of energy and micronutrient intake estimated by food records and 24 hour recalls, control and adjustment methods in practice. *Br J Nutr.* 2009;101 Suppl 2:S73-85.
24. Goode JP, Smith KJ, Kilpatrick M, Breslin M, Oddy WH, Dwyer T, et al. Retrospectively Estimating Energy Intake and Misreporting From a Qualitative Food Frequency Questionnaire: An Example Using Australian Cohort and National Survey Data. *Front Nutr.* 2021;8:624305.
25. Bronner F. Mechanisms of intestinal calcium absorption. *J Cell Biochem.* 2003;88(2):387-93.
26. Huijgen NA vdKM, Twigt JM, de Vries JHM, Eilers PHC, Steegers EAP, Laven JSE, Steegers-Theunissen RPM. The Preconception Dietary Risk score; a simple tool to assess an inadequate habitual diet for clinical practice. *e-SPEN Journal.* 2014;9(1):e13-e9.
27. Duquette MP, Payette H, Moutquin JM, Demmers T, Desrosiers-Choquette J. Validation of a screening tool to identify the nutritionally at-risk pregnancy. *J Obstet Gynaecol Can.* 2008;30(1):29-37.
28. Hrolfsdottir L, Gunnarsdottir I, Birgisdottir BE, Hreidarsdottir IT, Smarason AK, Hardardottir H, et al. Can a Simple Dietary Screening in Early Pregnancy Identify Dietary Habits Associated with Gestational Diabetes? *Nutrients.* 2019;11(8).
29. Van Dijk MR, Huijgen NA, Willemsen SP, Laven JS, Steegers EA, Steegers-Theunissen RP. Impact of an mHealth Platform for Pregnancy on Nutrition and Lifestyle of the Reproductive Population: A Survey. *JMIR Mhealth Uhealth.* 2016;4(2):e53.
30. Bjorn Jensen C, Thorne-Lyman AL, Vadgard Hansen L, Strom M, Odgaard Nielsen N, Cohen A, et al. Development and validation of a vitamin D status prediction model in Danish pregnant women: a study of the Danish National Birth Cohort. *PLoS One.* 2013;8(1):e53059.
31. Condo D, Makrides M, Skeaff S, Zhou SJ. Development and validation of an iodine-specific FFQ to estimate iodine intake in Australian pregnant women. *Br J Nutr.* 2015;113(6):944-52.
32. Zhou SJ, Schilling MJ, Makrides M. Evaluation of an iron specific checklist for the assessment of dietary iron intake in pregnant and postpartum women. *Nutrition.* 2005;21(9):908-13.
33. Balk EM, Adam GP, Langberg VN, Earley A, Clark P, Ebeling PR, et al. Global dietary calcium intake among adults: a systematic review. *Osteoporos Int.* 2017;28(12):3315-24.
34. Smith AM. Veganism and osteoporosis: a review of the current literature. *Int J Nurs Pract.* 2006;12(5):302-6.
35. Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D, Calcium. Dietary Reference Intakes for Calcium and Vitamin D. 2011.
36. Li K, Wang XF, Li DY, Chen YC, Zhao LJ, Liu XG, et al. The good, the bad, and the ugly of calcium supplementation: a review of calcium intake on human health. *Clin Interv Aging.* 2018;13:2443-52.
37. van der Windt M, van der Kleij RM, Snoek KM, Willemsen SP, Dykgraaf RHM, Laven JSE, et al. Impact of a Blended Periconception Lifestyle Care Approach on Lifestyle Behaviors: Before-and-After Study. *J Med Internet Res.* 2020;22(9):e19378.
38. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr.* 1985;39 Suppl 1:5-41.

39. Hosmer. Applied Logistic Regression, Third Edition. John Wiley and Sons, Inc.; 2013.

TABLES

Table 1. Participant characteristics and comparison in inadequate and adequate calcium intake in subgroups assessed in periconception period

