Supplements-Risk prediction models of natural menopause onset: a systematic review

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Supplementary Material 1. Detailed search strategy of the current study in each database.

Medline (Ovid)

1 ((predict* or risk) adj3 (early or onset or age or ages or time or timing or stage or stages or premature or late or natural) adj3 (menopaus* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or climact*)).ab,ti.

2 (predict* adj3 (menopaus* or climact*)).ab,ti.

3 ((age adj3 menopaus*) or ((time or timing) adj3 menopaus*)).ab,ti.

4 (onset adj3 menopaus*).ab,ti.

5 cessation of menstruation*.ab,ti.

6 final mens*.ab,ti.

7 (climact* adj3 (chang* or stage*)).ti,ab.

8 (((ovarian or reproductive*) adj (failur* or declin* or reserve* or aging* or ageing*)) and (menopaus* or climact*)).ti,ab.

9 late reproductive age*.ab,ti.

10 (loss adj1 fertil*).ab,ti.

11 (menopaus* adj3 transition*).ab,ti.

12 (approach* adj3 menopaus*).ab,ti.

13 "sensitivity and specificity"/ or "predictive value of tests"/ or roc curve/ or odds ratio/ or proportional hazards models/

14 (accuracy or ((risk or predict* or cox or hazard) adj5 (model* or abilit* or analys*)) or sensitivity or specifity or (predic* adj1 value*) or likelihood ratio* or c-statistic* or multivariab* or AUC or ((area-under or ROC) adj3 curve) or ((odd* or risk) adj3 ratio*)).ab,ti.

15 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ab,ti.

16 cohort studies/ or follow-up studies/ or exp longitudinal studies/ or prospective studies/

17 (cohort* or case-cohort* or nested case-control* or prospectiv* or (observ* adj (study or studies)) or longitudinal or follow-up or followup or followed-up or multivariate*).ab,ti.

18 exp animals/ not humans/

19 (letter or news or comment or editorial or congress or abstracts).pt.

20 or/3-12

21 or/13-15

22 or/16-17

23 20 and 21 and 22

24 1 or 2 or 23

25 24 not (18 or 19)

Embase (Ovid)

1 *menopause/ and (diagnostic accuracy/ or predictive value/)

2 "age at natural menopause"/ or "time to menopause"/ or (onset age/ and exp "menopause and climacterium"/)

3 ((predict* or risk) adj5 (early or onset or age or ages or time or timing or stage or stages or premature or late or natural) adj5 (menopaus* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or climact*)).ab,ti.

4 (predict* adj5 (menopaus* or climact*)).ab,ti.

5 ((age adj3 menopaus*) or ((time or timing) adj3 menopaus*)).ab,ti.

6 (onset adj3 menopaus*).ab,ti.

7 cessation of menstruation*.ab,ti.

8 final mens*.ab,ti.

9 (climact* adj3 (chang* or stage*)).ti,ab.

10 (((ovarian or reproductive*) adj (failur* or declin* or reserve* or aging* or ageing*)) and (menopaus* or climact*)).ti,ab.

11 late reproductive age*.ab,ti.

12 (loss adj1 fertil*).ab,ti.

13 (menopaus* adj3 transition*).ab,ti.

14 (approach* adj3 menopaus*).ab,ti.

15 "sensitivity and specificity"/ or "predictive value"/ or predictor variable/ or prediction/ or accuracy/ or diagnostic accuracy/ or diagnostic test accuracy study/ or receiver operating characteristic/ or odds ratio/ or proportional hazards model/

16 (accuracy or ((risk or predict* or cox or hazard) adj5 (model* or abilit* or analys*)) or sensitivity or specifity or (predic* adj1 value*) or likelihood ratio* or c-statistic* or multivariab* or AUC or ((area-under or ROC) adj3 curve) or ((odd* or risk) adj3 ratio*)).ab,ti.

17 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ab,ti.

18 "cohort analysis"/ or follow-up/ or exp longitudinal study/ or prospective study/ or exp case control study/ or exp case study/

19 (cohort* or case-cohort* or nested case-control* or prospectiv* or (observ* adj (study or studies)) or longitudinal or follow-up or followup or followed-up or multivariate*).ab,ti.

20 (exp animal/ or nonhuman/) not exp human/

21 (Editorial or Letter or Note or Erratum or Conference Paper or Conference Abstract or Conference Review).pt.

22 2 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

23 15 or 16 or 17

24 18 or 19

25 22 and 23 and 24

26 1 or 3 or 4 or 25

27 25 or 26

28 27 not (20 or 21)

Cochrane Central Register of Controlled Trials

ID Search Hits

#1 ((predict* or risk) NEAR/5 (early or onset or age or ages or time or timing or stage or stages or premature or late or natural) NEAR/5 (menopaus* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or climact*))

#2 (predict* NEAR/5 (menopaus* or climact*))

#3 ((age NEAR/3 menopaus*) or ((time or timing) NEAR/3 menopaus*))

#4 (onset NEAR/3 menopaus*)

#5 "cessation of menstruation"

#6 final NEXT mens*

#7 (climact* NEAR/3 (chang* or stage*))

#8 (((ovarian or reproductive*) NEXT (failur* or declin* or reserve* or aging* or ageing*)) AND (menopaus* or climact*))

#9 "late reproductive age"

#10 (loss NEAR/1 fertil*)

#11 (menopaus* NEAR/3 transition*)

#12 (approach* NEAR/3 menopaus*)

#13 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

#14 (accuracy or ((risk or predict* or cox or hazard) NEAR/5 (model* or abilit* or analys*)) or sensitivity or specifity or (predic* NEAR/1 value*) or likelihood ratio* or c-statistic* or multivariab* or AUC or ((area-under or ROC) NEAR/3 curve) or ((odd* or risk) NEAR/3 ratio*))

#15 (diagnos* NEAR/2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness))

#16 #14 OR #15

#17 (cohort* or case-cohort* or nested case-control* or prospectiv* or (observ* NEXT (study or studies)) or longitudinal or follow-up or followup or followed-up or multivariate*)

#18 #13 AND #16 AND #17

#19 #1 OR #2 OR #18

Web of Science Core Collection

#23 #21 AND #22

#22 DT=(article)

#21 #19 NOT #20

#20 TS=((animal* OR plant* OR rats OR mice OR murine OR rabbits OR pigs OR primate*) NOT (human* OR patient*))

