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Review

Calcium and Vitamin D Supplementation for Prevention of Preeclampsia: A Systematic Review and Network Meta-Analysis

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Received: 1 September 2017; Accepted: 13 October 2017; Published: 18 October 2017

Abstract: Vitamin D supplementation effects with or without calcium in pregnancy for reducing risk of preeclampsia and gestational or pregnancy induced hypertension are controversial. Literature was systematically searched in Medline, Scopus and Cochrane databases from inception to July 2017. Only randomized controlled trials (RCTs) in English were selected if they had any pair of interventions (calcium, vitamin D, both, or placebo). Systematic review with two-step network-meta-analysis was used to indirectly estimate supplementary effects. Twenty-seven RCTs with 28,000 women were eligible. A direct meta-analysis suggested that calcium, vitamin D, and calcium plus vitamin D could lower risk of preeclampsia when compared to placebo with the pooled risk ratios (RRs) of 0.54 (0.41, 0.70), 0.47 (0.24, 0.89) and 0.50 (0.32, 0.78), respectively. Results of network meta-analysis were similar with the corresponding RRs of 0.49 (0.35, 0.69), 0.43 (0.17, 1.11), and 0.57 (0.30, 1.10), respectively. None of the controls were significant. Efficacy of supplementation, which was ranked by surface under cumulative ranking probabilities, were: vitamin D (47.4%), calcium (31.6%) and calcium plus vitamin D (19.6%), respectively. Calcium supplementation may be used for prevention for preeclampsia. Vitamin D might also worked well but further large scale RCTs are warranted to confirm our findings.

Keywords: calcium; network meta-analysis; gestational hypertension; preeclampsia; prevention; systematic review; vitamin D

1. Introduction

Preeclampsia is a new onset of high blood pressure with proteinuria with/without end-organ or utero-placental dysfunction after 20 weeks of gestation. It is one of the major contributing causes of maternal-fetal morbidity and mortality worldwide [1]. Globally, 4.6% and 1.4% of all pregnancies developed preeclampsia and eclampsia, respectively [2]. The incidence in developed countries was approximately 3.4% [3], whereas it was varied from 1.8% to 16.7% in developing countries [4,5].

Approximately 10% to 15% of maternal death is directly associated with preeclampsia or eclampsia in low- and middle-income countries [6], whereas it was approximately one per 100,000 live births in developed countries [7]. It also related to life-threatening unfavorable outcomes in both mother (e.g., placental abruption, preterm delivery and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, etc.) and fetus (e.g., preterm birth, stillbirth, low birth weight, and small for gestational age, etc.) [8].

Previous evidence showed an inverse relationship between high blood pressure and calcium intake [9,10]. Numerous epidemiological and clinical studies [9–11], and later a series of systematic reviews [12–15] also demonstrated this association. Their results have suggested that calcium supplements (≥1 g/day) could lower the risk of preeclampsia [14]. As a result, the World Health Organization (WHO) has recommended to supplement calcium for pregnant women especially to high-risk population with a low calcium diet [16].

Vitamin D is involved in regulating bone metabolism, absorption of calcium and phosphate, and maintenance of muscle function [17]. Therefore, there might be a benefit of vitamin D supplementation in prevention of preeclampsia. However, systematic reviews [18,19] of randomized controlled trials (RCTs) did not show any benefit in prevention of preeclampsia, whereas other two systematic reviews [20,21] of observational studies did. These discrepancy results could be due to confounding bias in the latter or insufficient power in the former.

Although these pieces of evidence suggest benefits from both calcium and vitamin D supplements, it is still unclear which supplement or a combination of them is most beneficial for preventing preeclampsia and gestational hypertension (GH) or pregnancy induced hypertension (PIH). We therefore conducted a systematic review and a network meta-analysis (NMA) of RCTs with the aims of directly and indirectly comparing the effect of supplementations of calcium, vitamin D, both, and neither on preeclampsia and GH/PIH.

2. Materials and Methods

A conventional pairwise meta-analysis can directly compare the efficacy or safety of exactly two treatments in head-to-head clinical trials that can comparative by use simple method of direct meta-analysis. However, in real practice, there are often many potential treatments for a single disease. NMA is an extension of standard pairwise meta-analysis that provides comprehensive comparative treatment effects by combining both direct and indirect evidence. Because of the possibility to combine evidence from different treatment comparisons, and because they can identify the single best available treatment for decision-making, NMA are becoming increasingly attractive to clinicians.