Characteristic	*Missing N	Total (n = 694)	Total (n = 694)	Calcium intake <750 mg/day (n = 201)	Calcium intake <750 mg/day (n = 201)	Calcium intake >750 mg/day (n = 493)	Calcium intake >750 mg/day (n = 493)	P
Age at conception	142	32.8	± 4.37	32.3	± 4.52	33.0	± 4.37	.095
Education	158							
Higher		336	(62.7)	90	(56.6)	246	(65.3)	.147
Middle		163	(30.4)	55	(34.6)	108	(28.6)	
Lower		37	(6.9)	14	(8.8)	23	(6.1)	
Ethnicity	171							
Dutch		453	(86.6)	126	(82.9)	327	(88.1)	.053
Non-Dutch		28	(5.4)	7	(4.6)	21	(5.7)	
Western								
Non-Western		42	(8.0)	19	(12.5)	23	(6.2)	
Periconceptional:								
BMI	0	24.1	± 3.98	24.0	± 3.88	24.1	± 4.02	.613
Daily caloric intake (kCal)	0	2127	± 531	1902	± 328	2219	± 569	<.001
Diet	153	47	(8.7)	13	(8.1)	34	(8.9)	.072
Vegetarian		22	(4.1)	3	(1.9)	19	(5.0)	
Vegan		2	(0.4)	2	(1.3)	0	(0.0)	
Macrobiotic		1	(0.2)	0	(0.0)	1	(0.3)	
Other		22	(4.1)	8	(5.0)	14	(3.7)	
Calcium intake	694							
>1000 mg/day		278	(40.1)	-	-	-		
>750 mg/day		493	(71.0)	-	-	-		
>500 mg/day		658	(94.8)	-	-	-		

Footnote table 1:

*Mean ± SD for continuous variables, n (valid %) for categorical variables;

Table 2. Potential predictors: food categories and subcategories with their calcium contents and consumed quantities sorted by calcium contents per serving in descending order.

		Serving size (g)	Calcium content (mg) [NEVO]**	Calcium content (mg) [NEVO]**	Calcium content (mg) [NEVO]**	Consumption [Study cohort]	Consumption [Study cohort]	Consumption [Study cohort]
Food category	Subcategory		Per 100g	Per serving (%RDI)	Per serving (%RDI)	% of women	Quantity per person* median (IQR)	Quantity per person* median (IQR)
Cheese		30	637	191	(19.1)	96.4	21.3	(9.8, 36.5)
	20+ and 30+ cheese	30	1025	308	(30.8)	94.5	16.4	(6.7, 31.0)
	40+ and 48+ cheese	30	881	264	(26.4)			
Yogurt or curd		150	126	189	(18.9)	67.7	21.0	(0.0, 85.5)
Milk		150	121	182	(18.2)	76.7	86.0	(4.1, 200.0)
Soy drinks, milk or dessert		150	110	165	(16.5)	23.9	0.0	(0.0, 0.0)
Meat substitutes		80	173	138	(13.8)	26.1	0.0	(0.0, 3.1)
Dairy drinks		150	81	121	(12.2)	43.1	0.0	(0.0, 28.0)
Fish		130	59	77	(7.7)	82.1	14.7	(5.4, 17.9)
	Smoked, steamed or canned fish	130	123	160	(16.0)	28.4	0.0	(0.0, 2.3)
Vegetables		100	56	56	(5.6)	97.1	55.2	(31.0, 83.7)
	Green leafy vegetables	100	113	113	(11.3)	88.8	22.0	(8.5, 34.9)
Nuts and seeds		25	200	50	(5.0)	74.8	3.7	(0.0, 11.1)

Footnote table 2: Calcium contents are calculated from NEVO data, consumption quantities are extracted from the Predict database

*Quantity in grams per day

Example: 76.7% of participants consumed milk, with a median daily quantity of 86g. Milk contains 121 mg

calcium per 100g, one portion size is 150g, which translates into 182mg calcium and an RDI attribution of 18.2% per portion.

Table 3. Logistic regression model for calculating the probability of having an adequate calcium intake in pregnancy.

		β	95% CI	95% CI	p
			Lower	Upper	
Cheese	Cheese				
	None	0	ref		
	1-3/week	1.001	0.057	1.945	0.037
	3-7/week	2.240	1.284	3.196	<.001
Milk	[?]1/day	3.849	2.814	4.884	<.001
	Milk				
	<3/week	0	ref		
	3-7/week	0.635	0.083	1.187	0.024
Yogurt/curd	[?]1/day	2.887	2.272	3.502	<.001
	Yogurt/curd				
	<1/week	0	ref		
	1-3/week	0.791	0.267	1.315	0.003
	>3/week	1.529	1.009	2.049	<.001

Footnote Table 3:

Predicted probability can be calculated by the following equation: $(e^{-2.858+\beta\text{Cheese}+\beta\text{Milk}+\beta\text{Yogurt}})/(1+e^{-2.858+\beta\text{Cheese}+\beta\text{Milk}+\beta\text{Yogurt}})$

Example: someone consuming 3-7 weekly portions of cheese has a 2.240 higher odds of having an adequate calcium intake than someone consuming no cheese. For example, a person consuming 5 weekly portions of cheese ($\beta=2.240$), at least one portion of milk per day ($\beta=2.887$) and no yogurt/curd ($\beta=0$) has the following predicted probability of having an adequate calcium intake: $(e^{-2.858+2.240+2.887+0})/(1+e^{-2.858+2.240+2.887+0})=0.927$.