#19	#1 OR #2 OR #18
#18	#13 AND #16 AND #17
#17	TS=((cohort* or case-cohort* or nested case-control* or prospectiv* or (observ* NEAR/0 (study or studies)) or longitudinal or follow-up or followup or followed-up or multivariate*))
#16	#14 OR #15
#15	TS=(diagnos* NEAR/2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness))
#14	TS=((accuracy or ((risk or predict* or cox or hazard) NEAR/5 (model* or abilit* or analys*)) or sensitivity or specifity or (predic* NEAR/1 value*) or likelihood ratio* or c-statistic* or multivariab* or AUC or ((area-under or ROC) NEAR/3 curve) or ((odd* or risk) NEAR/3 ratio*)))
#13	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#12	TS=(approach* NEAR/3 menopaus*)
#11	TS=(menopaus* NEAR/3 transition*)
#10	TS=((loss NEAR/1 fertil*))
#9	TS=("late reproductive age")
#8	TS=(((ovarian or reproductive*) NEAR/0 (failur* or declin* or reserve* or aging* or ageing*)) AND (menopaus* or climact*))
#7	TS=(climact* NEAR/3 (chang* or stage*))
#6	TS=(final NEAR/0 mens*)
#5	TS=("cessation of menstruation")
#4	TS=((onset NEAR/3 menopaus*))
#3	TS=(((age NEAR/3 menopaus*) or ((time or timing) NEAR/3 menopaus*)))
#2	TS=((predict* NEAR/5 (menopaus* or climact*)))
#1	TS=(((predict* or risk) NEAR/5 (early or onset or age or ages or time or timing or stage or stages or premature or late or natural) NEAR/5 (menopaus* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or climact*)))

Google scholar 300 most relevant results (out of 17’000 results in total)

Prediction|predict|predicting|predictor|predictors|determinate|determinant|determine|timing|diagnosis "age at menopause"|"age at natural menopause"|"menopause onset"|"onset of menopause"|"menopause stage" study|trial -rat -rats -mouse –mice

Supplementary material 2. Detailed explanation of all prediction models in the included studies.

Age

We identified seven articles (1-7) examining age as sole predictor of MP onset. The C-statistics of age in predicting MP onset in five articles ranged from 0.83 to 0.88 (1-5), while one article (7) showed an AUC of 0.82 (95% confidence interval CI 0.71-0.93) and finally, Taylor's study (6) showed poor sensitivity and good specificity of age in forecasting MP within 2 or 4 years (sensitivity 42.4% (95% CI 26.8-60.0) and 40% (95% CI 28.3-52.3), specificity 87.4% (95% CI 82.9-91.1) and 94.8% (95% CI 90.2-97.4), respectively.

Minor improvements were observed in prediction models by adding other predictors to age. The model performance of Dolleman et al. 2014 (3) improved minimally by adding mothers' ANM from C-statistics of 0.84 (95% CI 0.78-0.90) to 0.85 (95% CI 0.79-0.91). They also studied ANM of the mother as a sole predictor (C-statistic 0.63, 95% CI 0.54-0.72). Dolleman et al. 2015 (4) showed a minor improvement by including body mass index (BMI), packyears of smoking and menstrual cycle status (C-statistic from 0.88 to 0.89).

Anti-Müllerian Hormone (AMH) AMH as predictor of ONM was used in 11 articles (1-5,7-12). AMH as a sole predictor of MP onset provided a C-statistics ranging from 0.70 to 0.87. (1,2,7,8). Adding age into the models using AMH improved predictive ability in all articles (C-statistics 0.86 – 0.90) (1,2,7).

Some articles developed risk prediction models by determining AMH at a certain age or age group. De Kat et al. (8) measured AMH at age 20, 25, 30 and 35 with moderate C-statistics (0.62 –0.71). Finkelstein et al. (9) tested prediction models by using different AMH thresholds (< 10 pg/ml and < 100 pg/ml) for prediction times of 1, 2 and 3 years. Sensitivity would depend on age, with AMH threshold < 100 pg/ml showing better sensitivity (65% – 76%) in the age group < 48 years, and AMH threshold < 10 pg/ml showing better sensitivity (70%– 82%) at age group > 51 years. The performance of the model developed by Gohari et al. (10) was higher at age 43 with time prediction of 3 years (AUC 0.967). The AUC deteriorated with increasing age (45, 47, and 49 years of age) at which the blood samples were taken, but still showed a good model performance.

Several articles (2,4,8,9) combined AMH with lifestyle factors like oral contraception use, smoking or BMI. The multivariable model (AMH, age + smoking either at baseline or follow-up) of Depmann, et al. 2016 (2) showed a C-statistic of 0.87, which corresponded to an improvement of performance relative to the univariable model (AMH, C-statistic 0.78). The article by Finkelstein et al. tested the predictive ability of AMH, age and BMI, reporting an AUC varying between 0.881 and 0.896; the prediction was similar across different times of follow-up (1, 2 or 3 years) (9). Dolleman, et al. 2015 model (4) included age, BMI and packyears of smoking as well as menstrual cycle status (i.e., regular/irregular, pregnant or taking oral contraceptives) and presented high C-statistics (0.91). The article of De Kat et al. (8), which did not include age in their risk prediction model (AMH + OC use + and smoking), showed the worst model performance (C-statistic 0.70).

Only three articles (5,7,13) included age and other biomarkers besides AMH and presented model performance. Two studies presented their models by predicting MP onset in 5 and 4 years, respectively and found very good model performances (5,7). The C-statistics of the final model (including AMH, age, FSH and AFC) of Kim et al. (5) was 0.91, whereas the AUC of the model of van Rooij et al. (7) including AMH, age and Inhibin B was 0.92 (95% CI 0.86-0.99). On the other hand, the model (including AMH at baseline, age at baseline and storage time of baseline AMH) of Tehrani et al. 2021 (13) showed a moderate C-statistic (C-statistic 0.71, 95% CI 0.69-0.73).

Tehrani et al. 2014 (12) published a cross-validation article of two existing models that predict menopausal age with AMH and age. The C-statistics ranged from 0.72 to 0.88. It is one of the articles that performed the calibration. After calibration of the SRV (Scheffer, van Rooij and de Vet) model on the TLGS (Tehran Lipid and Glucose Study) data, the slope was 0.99, the intercept -0.26 and the shape parameter 1.13. The TLGS model on the SRV data had a slope of 0.30, an intercept of 12.66 and a shape parameter of 0.62.