This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA), extension of network meta-analyses [22]. The review protocol has been registered with the international prospective register of systematic review (PROSPERO number CRD42015025389).

2.1. Search Strategy

Studies were located from Medline via PubMed, Scopus databases, and Cochrane library/Cochrane Central Register of Controlled Trials. The search terms and strategies were constructed based on PICO (i.e., patient, intervention, comparator, and outcome) as described in detail in Appendix A. These strategies were modified to suit each search engine where appropriate.

Study identification was done in two phases. First, all previous systematic reviews of calcium and vitamin D supplementations in pregnant women published since inception of each database to July 2017 were identified. Then, only individual RCTs included in these previous reviews were selected. Second, all individual RCTs on the same topic published from inception to July 2017 were identified. The reference lists of the retrieved studies were also checked to identify more relevant publications. Where there were multiple publications from the same author(s) on the same topic, the most complete and recent study was included.

2.2. Study Selection

Identified studies from Medline, Scopus and Cochrane were imported into EndNote X7 and duplicate studies were removed. The selected studies were independently screened by title and abstract by two reviewers (W.K. and V.T.). Full texts were retrieved if decisions could not be reached from information provided in the abstract. Disagreements regarding selection were resolved by consensus or discussion with a third reviewer (S.A.V.). We contacted authors by email up to three times if data were insufficient. If there was no response after three attempts, then the study was excluded.

All RCTs conducted in humans and published in English were included if they met all of the following criteria: (1) included pregnant women of any gestational age; (2) compared outcomes of interest between any pair of the following supplementation groups: calcium, vitamin D, combined calcium and vitamin D, and placebo/no supplementation; and (3) had at least one of the outcomes of interest including preeclampsia, eclampsia, GH or PIH. Studies were excluded from the review if they were crossover trials, included multiple pregnancies, or after three unsuccessful attempts requesting data from authors in the case of insufficient data.

2.3. Interventions

Interventions were any of following supplements regardless of dosage and duration of supplements: calcium, vitamin D, combined calcium and vitamin D. The control group could be placebo, a standard supplementation (e.g., folic acid), or no supplementation.

2.4. Outcomes of Interest

The primary outcome of interest was preeclampsia, eclampsia, and GH/PIH, which were defined as per the original studies. Generally, preeclampsia was a new onset hypertension (i.e., systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg for two occasions at least 4 h apart) and any of the following: proteinuria (dipstick urine 2+ or ≥300 mg/24 h), end-organ dysfunction, or utero-placental dysfunction after 20 weeks of gestation [23]. An early-onset preeclampsia occurred before 34 weeks of gestation, otherwise it was a late-onset preeclampsia. Eclampsia is a convulsive condition occurring in preeclampsia patients. GH/PIH is a new onset hypertension presenting after 20 weeks of gestational age without significant proteinuria [23].

2.5. Data Extraction

Two reviewers (W.K. and V.T.) independently extracted the relevant data (participants, interventions and outcome characteristics) and these were recorded using a standardized data extraction form (Appendix B). Co-variables such as mean age, gestational age at enrolment and delivery, gravida, parity, body mass index (BMI), smoking, diabetes mellitus, and duration of supplementation were also extracted. If duration of supplementation was not reported, it was calculated by subtracting gestational age at delivery with gestational age at initiating. If gestational age at delivery of that study was not reported, mean gestational age at delivery, i.e., 38 weeks, was used. Data entry, cleaning and checking were performed separately for each reviewer. The two datasets were compared and validated, and any disagreement resolved by consensus.

2.6. Risk of Bias Assessment

Study quality was independently assessed by two reviewers (W.K. and V.T.) using the Cochrane Collaboration tool for assessing risk of bias in RCTs version 5.1.0 [24], see Appendix C. The following seven domains were evaluated: selection bias (sequence generation and concealment), performance bias (blinding of participants and assessors), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), selective outcome reporting, and other bias. Each item was classified as low, high, or an unclear risk of bias (if there was insufficient information).

2.7. Statistical Analysis

2.7.1. Direct Meta-Analysis

For studies reporting frequency data of supplementation and preeclampsia, log risk ratio (RR) along with its variance and the 95% confidence interval (CI) were estimated for each study. The RRs were then directly pooled across studies using fixed-effect model (i.e., inverse variance method) if heterogeneity was absent, otherwise a random-effect model (i.e., DerSimonian and Laird method) was used.