Table 4. Classification table based on the Logistic Regression Model for estimating the adequacy of calcium intake in pregnancy.

	Observed	Observed	
Classified	>750mg/day	<750mg/day	Total
Adequate	399	46	445
Inadequate	94	155	249
Total	493	201	694

Footnote table 4:

Sensitivity 80.9%; specificity 77.1%; PPV 89.7%; NPV 62.2%

PPV = positive predictive value

NPV = negative predictive value

Table S1. Classification of food categories into intake frequency ranges with corresponding daily quantities

Category	Intake frequency	Quantity (g/day)
Cheese	none 1-3/week 3-7/week [?]1/day	0 1-13 13-30 >30
Milk	<3/week 3-7/week [?]1/day	<65 65-150 >150
Yogurt and curd	none 1-3/week >3week	0 1-65 >65

FIGURE LEGENDS

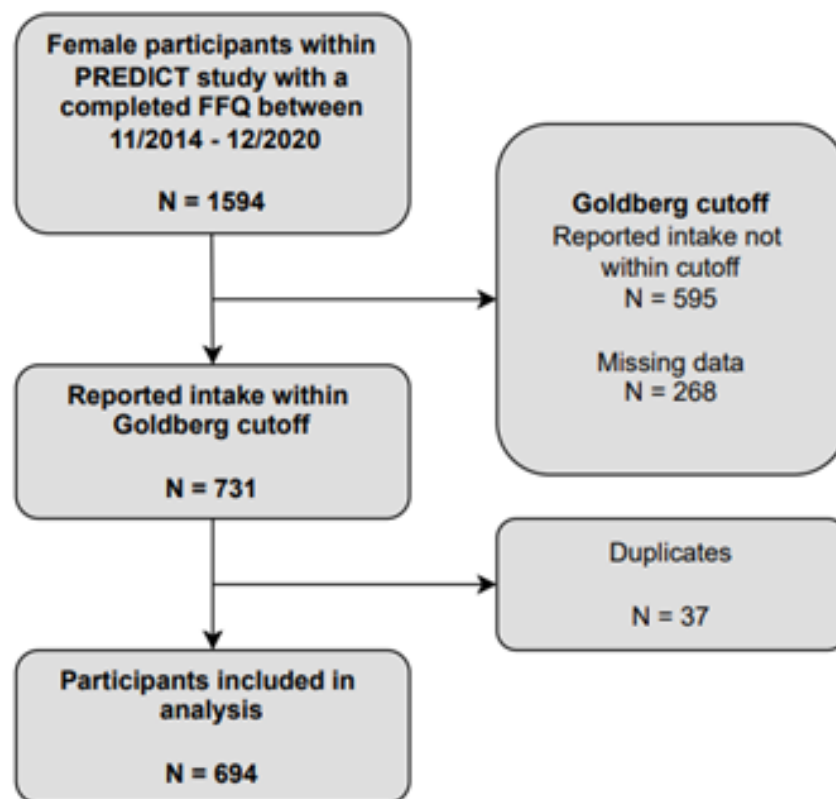
Figure 1 - Flow chart of case selection from PREDICT study according to eligibility criteria.