AMH decline rate Tehrani et al. 2020 (11), Tehrani et al. 2021 (13) and De Kat et al. (8) integrated AMH decline rate into their models. The multivariable models developed by Tehrani et al. 2020 (11) showed a C-statistics ranging from 0.72 to 0.81. The latter value resulted due to the addition of sample storage time to the model. De Kat et al. (8) presented a moderate model performance when only AMH decline rate was integrated in the model (C-statistic 0.65, 95% CI 0.63-0.67). By adding

either age or lifestyle factors, C-statistics improved slightly (C-statistics 0.70). Tehrani, et al. 2021(13) presented their prediction models using two common statistical models, including time-dependent Cox regression and Cox proportional-hazards regression models. Using Cox proportional-hazards models, the predictive performance of their model including age at baseline and baseline AMH values showed a C-statistics of 0.71 (95% CI 0.69-0.73). Adding the AMH annual decline rate to the previous model improved the C-statistics by 3% (C-statistics (0.74, 95% CI 0.71-0.76). Findings based on time-dependent Cox regression analysis including AMH measurement at each time point and baseline age as predictors found a C-statistic of 0.64 (95% CI 0.61-0.67). Adding annual AMH decline rate to the previous model improved the C-statistic by 21% (C-statistics (0.85, 95% CI 0.83-0.87).

Follicle-stimulating hormone (FSH) The univariable models of Broer et al. (1) and Depmann et al. 2016 (2) using FSH as a predictor (2) showed C-statistics of 0.70 and 0.66, respectively. The AUC of van Rooij et al. (7) was 0.72 (95% CI 0.56-0.88). After adjusting for age, the model performance of all three mentioned articles improved (Depmann 0.85, Broer 0.88, and van Rooij 84). The multivariable model of Kim et al. (5) including FSH and age showed a C-statistics of 0.86.

Two articles (2,9) added as predictors a lifestyle factor (either smoking or BMI) to their model with FSH and age. Inclusion of smoking at baseline additionally to FSH and age did not improve C-statistics (0.85) in the article by Depmann et al. 2016 (2), while the addition of smoking at follow up slightly improved C-statistics (0.86). The multivariable model (FSH, age and BMI) of Finkelstein et al. (9) showed good performance (AUC: 0.871-0.885) in predicting 1, 2 or 3 years of MP onset. The article did not provide information on individual markers.

First, Greendale et al. (14) determined candidate marker (Estradiol, FSH or N-telopeptide) or a combination that best predicted different landmarks (2 years before final menstrual period (FMP), one year before FMP and FMP itself), then a multivariable model was developed. The article only provided AUC of N-telopeptide in their univariable model (see below), but not of FSH or Estradiol. Their multivariable model, consisting of FSH and Estradiol, showed AUC ranging from 0.775 – 0.855 (depending on the landmarks they set, see above). By adding N-telopeptide to FSH and Estradiol, AUC slightly improved (0.778-0.863). Finally, the best prediction performance showed

the multivariable model consisting of FSH, Estradiol, age, menopausal transition stage, race/ethnicity and time of venipuncture (AUC 0.902-0.945).

N-telopeptide Only one of the included articles developed a risk prediction model using N-telopeptide (14), in which the area under the curve at 2 years before the FMP, 1 year before the FMP and at the time FMP was 0.594, 0.617 and 0.669, respectively.

Inhibin B Of the included articles, only van Rooij et al. (7) tested Inhibin B as a predictor of MP onset with a prediction time of 4 years. The AUC of the biomarker alone was 0.76 (0.63-0.89), while adding age in the model improved the AUC to 0.88 (95% CI 0.78-0.98) after taking the age of the women into account.

Estradiol van Rooij et al. (6) showed in their article that Estradiol alone had poor predictive accuracy (AUC 0.55, 95% CI 0.35-0.75). After adjusting for age, the AUC was greatly improved to 0.83 (95% CI 0.72-0.94).

Antral follicle count (**AFC**) Broer et al. (1) and Depmann et al. 2016 (2) presented a C-statistic for AFC of 0.84 and 0.79, respectively. The van Rooij article (7) found an AUC of 0.80 (95% CI 0.69-0.91). After adding age to the prediction models, the accuracy improved in all above-mentioned studies (Broer: 0.88, Depmann: 0.85 and van Rooij: 0.84, 95% CI 0.73-0.94). Depmann et al. 2016 (2) pointed out no difference between adding age and smoking either at baseline or at follow up to the AFC (both with C-statistic of 0.85). The risk prediction model developed by Kim et al. (5) slightly improved by adding FSH to AFC and age (C statistic of 0.86 compared to 0.84); Additionally, a combination of age, AMH and AFC resulted in a highest predictive performance (C-statistic 0.91).

Menstrual cycle irregularities and vasomotor symptoms Taylor et al. (6) tested whether 6 menstrual cycle irregularities (listed alphabetically below) and climacteric symptoms would forecast MP within 2 or 4 years.

If the most recent menstrual period was more than 90 days ago (a), the sensitivity and specificity for predicting natural MP within 2 or 4 years were 40.6% (95% CI 24.7-58) and 99.2% (95% CI 97.2-99.9), 21.9% (95% CI 13.1-33.5) and 100% (95% CI 97.8-100), respectively.

If amenorrhoea of 60 days or more occurred during the previous year (b), the sensitivity was 93.9% (MP within 2 years, 95% CI 80.6-98.9) and 64.6% (95% CI 52.3-75.5) and specificity 90.8% (MP within 4 years, 95% CI 86.7-94.0) and 97.1% (95% CI 93.4-98.9).

If women reported cycle length that varied by ≥ 19 days (c), the sensitivity and specificity for developing ONM within 2 years were 100% (95% CI 89.5-100) and 76.1% (95% CI 70.3-81.2), and for MP within 4 years 76.2% (95% CI 64.4-85.3) and 87.7% (95% CI 81.7-92.1), respectively.

Risk prediction models of women with a variable cycle length (d) showed very poor sensitivity (48.5%, 95% CI 31.6-65.3 and 29.3%, 95% CI 19.0-41.5) with good specificity (97.3%, 95% CI 94.5-98.7 and 98.8%, 95% CI 95.7-99.8) within 2 and 4 years, respectively.

Women with a cycle less regular than it had been at age 40 (e) showed sensitivity/specificity for prediction of MP within 2 and 4 years of 87.1% (95% CI 71.2-95.5)/74.2% (95% CI 68.4-79.3) and 72.6% (CI 95% 59.7-82.4)/84.8% (95% CI 78.4-89.6), respectively.

If a change in the duration or heaviness of menstrual flow compared with age 40 (f) has been detected, the sensitivity was good (MP within 2 years: 90.9% (95% CI 76.1-97.5), MP within 4 years: 87.7% (95% CI 77.1-94.2), accompanied by poor specificity (MP within 2 years: 23% (95% CI 18.2-28.5), MP within 4 years: 26% (95% CI 19.9-33.2)).