Heterogeneity was assessed by Cochrane's Q test and I^2 statistic, respectively. If it was present ($p < 0.1$ or $I^2 \geq 25\%$), a source of heterogeneity was explored by fitting characteristics of subjects (i.e., mean age, mean gestational age), clinical data (i.e., dosage, and duration of supplement), and methodological characteristics (i.e., definition of outcome measurements, setting of the study) in a meta-regression model one by one. Sensitivity analysis by excluding the outlier studies and/or a subgroup analysis according to that factor was performed.

2.7.2. Network Meta-Analysis

Network meta-analysis was applied to indirectly compare effects of supplementation. A two-stage multivariate meta-analysis was applied as follows: Coefficients (i.e., *lnRR*) and variance-covariance of treatment comparisons were estimated for each study using a Poisson model. These parameters were then pooled across studies using a multivariate meta-analysis with maximum likelihood function [25]. Between-study variance and covariance of comparisons were considered using unstructured method. Effects between active versus active supplementation were then compared using a linear combination of the multivariate meta-analysis model.

The inconsistency assumption (i.e., whether direct effects agree with the indirect effects) was checked and explored using a design-treatment interaction model, and an inconsistency factor (IF, i.e., $ln(RR_{direct})$-$ln(RR_{indirect}))$ was then estimated. Violation of consistency was assumed if the IF was significantly different from 0. All pairwise comparisons between direct and indirect effects, were estimated and displayed. In addition, small study effect for the whole network was assessed by constructing a comparison-adjusted funnel plot taking into account different comparisons [26]. This plots the difference of each study's i observed *ln(RR)* of newer versus older supplement (y_{iXY}) vs. the comparison's mean ln(RR, μ_{XY}) against its variance. Supplementations were coded from older to newer as 1, 2, 3, 4 for placebo, calcium, vitamin D, and calcium plus vitamin D, respectively. In the absence of small-study effects, we expected the studies to form an inverted funnel centered at zero, i.e., the comparison-adjusted funnel plot should be symmetrical around the zero line. Finally, a predictive probability of best intervention was estimated using surface under a cumulative ranking curve (SUCRA). Efficacy of supplementation was then ranked by predicting probability.

All analyses were performed using STATA version 14.2 [27]. p-values < 0.05 were considered as statistically significant, except for the test of heterogeneity where $p < 0.10$ was used.

3. Results

3.1. Study Selection and Characteristics

The schema for selection of studies is displayed in Figure 1. Searching for previous systematic reviews identified 188 review studies. Among these, 159 review studies were excluded for reasons describe in Figure 1, leaving 29 review studies with individual 71 RCTs that were eligible for further assessment. In searching for individual studies, 535 studies were identified for screening titles and abstracts. Among these, 460 studies were excluded leaving 75 individual RCTs that met inclusion criteria for further assessment. After removing duplicates with searching from systematic reviews, 78 RCTs were eligible for assessing full-text. Of these, only 27 RCTs studies met our inclusion criteria

and were considered for quantitative synthesis. Among these, 12, 3, and 12 RCTs studies reported preeclampsia, GH or PIH, and both outcomes, respectively.