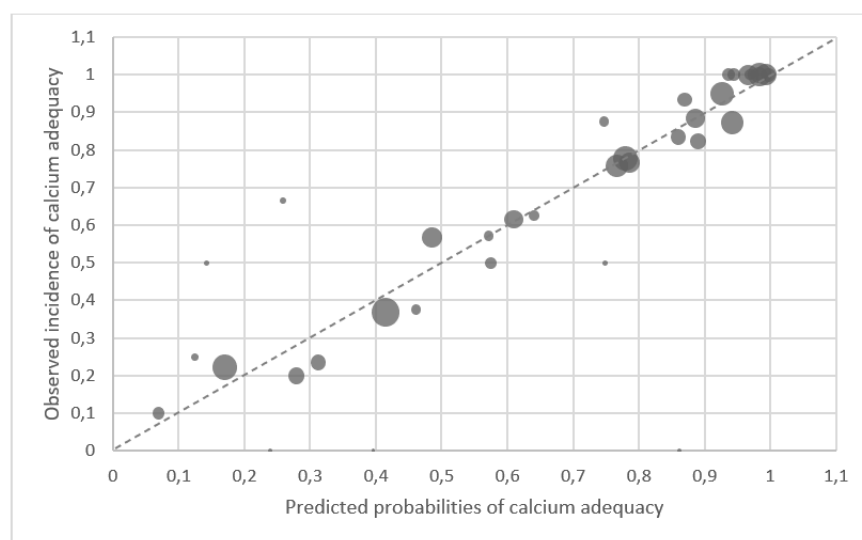
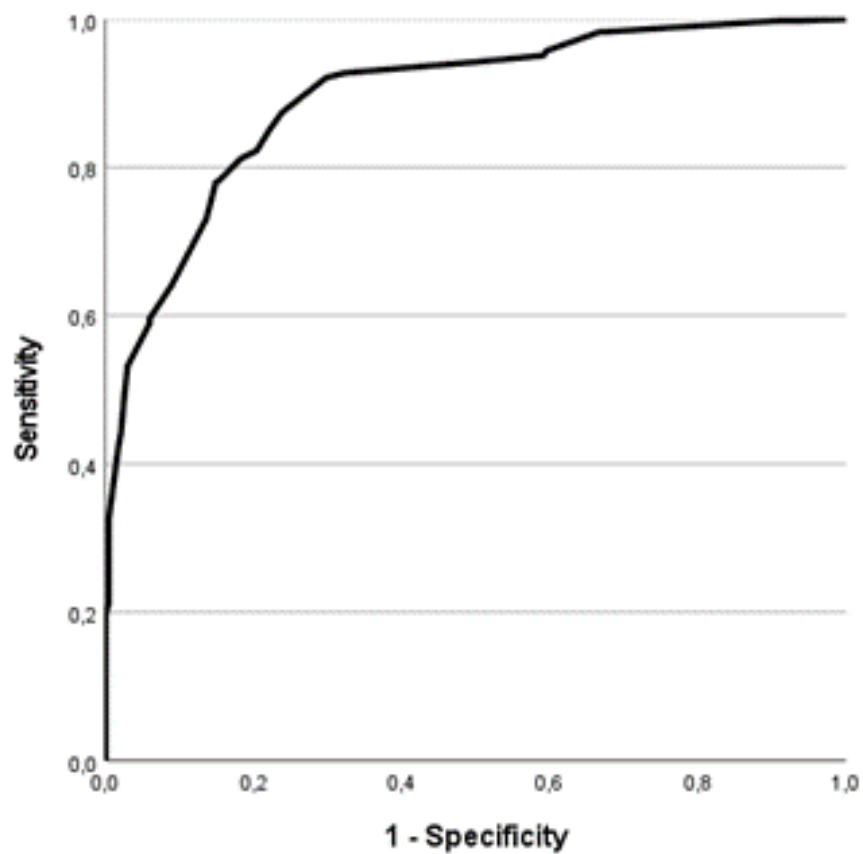
Figure 2 - ROC curve for classifying adequacy of calcium intake and model performance measures for the selected prediction model*Subscript*: Area under the curve 0.858, Brier score 0.136

Figure 3 – Calibration plot for the selected prediction model*Subscript*: Hosmer and Lemeshow statistic $p=0.499$. The number of participants with intake ranges corresponding to the predicted probability on the horizontal axis is represented by the size of the dots.

Figure 4 – Screening tool based on the prediction model for having an adequate calcium intake with color coding for high (red), medium (orange) and low (green) risks of having an inadequate calcium intake*Subscript*: User instructions: choose the block corresponding with the intake of cheese. From there, combine the intakes of milk and yogurt/curd as a cross table to find the predicted probability of having an adequate calcium intake and color coded risk score of having an inadequate intake.

Figure S1 - Test classification measures at different probability cut-off points for the test positivity criterion





		Yogurt					
		<1/week	1-3/week	>3/week	<1/week	1-3/week	>3/week
		Cheese: none			Cheese: 1-3/week		
Milk	<3/week	0.070	0.143	0.258	0.170	0.312	0.486
	3-7/week	0.125	0.239	0.396	0.279	0.461	0.641
	≥1/day	0.575	0.749	0.862	0.786	0.890	0.944
		Cheese: 4-7/week			Cheese: ≥1/day		
Milk	<3/week	0.415	0.610	0.766	0.780	0.886	0.942
	3-7/week	0.572	0.747	0.860	0.870	0.936	0.969
	≥1/day	0.927	0.966	0.983	0.984	0.993	0.997