The sensitivity was poor when using climacteric symptoms like hot flashes or night sweats during the previous week (30.3% (95% CI 16.1-48.5) and 23.1% (95% CI 14.3-35.3)), while the specificity was good (86.2% (95% CI 81.4-89.9) and 87.1% (95% CI 81.3-91.6)) within 2 years and 4 years, respectively.

Supplementary Table 1. Characteristics of the 14 included studies.

Author, Year of Publication	Country	Study design	Funding source	Number of participants	Range of Age at start	Exclusion criteria
Broer, 2011	The Netherlands	Three prospective cohort studies	No external funds	185	21-46	Exclusion criteria for cohort number 1: ovarian surgery or ovarian abnormalities. Exclusion criteria for cohort number 2: adnexal surgery or a history of infertility Exclusion criteria for cohort number 3: endocrine disorders, relevant disease or infertility treatment. In addition, Women who were using hormone therapy for medical reasons or as contraceptives or hormonal replacement therapy were excluded. Also, women who underwent surgery leading to removal of the uterus and/or one or both ovaries were excluded from the analysis.
de Kat, 2019	The Netherlands	Doetinchem Cohort Study	National Institute for Public Health and the Environment, which works under the authority of the Ministry of Health, Welfare, and Sport of the Netherlands.	2434	Mean age:36.1 ± 8.1	Women without an available blood sample, women who experienced surgical menopause (i.e., a bilateral oophorectomy), women with an age at menopause or hysterectomy before the baseline visit, and women with an unknown menopausal status (e.g., due to undergoing a hysterectomy after initiation of the study).
Depmann, 2016	The Netherlands	Three prospective cohort studies	No external funds	155	21-46	Exclusion criteria for cohort number 1: ovarian surgery or ovarian abnormalities. Exclusion criteria for cohort number 2: adnexal surgery or a history of infertility. Exclusion criteria for cohort number 3: endocrine disorders, relevant disease or infertility treatment. In addition, women who underwent surgical removal of the uterus or one or both ovaries, either at baseline or at the most recent follow up were excluded from analyses.

Author, Year of Publication	Country	Study design	Funding source	Number of participants	Range of Age at start	Exclusion criteria
Dolleman, 2014 **(study group 2)**	The Netherlands	two pooled cohort of women	No external funds	150	Median: 35.5 (33-38.5)	Women who underwent gynaecological surgery were censored at the time of operation, and women taking hormonal medication were censored at the age at treatment initiation. If this information was missing, these women were excluded.
Dolleman, 2015	The Netherlands	Doetinchem Cohort Study	National Institute for Public Health and the Environment which works under the authority of the Ministry of Health, Welfare and Sport of The Netherlands	1163	20-59	Women were excluded if they were post-menopausal at the start of the study, if they had undergone hysterectomy or (uni-or bilateral) oophorectomy, if information on their reproductive status or AMH was missing at baseline, or if they did not participate in the third and fourth examination round.
Finkelstein, 2020	USA	SWAN cohort	National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH)	1537	42-63	Having a hysterectomy, bilateral ovariectomy, or taking hormone therapy. In addition for 1108 women, a blood sample was obtained after the FMP but before 365 days without menstrual bleeding had elapsed, so that, at the time these blood samples were obtained, the date of the FMP had not yet been established.
Gohari, 2016	Iran	TLGS cohort	No external funds	266	20-50	History of endocrine disorders, hysterectomy, oophorectomy, or any other kind of ovarian surgery.
Greendale, 2013	USA	SWAN cohort	National Institutes of Health, Department of Health and Human Services, National Institute on Aging, National Institute of Nursing Research,	554	42-52	Use of medications that affect menstruation or endogenous hormones, pregnancy, no menstrual period in the 3 months before, no intact uterus, no ovaries.

Author, Year of Publication	Country	Study design	Funding source	Number of participants	Range of Age at start	Exclusion criteria
			Office of Research on Women's Health			
Kim, 2016	USA	Cohort from CARDIA	National Institutes of Health	426	18-30	Lack of ovaries, pregnancy.
Taylor, 2004	USA	Cohort	National Institute on Aging	326	44-56	Intake of hormonal medication during the year before, chemotherapy, radiotherapy, pregnancy
Tehrani, 2014	Iran/Nether-lands	TLGS cohort and Glucose Study, the Scheffer/ van Rooij/de Vet	Andromed, Ardana, Auxogyn, Ferring, Gedeon Richter, Genovum, Merck Serono, MSD, Organon, Pantharei Bioscience, PregLem, Roche, Schering, Schering Plough, Watson Laboratories, Wyeth	SRV: 185 TLGS: 266	SRV: 21-46 TLGS: 20-50	Irregular or unpredictable cycles, history of infertility or endocrine disorders, use of contraceptives for at least 3 months, history of ovarian or uterine surgery.
Tehrani, 2020	Iran	TLGS cohort	n.r.	959	20-50	History of hysterectomy, oophorectomy or any other kind of ovarian surgery, irregular and unpredictable menstrual cycles, age < 20 or > 50y.
van Rooij, 2004	Netherlands	Cohort of a longitudinal study on ovarian function	n.r.	81	25-46	Infertility, use of hormonal contraceptives 3 months before the study, ovarian surgery, ovarian abnormalities.
Tehrani, 2021	Iran	TLGS cohort	n.r.	901	18-50	being currently pregnant; a history of hysterectomy, oophorectomy, or any type of ovarian surgery; premature menopause before the age of 40 years; all those women age < 40 at the end of study; current use of psychotropic or hormonal medications, including

Author, Year of Publication	Country	Study design	Funding source	Number of participants	Range of Age at start	Exclusion criteria
						hormonal contraceptives or hormone therapies; and serious diseases known to interfere with the ovarian function, such as breast or endometrial cancer and endocrine disorders.

Abbreviations: n.r., not reported; SWAN, The Study of Women's Health Across the Nation; TLGS, Tehran Lipid and Glucose Study; SRV, the Scheffer/van Rooij/de Vet

Supplementary Table 2. Details of the prediction models of 14 included studies to predict menopause onset.