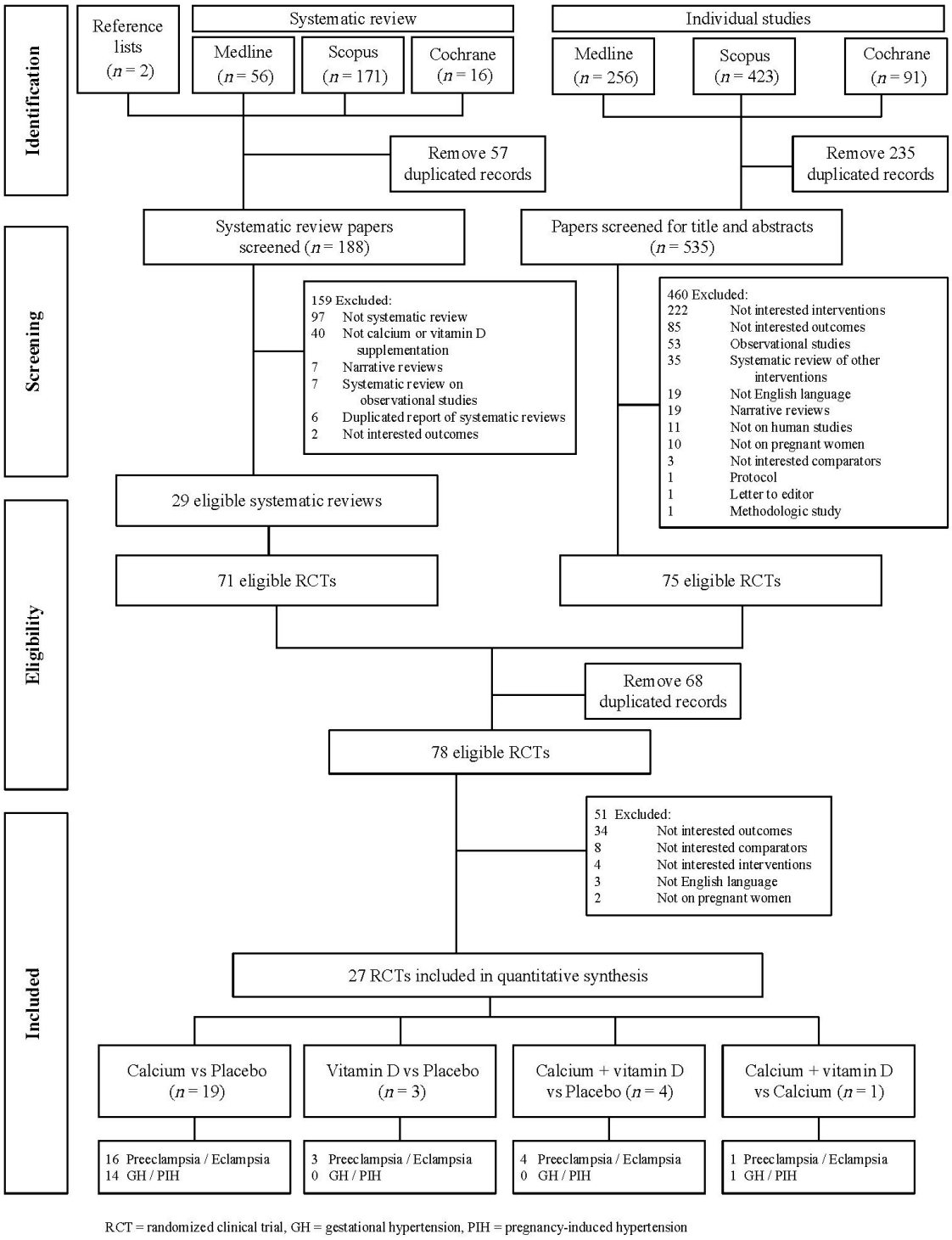

Figure 1. Flow of selection of studies.

The characteristics of the 27 RCTs are described in Table 1. Among these, 19 studies (n = 26,299) compared calcium vs. placebo [11,28–45], three studies (n = 357) [46–48] compared vitamin D vs. placebo, four studies (n = 1169) [49–52] compared calcium plus vitamin D vs. placebo, and one study (n = 175) [53] compared calcium plus vitamin D vs. calcium.

Table 1. Characteristics of included studies.