Study	Sample size	Number and percentage of women reaching menopause	Follow up period (years)	Time period	Prediction time (years)	Model	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	C-Statistics (95% CI)
Broer, 2011	185	48 (25.9%)	11	1996-2010	n.r.	Univariable:	-	-	-	+
						Age	-	-	-	0.87
						AMH	-	-	-	0.86
						AFC	-	-	-	0.84
						FSH	-	-	-	0.70
						Multivariate (adjusted for age):	-	-	-	+
						AMH	-	-	-	0.90
						AFC	-	-	-	0.88
						FSH	-	-	-	0.88
De Kat, 2019	2434 [a]	1298 (53%)	20	1987-2019	n.r.	AMH	-	-	-	0.70 (0.68-0.72)
						AMH + OC use + and smoking	-	-	-	0.70 (0.68-0.72)
						AMH decline rate	-	-	-	0.65 (0.63-0.67)
						AMH + OC use + smoking + decline rate	-	-	-	0.70 (0.68-0.72)
						AMH + OC use + smoking + decline rate + decline rate × age interaction	-	-	-	0.70 (0.68-0.71)
						AMH at age 20	-	-	-	0.62 (0.60-0.64)
						AMH at age 25	-	-	-	0.64 (0.62-0.66)
						Decline rate age between age 20-25	-	-	-	0.70 (0.68-0.71)
						AMH and decline rate between age 20-25	-	-	-	0.69 (0.67-0.70)

						AMH at age 30	-	-	-	0.70 (0.69-0.72)
						Decline rate between age 25-30	-	-	-	0.70 (0.68-0.71)
						AMH and decline rate between age 25-30	-	-	-	0.70 (0.68-0.71)
						AMH at age 35	-	-	-	0.71 (0.69-0.72)
						Decline rate between age 30-35	-	-	-	0.70 (0.68-0.72)
						AMH and decline rate between age 30-35	-	-	-	0.70 (0.69-0.72)
Depmann, 2016	155	81 (52.2%)	14	1992-2013	n.r.	Univariable:	-	-	-	+
						Age at baseline	-	-	-	0.85
						FSH	-	-	-	0.66
						AMH	-	-	-	0.78
						AFC	-	-	-	0.79
						Multivariate (adjusted for age at baseline):	-	-	-	+
						FSH	-	-	-	0.85
						AMH	-	-	-	0.86
						AFC	-	-	-	0.85
						Multivariate (adjusted for age and smoking at baseline):	-	-	-	+
						FSH	-	-	-	0.85
						AMH	-	-	-	0.87
						AFC	-	-	-	0.85
						Multivariate (adjusted for age and smoking at follow-up):	-	-	-	+
						FSH	-	-	-	0.86
						AMH	-	-	-	0.87
						AFC	-	-	-	0.85
	150	46 (30.6%)	12	n.r.	n.r	Univariable:	-	-	-	+

Dolleman, 2014 (**study group 2**)						Daughter's age	-	-	-	0.84 (0.78-0.90)
						Mother's ANM	-	-	-	0.63 (0.54-0.72)
						Daughter's AMH	-	-	-	0.86 (0.81-0.91)
						Multivariate:	-	-	-	+
						Daughter's age + mother's ANM	-	-	-	0.85 (0.79-0.91)
						Daughter's age + daughter's AMH	-	-	-	0.91 (0.88-0.94)
						Daughter's age + mother's ANM + daughter's AMH	-	-	-	0.92 (0.88-0.96)
Dolleman, 2015	1163 [b]	527 (45.3%)	10	1993-2007	n.r	Age	-	-	-	0.88
						Age + BMI + packyears of smoking + menstrual cycle status	-	-	-	0.89
						AMH + age + BMI + packyears of smoking + menstrual cycle status	-	-	-	0.91
Finkelstein, 2020	1537	n.r	2	1996-1998	1	AMH + age + BMI	-	-	0.881 (0.873-0.889)	-
						FSH + age + BMI	-	-	0.885 (0.876-0.893)	-
					2	AMH + age + BMI	-	-	0.891 (0.884-0.900)	-
						FSH + age + BMI	-	-	0.877 (0.869-0.885)	-
					3	AMH + age + BMI	-	-	0.896 (0.889-0.903)	-

						FSH + age + BMI	-	-	0.871 (0.864-0.880)	-
					1	AMH <10 pg/mL for women age <48 years	71 (64-78)	-	-	-
					2	AMH <10 pg/mL for women age <48 years	60 (53-66)	-	-	-
					3	AMH <10 pg/mL for women age <48 years	47 (42-53)	-	-	-
					1	AMH <10 pg/mL for women age 48-51 years	73 (68-77)	-	-	-
					2	AMH <10 pg/mL for women age 48-51 years	62 (58-66)	-	-	-
					3	AMH <10 pg/mL for women age 48-51 years	54 (50-57)	-	-	-
					1	AMH <10 pg/mL for women age ≥51 years	82 (78-85)	-	-	-
					2	AMH <10 pg/mL for women age ≥51 years	75 (72-79)	-	-	-
					3	AMH <10 pg/mL for women age ≥51 years	70 (66-73)	-	-	-
					1	AMH <100 pg/mL for women age <48 years	-	65 (61-68)	-	-
					2	AMH <100 pg/mL for women age <48 years	-	70 (66-73)	-	-
					3	AMH <100 pg/mL for women age <48 years	-	76 (72-80)	-	-
					1	AMH <100 pg/mL for women age 48-51 years	-	46 (42-50)	-	-
					2	AMH <100 pg/mL for women age 48-51 years	-	57 (52-62)	-	-
					3	AMH <100 pg/mL for women age 48-51 years	-	68 (62-74)	-	-
					1	AMH <100 pg/mL for women age ≥51 years	-	27 (22-32)	-	-
					2	AMH <100 pg/mL for women age ≥51 years	-	39 (31-47)	-	-

					3	AMH <100 pg/mL for women age ≥51 years	-	53 (42-64)	-	-
Gohari, 2016	266	63 (23.7 %)	6.5	1999-2006	3	AMH + age at making prediction was 43	-	-	0.987	-
						AMH + age at making prediction was 45	-	-	0.932	-
						AMH + age at making prediction was 47	-	-	0.961	-
						AMH + age at making prediction was 49	-	-	0.881	-
					4	AMH + age at making prediction was 43	-	-	0.969	-
						AMH + age at making prediction was 45	-	-	0.939	-
						AMH + age at making prediction was 47	-	-	0.939	-
						AMH + age at making prediction was 49	-	-	0.863	-
					5	AMH + age at making prediction was 43	-	-	0.967	-
						AMH + age at making prediction was 45	-	-	0.948	-
						AMH + age at making prediction was 47	-	-	0.867	-
						AMH + age at making prediction was 49	-	-	0.807	-
Greendale, 2013	554	n.r	10	1996-2007	2 years before FMP [c]	FSH + Estradiol Treshold > 0.3 Treshold > 0.4 Treshold > 0.5 Treshold > 0.6	 85 75 67 59	 77 89 96 98	0.775	-
					1 year before FMP [d]	FSH + Estradiol Treshold > 0.3 Treshold > 0.4 Treshold > 0.5 Treshold > 0.6	 80 75 72 62	 92 95 96 97	0.819	-
					FMP [e]	FSH + Estradiol Treshold > 0.3	 89	 90	0.855	-

						Treshold > 0.4 Treshold > 0.5 Treshold > 0.6	84 70 52	92 94 97		
	472	n.r.	10	1996-2007	2 years before FMP [c]	N-telopeptide	-	-	0.594	-
					1 year before FMP [d]	N-telopeptide	-	-	0.617	-
					FMP [e]	N-telopeptide	-	-	0.669	-
					2 years before FMP [c]	FSH + Estradiol + N-telopeptide	-	-	0.778	-
					1 year before FMP [d]	FSH + Estradiol + N-telopeptide	-	-	0.822	-
					FMP [e]	FSH + Estradiol + N-telopeptide	-	-	0.863	-
	552	n.r.	10	1996-2007	2 years before FMP [c]	FSH + Estradiol + age + menopause transition stage + race/ethnicity + time of venipuncture (in early follicular phase = cycle days 2-5 = in-window)	-	-	0.902	-
					1 year before FMP [d]	FSH + Estradiol + age + menopause transition stage + race/ethnicity + time of venipuncture (in early follicular phase = cycle days 2-5 = in-window)	-	-	0.926	-
					FMP [e]	FSH + Estradiol + age + menopause transition stage + race/ethnicity + time of venipuncture (in early follicular phase = cycle days 2-5 = in-window)	-	-	0.945	-
Kim, 2016	426 [f]	n = 55, 13%	10	2001-2011	5	Age	-	-	-	0.83
						Age + AMH	-	-	-	0.91
						Age + AFC	-	-	-	0.84
						Age + FSH	-	-	-	0.86
						Age + AMH + FSH	-	-	-	0.91
						Age + FSH + AFC	-	-	-	0.86

						Age + AMH + AFC	-	-	-	0.91
						Age + AMH + FSH + AFC	-	-	-	0.91
	359 [g]	n.r.	10	2001-2011	5	Age	-	-	-	0.82
						Age + AMH	-	-	-	0.91
						Age + AFC	-	-	-	0.84
						Age + FSH	-	-	-	0.86
						Age + AMH + FSH	-	-	-	0.92
						Age + FSH + AFC	-	-	-	0.87
						Age + AMH + AFC	-	-	-	0.91
						Age + AMH + FSH + AFC	-	-	-	0.92
	327 [h]	n.r.	10	2001-2011	5	Age	-	-	-	0.81
						Age + AMH	-	-	-	0.91
						Age + AFC	-	-	-	0.82
						Age + FSH	-	-	-	0.84
						Age + AMH + FSH	-	-	-	0.91
						Age + FSH + AFC	-	-	-	0.84
						Age + AMH + AFC	-	-	-	0.91
						Age + AMH + FSH + AFC	-	-	-	0.91
	306 [i]	n.r.	10	2001-2011	5	Age	-	-	-	0.86
						Age + AMH	-	-	-	0.94
						Age + AFC	-	-	-	0.86
						Age + FSH	-	-	-	0.89
						Age + AMH + FSH	-	-	-	0.94
						Age + FSH + AFC	-	-	-	0.89
						Age + AMH + AFC	-	-	-	0.95
						Age + AMH + FSH + AFC	-	-	-	0.95
Taylor, 2004	326	n.r.	4.8	1993-1997	Within 2 years	More than 90 days since the most recent menstrual period	40.6 (24.7-58)	99.2 (97.2-99.9)	-	-

					Within 4 years	More than 90 days since the most recent menstrual period	21.9 (13.1-33.5)	100 (97.8-100)	-	-
					Within 2 years	60 or more days of amenorrhea during the previous year	93.9 (80.6-98.9)	90.8 (86.7-94.0)	-	-
					Within 4 years	60 or more days of amenorrhea during the previous year	64.6 (52.3-75.5)	97.1 (93.4-98.9)	-	-
					Within 2 years	Cycle lengths that varied by 19 or more days	100 (89.5-100)	76.1 (70.3-81.2)	-	-
					Within 4 years	Cycle lengths that varied by 19 or more days	76.2 (64.4-85.3)	87.7 (81.7-92.1)	-	-
					Within 2 years	Cycle length too variable to report a usual length	48.5 (31.6-65.3)	97.3 (94.5-98.7)	-	-
					Within 4 years	Cycle length too variable to report a usual length	29.3 (19.0-41.5)	98.8 (95.7-99.8)	-	-
					Within 2 years	Cycles less regular than they had been at age 40	87.1 (71.2-95.5)	74.2 (68.4-79.3)	-	-
					Within 4 years	Cycles less regular than they had been at age 40	72.6 (59.7-82.4)	84.8 (78.4-89.6)	-	-
					Within 2 years	Change in the duration or heaviness of menstrual flow compared with age 40	90.9 (76.1-97.5)	23 (18.2-28.5)	-	-
					Within 4 years	Change in the duration or heaviness of menstrual flow compared with age 40	87.7 (77.1-94.2)	26 (19.9-33.2)	-	-
					Within 2 years	Hot flashes or night sweats during the previous week	30.3 (16.1-48.5)	86.2 (81.4-89.9)	-	-
					Within 4 years	Hot flashes or night sweats during the previous week	23.1 (14.3-35.3)	87.1 (81.3-91.6)	-	-
					Within 2 years	Age ≥ 50 years	42.4 (26.8-60.0)	87.4 (82.9-91.1)	-	-
					Within 4 years	Age ≥ 50 years	40 (28.3-52.3)	94.8 (90.2-97.4)	-	-
Tehrani, 2014	185	n = 48, 25.9%	11	n.r.	n.r.	Age + AMH (SRV model on SRV data)	-	-	-	73 (65-82)
	266	n = 63, 23.7%	6	n.r.	n.r.	Age + AMH (SRV model on TLGS data)	-	-	-	82 (75-88)
	266	n = 63, 23.7%	6	n.r.	n.r.	Age + AMH (TLGS model on TLGS data)	-	-	-	88 (83-94)