Author (Year)	Country	Outcome	Study Period (Months)	Type of Pregnancy	*n* Control	*n* Intervention	Supplement Started GA (Weeks)	Mean Age (Years)	Mean GA at Enrolment (Weeks)	Mean GA at Delivery (Weeks)	SBP (mmHg)	DBP (mmHg)	BMI (kg/m^2)	Weight Gain (g/Week)	Nulliparity (%)
Calcium vs. Placebo															
Aghamohammadi (2015) [28]	Iran	PE	-	High Risk Women	40	40	<20 weeks	37.15	-	-	-	-	26.8	-	-
Almirante (1998) [29]	Philippines	PE	-	High Risk Women	210	212	<20 weeks	-	18.00	-	-	-	-	-	100.00
Bassaw (1998) [30]	Bangladesh	Both	36	Low Risk Women	250	81	<20 weeks	27	-	38.6	-	-	-	-	-
Belizan (1991) [31]	Argentina	Both	33	High Risk Women	588	579	≥20 weeks	23.70	20.80	-	103.95	66.45	-	-	100.00
Crowther (1999) [32]	Australian	Both	53	Low Risk Women	229	227	≥20 weeks	24.70	18.37	-	115.80	68.20	26.60	-	100.00
Kumar (2009) [33]	New Delhi	PE	36	Low Risk Women	251	273	<20 weeks	21.85	17.83	38.44	113.19	74.00	23.35	-	-
Levine (1997) [34]	US	Both	36	Low Risk Women	2294	2295	<20 weeks	21.00	17.15	38.90	106.50	59.70	-	-	100.00
Lopez-Jaramillo (1997) [35]	Ecuador	PE	56	High Risk Women	135	125	≥20 weeks	15.99	20.00	39.13	-	-	-	414.19	100.00
Lopez-Jaramillo (1990) [37]	Ecuador	Both	30	Low Risk Women	34	22	≥20 weeks	19.4	-	-	-	-	-	-	100.00
Lopez-Jaramillo (1989) [36]	Ecuador	GH/PIH	30	Low Risk Women	43	49	≥20 weeks	18.47	23.00	-	-	-	-	430.80	100.00
Nenad (2011) [38]	Serbia	Both	-	Low Risk Women	4588	4590	<20 weeks	-	18.50	-	-	-	-	-	100.00
Niromanesh (2001) [39]	Iran	Both	-	High Risk Women	15	15	≥20 weeks	23.15	29.70	38.60	-	-	-	-	-
Puwar (1996) [40]	India	Both	15	Low Risk Women	93	97	≥20 weeks	21.93	18.07	37.50	103.02	63.32	-	-	100.00
Rogers (1999) [41]	Hong Kong	GH/PIH	30	High Risk Women	75	144	≥20 weeks	27.31	21.67	38.9	-	-	-	-	100.00
Sanchez-Ramos (1994) [42]	Florida	Both	55	High Risk Women	34	29	≥20 weeks	18.38	24.44	-	113.50	64.01	-	-	100.00
Villar (1987) [11]	Baltimore, Argentina	GH/PIH	36	Low Risk Women	27	25	≥20 weeks	21.10	-	-	-	-	-	388.2	100.00
Villar (1990) [44]	Baltimore	Both	36	High Risk Women	88	90	≥20 weeks	16.25	23.55	38.55	102.75	61.10	-	-	85.26

Table 1. *Cont.*

Author (Year)	Country	Outcome	Study Period (Months)	Type of Pregnancy	*n* Control	*n* Intervention	Supplement Started GA (Weeks)	Mean Age (Years)	Mean GA at Enrolment (Weeks)	Mean GA at Delivery (Weeks)	SBP (mmHg)	DBP (mmHg)	BMI (kg/m^2)	Weight Gain (g/Week)	Nulliparity (%)
Villar (2006) [43]	Argentina, Egypt, India, Peru, South Africa, Vietnam	Both	21	Low Risk Women	4161	4151	<20 weeks	22.65	15.10	-	105.05	60.80	21.90	-	100.00
Wanchu (2001) [45]	India	PE	-	High Risk Women	50	50	≥20 weeks	-	14.2	-	111.57	72.45	-	-	100.00
Vitamin D vs. Placebo															
Asemi (2013) [46]	Iran	PE	4	High Risk Women	27	27	≥20 weeks	17.44	26	-	-	-	30.8	-	-
Naghshineh (2016) [47]	Iran	PE	5	High Risk Women	70	68	<20 weeks	25	-	37.4	-	-	-	-	100.00
Sablok (2015) [48]	India	PE	36	High Risk Women	57	108	<20 weeks	-	-	-	-	-	-	-	100.00
Calcium plus Vitamin D vs. Placebo															
Asemi (2012) [49]	Pakistan	PE	11	High Risk Women	25	24	≥20 weeks	24.9	-	-	-	-	27.58	-	100.00
Marya (1987) [50]	India	PE	-	Low Risk Women	200	200	≥20 weeks	-	22.00	-	-	-	-	-	-
Taherian (2002) [52]	Iran	PE	36	Low Risk Women	330	330	≥20 weeks	21.55	20.00	38.80	97.25	57.88	22.55	10.25 *	-
Samimi (2015) [51]	Iran	PE	6	High Risk Women	30	30	≥20 weeks	27.2	-	-	111.7	72.4	26.5	-	-
Calcium plus Vitamin D vs. Calcium															
Hossain (2014) [53]	Pakistan	Both	21	Low Risk Women	89	86	≥20 weeks	25.57	20.00	37.61	-	-	23.64	-	-

n = number of subjects, GA = Gestational Age (weeks), SBP = Mean Systolic Blood Pressure (mmHg), DBP = Mean Diastolic Blood Pressure (mmHg), BMI = Mean Body Mass Index (kg/m^2), PE = Preeclampsia only, GH/PIH = Gestational Hypertension or Pregnancy Induced Hypertension only, Both = Both PE or GH/PIH, * Mean weight gain in kg.