	185	n = 48, 25.9%	11	n.r.	n.r.	Age + AMH (TLGS model on SRV data)	-	-	-	72 (63-81)
Tehrani, 2020	959	n = 529, 55.2%	14	1998-?	n.r.	Age + AMH	-	-	-	70 (67-71)
						Age + AMH + annual AMH decline rate	-	-	-	78 (75-80)
						Age + Age-specific-AMH + annual AMH decline rate	-	-	-	72 (69-74)
						Age + AMH + annual AMH decline rate + sample storage time	-	-	-	81 (79-83)
van Rooij, 2004	81	N = 14 had cycle fluctuations	5	1996-?	4	Age	-	-	82 (71-93)	-
						AMH	-	-	87 (79-96)	-
						Age + AMH	-	-	89 (81-97)	-
						AFC	-	-	80 (69-91)	-
						Age + AFC	-	-	84 (73-94)	-
						FSH	-	-	72 (56-88)	-
						Age + FSH	-	-	84 (74-94)	-
						Inhibin B	-	-	76 (63-89)	-
						Age + Inhibin B	-	-	88 (78-98)	-
						Estradiol	-	-	55 (35-75)	-
						Age + Estradiol	-	-	83 (72-94)	-
						Age + AMH + Inhibin B	-	-	92 (86-99)	-
Tehrani, 2021	901	522	18	1998-2016	n.r	Baseline AMH value + age at baseline + storage time of baseline AMH	-	-		0.71(0.69-0.73)
						Baseline AMH+ Second AMH value + age at baseline + storage times of baseline + second AMH measures	-	-	-	0.7(0.68-0.72)
						Baseline AMH +Log(annual AMH decline rate) + age at baseline + storage times of baseline + second AMH measures	-	-	-	0.74 (0.71–0.76)
						Baseline AMH+ Second AMH value + Log(annual AMH decline rate) +	-	-	-	0.73 (0.70–0.75)

						age at baseline + storage times of baseline + second AMH measures				
						AMH value + age at baseline	-	-	-	0.64 (0.61–0.67)
						AMH values + age at baseline + storage time of AMH)	-	-	-	0.85 (0.83–0.87)
						Log (annual AMH decline rate) + age at baseline + storage time of AMH)	-	-	-	0.84 (0.83–0.85)
						AMH value + Log (annual AMH decline rate) + age at baseline + storage time of AMH)	-	-	-	0.85 (0.83–0.87)

Abbreviations: CI, Confidence interval; AUC, Area under the curve; FSH, Follicle stimulation hormone; AMH, Anti-Mullerian Hormone; AFC, Antral follicle count; ANM, age at natural menopause; OC, oral contraceptive; ANM, age at natural menopause; n.r., not reported

[a] Women who were using oral contraceptives were also included in the final analysis.

[b] Pregnant women, women who were taking hormonal replacement therapy and OC users were also included in the final analysis.

[c] Equals 3 years before menopause onset

[d] Equals 2 years before menopause onset

[e] Equals 1 year before menopause onset

[f] All women

[g] Women not using estrogen

[h] Women with regular menses only

[i] No women with dominant follicle

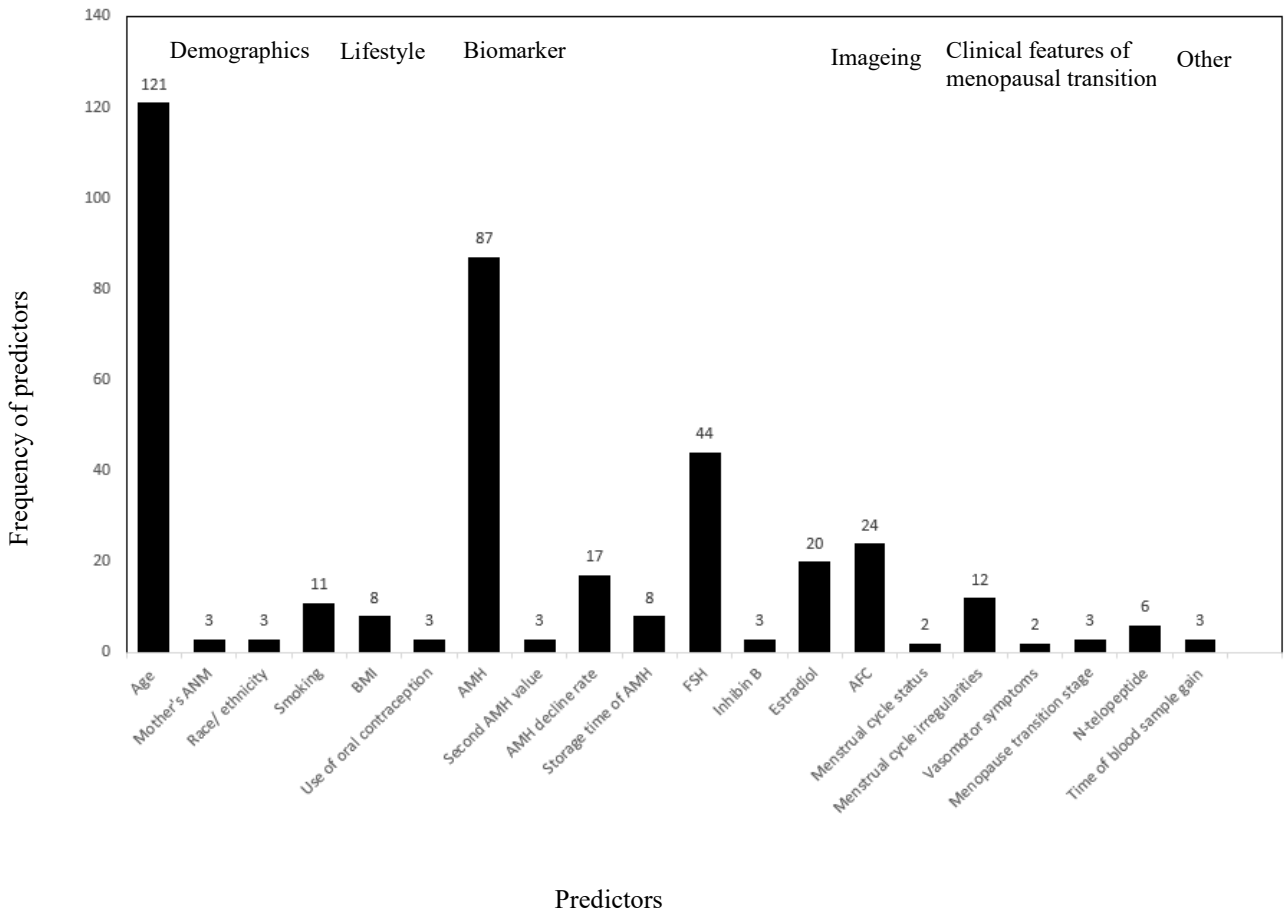
Supplementary Table 3. The detailed summary of risk of bias (ROB) assessment for included studies according to the Prediction model Risk Of Bias Assessment Tool (PROBAST).

Study	Participants		ROB	AP	Predictors			ROB	AP	Outcome						ROB	AP	Analysis									ROB	Overall AP	Overall ROB
Broer, 2011	✓	✓	✓	✓	×	✓	×	×	×	✓	✓	✓	✓	✓	?	?	✓	✓	✓	✓	×	✓	✓	×	×	?	×	×	×
de Kat, 2019	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	✓	?	?	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	?	✓	×
Depmann, 2016	✓	✓	✓	✓	×	✓	×	×	×	✓	✓	✓	✓	✓	?	?	✓	✓	✓	✓	×	✓	✓	×	×	?	×	×	×
Dolleman, 2014	✓	✓	✓	✓	×	✓	×	×	×	✓	✓	✓	✓	✓	?	?	✓	✓	✓	✓	×	✓	✓	×	×	✓	×	×	×
Dolleman, 2015	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	✓	?	?	✓	✓	✓	✓	✓	✓	?	×	✓	✓	×	✓	×
Finkelstein, 2020	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	×	×	✓	×	×	✓	?	×	✓	×
Gohari, 2016	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	×	✓	?	✓	×	?	×	✓	×
Greendale, 2013	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	?	×	✓	×	✓	×	?	×	✓	×
Kim, 2016	✓	✓	✓	✓	✓	✓	×	×	✓	✓	?	?	✓	✓	✓	?	?	×	✓	✓	×	✓	×	×	✓	?	×	?	×
Taylor, 2004	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	?	✓	?	?	?	✓	✓	×	×	?	×	×	?	×	?	×
Tehrani, 2014	✓	✓	✓	✓	×	✓	×	×	×	✓	✓	✓	✓	✓	?	?	✓	✓	✓	✓	×	✓	✓	✓	✓	?	×	×	×
Tehrani, 2020	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	✓	?	?	✓	✓	✓	✓	?	✓	?	✓	✓	✓	?	✓	×
van Rooij, 2004	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	?	×	✓	×	×	✓	×	×	✓	×
Tehrani, 2021	✓	✓	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	✓	?	?	✓	✓	✓	✓	✓	✓	✓	×	×	?	×	✓	×

✓ ? ×

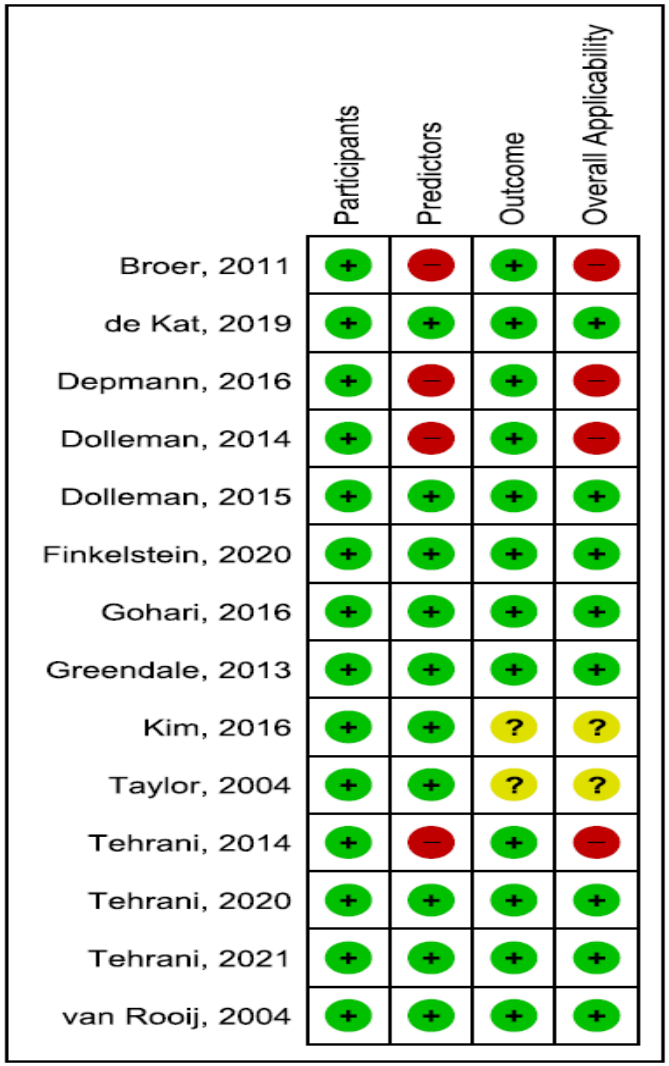
Abbreviations: ROB, risk of bias; AP, applicability

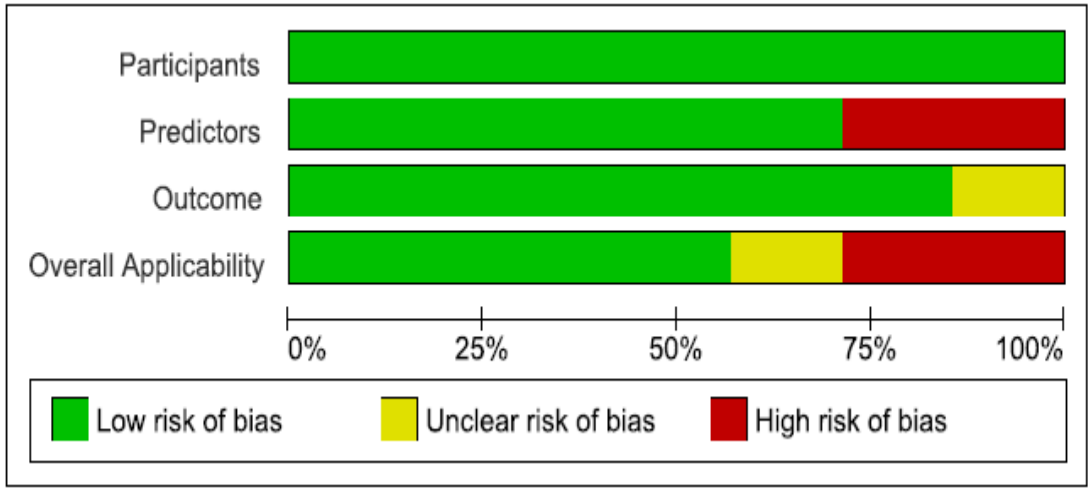
✓ indicates low ROB/low concern regarding applicability
× indicates high ROB/high concern regarding applicability
? indicates unclear ROB/unclear concern regarding applicability



Supplementary Figure 1. Frequency of predictors used in prediction models.

ANM; age of natural menopause, BMI: body mass index, AMH; anti-müllerian hormone, FSH; follicle-stimulating hormone, AFC; antral follicle count





Supplementary Figures 2 and 3. Summary of applicability of 14 included studies.

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