Cross-tabulated data for these interventions with preeclampsia and GH/PIH are described in Tables S1 and S2. Individual sample sizes ranged from 30 to 9178 with a median of 178. The types of pregnant women varied, 48.2% (13/27) of RCTs studies in low risk pregnancies and 51.9% (14/27) RCTs studies in high risk pregnancies, e.g., adolescent pregnancy, elderly pregnancy, and nulliparity. The mean age ranged from 16 to 37.2 years, and mean gestational age at enrolment and at delivery ranged from 14.2 to 29.7 and 37.4 to 39.1 weeks, respectively.

3.2. Risk of Bias Assessment

Risk of bias assessment was performed for each RCT (Table S3) and summarized in Figure S1. Among 27 RCTs, three studies [29,37,38] were conference abstracts, thus the risk of bias could not be assessed because authors did not publish full articles. In the remaining 24 studies, sequence generation was clearly described in 17 trials (70.8%), whereas five trials (20.8%) were unclear. Allocation concealment was adequately performed in 13 trials (54.2%). Most studies (16/24) reported about blinding of participants and blinding of outcome assessors, whereas 12 trials (50%) reported incomplete outcome data. Haft of RCTs (12/24) had low risk of bias for selective outcome reports, and intention-to-treat (ITT) analysis was used in 15/24 trials.

3.3. Direct Meta-Analysis

3.3.1. Preeclampsia

Direct comparisons with calcium vs. placebo, vitamin D vs. placebo and calcium plus vitamin D vs. placebo in preeclampsia were pooled across 16 RCTs (n = 12,876 vs. 13,060), three RCTs (n = 203 vs. 154) and four RCTs (n = 584 vs. 585), respectively. These corresponding pooled effects were 0.54 (95% CI: 0.41, 0.70), 0.47 (95% CI: 0.24, 0.89) and 0.50 (95% CI: 0.32, 0.78), respectively (see Figure S2a–e). This indicated that calcium, vitamin D and calcium plus vitamin D supplementations could reduce preeclampsia risk by approximately 46%, 53% and 50% when compared with placebo, respectively.

Sources of heterogeneity for the pooled calcium vs. placebo effect were explored using a meta-regression, as mentioned in the Materials and Methods Section. Only type of pregnancy (low versus high risk pregnancy) and duration of calcium supplementation (>18 vs. ≤18 weeks) could reduce the degree of heterogeneity from 72.6% to 61.84% and 61.51%, respectively. Subgroup analysis was therefore performed accordingly. The protective effect of calcium supplementation was greater in high risk pregnancies than low risk pregnancies with a pooled RR of 0.42 (95% CI: 0.28, 0.64) and 0.69 (95% CI: 0.52, 0.91), respectively (see Figure S2a). The calcium supplement effect was also higher in pregnant women whose supplement durations were 18 weeks or shorter but not for longer than 18 weeks with the pooled RRs of 0.36 (95% CI: 0.23, 0.54) and 0.69 (95% CI: 0.53, 0.91), see Figure S2b. In addition, subgroup analysis by country of setting (developing and developed countries) showed significant preventive effects of calcium in developing countries but not for developed countries with the pooled RR of 0.50 (95% CI: 0.35, 0.70) and 0.52 (95% CI: 0.26, 1.07), respectively (see Figure S2c).

3.3.2. GH/PIH

Fourteen RCTs compared effects of calcium vs. placebo on risk of GH or PIH (n = 12,394 vs. 12,519), but only one RCT compared calcium plus vitamin D versus calcium (see Table S2). Effects of calcium compared to placebo were heterogeneous (I^2 = 64.8%) with the pooled RR of 0.77 (95% CI: 0.65, 0.92). Sources of heterogeneity were next explored, as none were identified as a source of heterogeneity.

3.4. Network Meta-Analysis

Data from 24 RCTs were used in a network meta-analysis (see Table S1). Only studies on preeclampsia were included in indirect comparison, because there was a lack of RCT studies which reported on effect of vitamin D alone or combination with calcium for GH or PIH causing insufficient data for pooling.

All interventions were mapped in a network plot (Figure S3). The size of each node was proportional to the number of included studies, whereas the edge of each comparison was weighted by the number of pregnant women for that comparison. Two indirect comparisons were performed by "borrowing" data from common comparators in the network, i.e., vitamin D vs. calcium and calcium plus vitamin D vs. vitamin D, respectively.

The network meta-analysis indicated calcium significantly reduced risk of preeclampsia by 51% when calcium was used as prophylaxis when compared with placebo (RR of 0.49, 95% CI: 0.35, 0.69). Vitamin D alone also seemed to be as effective as calcium alone. It could reduce risk of preeclampsia by 57% when compared to placebo with a pooled RR of 0.43 (95% CI: 0.17, 1.11), but it was not statistically significant. When compared indirectly with placebo or no supplement, calcium plus vitamin D showed non-statistically significant reduction in preeclampsia (RR 0.57, 95% CI: 0.30, 1.10) (Figure 2).

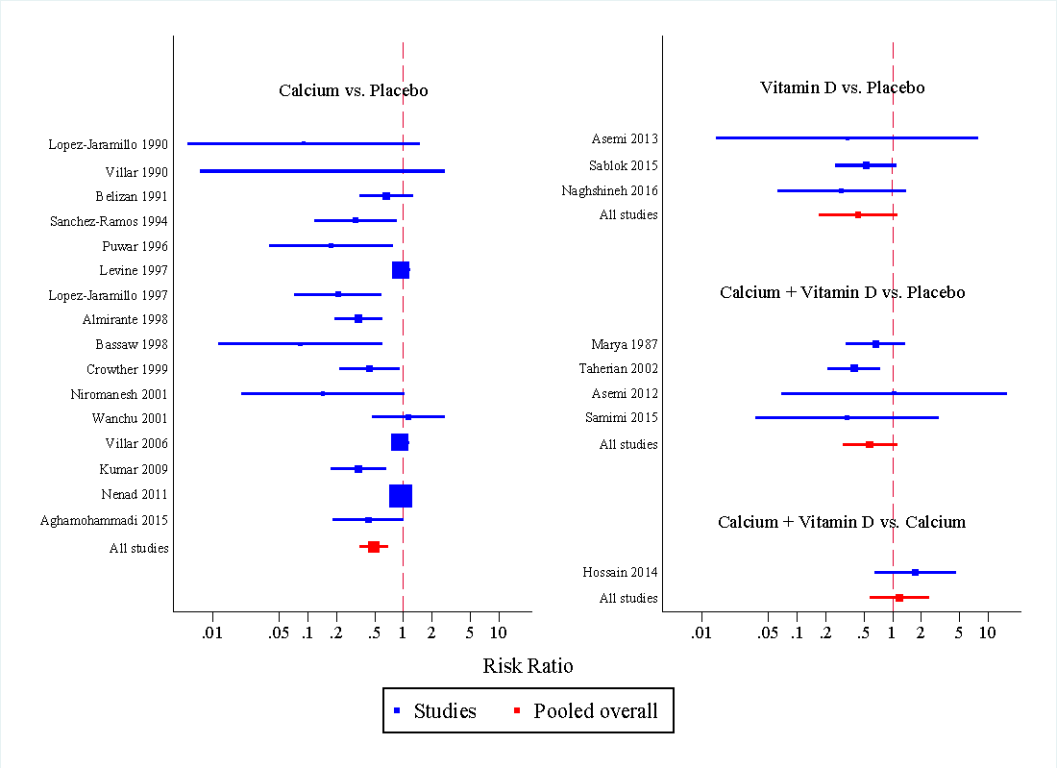

Figure 2. Forest plot of intervention effects compared to placebo on preeclampsia: a network meta-analysis.

All multiple comparisons were further estimated (Table 2) suggesting vitamin D alone seemed to be better than calcium supplement alone but this was not statistically significantly different with pooled RRs of 0.89 (95% CI: 0.33, 2.41). Combination of vitamin D with calcium did not seem effective on prevention of preeclampsia when compared with calcium alone (RR 1.18, 95% CI: 0.58, 2.37) or vitamin D alone (RR 1.33, 95% CI: 0.42, 4.18) (Table 2).

Ranking of all interventions was performed using the method of SUCRA, a summary statistic for the cumulative ranking and probability of ranking (Table 2 and Figure S4). SUCRA ranges from 0 to 1, where 1 reflects the best treatment with no uncertainty and 0 reflects the worst treatment with no uncertainty. Our findings suggested that vitamin D was the first rank, followed by calcium, and then calcium plus vitamin D. The estimated ranking probabilities for these corresponding supplements were 47.4%, 31.6%, and 19.6%, respectively. Furthermore, a design-by-treatment inconsistency model was applied which suggested that there was no evidence of inconsistency between direct and indirect effects (Chi-square test = 0.42, $p = 0.517$). In addition, transitivity was further indirectly assessed by exploring and comparing characteristics of pregnant women across four supplement arms (i.e., calcium

versus placebo, vitamin D versus placebo, calcium plus vitamin D versus placebo, and calcium plus vitamin D versus calcium (see Table S4)). This indicated that their characteristics were not much different; for instance, mean gestational age at initiating supplementation raged from 20 to 21.8 weeks, mean maternal age ranged from 21.2 to 25.6 years, and mean gestational age at delivery ranged from 37.4 to 38.8. However, mean BMI was quite different, which ranged from 23.6 to 30.8 kg/m^2.

Table 2. Estimation of multiple supplementation effects on preeclampsia.

Intervention	Calcium	Vitamin D	Calcium + Vitamin D
Calcium	0.49 (0.35 0.69) * {66.1, 31.6}	0.89 (0.33, 2.41) *†	1.18 (0.58, 2.37) *‡
Vitamin D		0.43 (0.17, 1.11) † {70.7, 47.4}	1.33 (0.42, 4.18) †‡
Calcium + Vitamin D			0.57 (0.30, 1.10) ‡ {52.2, 19.6}

Values are expressed as pooled RR along with 95% CIs in round parentheses; on diagonal cells comparing supplement vs. placebo, off the diagonal cells comparing column vs. row supplements; values < 1 indicates that the intervention listed in the column is more effective than the one in the row; Values in the diagonal in curly parentheses indicate surface under the cumulative ranking curve and the probability of being the best treatment. The larger is the surface under the cumulative ranking curve or probability of being the best treatment, the better is the treatment. * Calcium vs. Placebo: 16 RCTs, n = 12,876 vs. 13,060, number of PE cases = 722 vs. 931; † Vitamin D vs. Placebo: 3 RCTs, n = 203 vs. 154, number of PE cases = 20 vs. 14; ‡ Calcium + Vitamin D vs. Placebo: 4 RCTs, n = 584 vs. 585, number of PE cases = 27 vs. 55; *‡ Calcium + Vitamin D vs. Calcium: 1 RCT, n = 89 vs. 86, number of PE cases = 10 vs. 6; *† Calcium vs. Vitamin D: 19 RCTs, n = 25,936 vs. 357, number of PE cases = 722 vs. 14; †‡ Calcium + Vitamin D vs. Vitamin D: 7 RCTs, n = 1169 vs. 357, number of PE cases = 55 vs. 14.

A comparison-adjusted funnel plot was constructed indicating asymmetry of the funnel, i.e., there might be small study-effects, particularly from studies with calcium versus placebo (Figure S5). Sample sizes of all studies ranged from 30 to 9178, with a median of 178. A sensitivity analysis was then performed by excluding studies whose sample sizes were small, i.e., those that were in the first quartile of smallest sample size. Three RCTs [37,39,42] comparing calcium vs. placebo (n = 49), one [46] comparing vitamin D vs. placebo (n = 54) and two [49,51] comparing calcium plus vitamin D vs. placebo (n = 109) were excluded. However, the results did not show much difference from pooling all trials. The pooled RRs were 0.54 (95% CI: 0.38, 0.78) and 0.44 (95% CI: 0.17, 1.18) for calcium vs. placebo and vitamin D vs. placebo, respectively. Thus, there was little effect of small study influence on our pooled estimates.

Finally, numbers needed to treat (NNT) for calcium vs. placebo (16 RCTs, n = 12,876 vs. 13,060), vitamin D vs. placebo (3 RCTs, n = 203 vs. 154) and calcium plus vitamin D vs. placebo (4 RCTs, n = 584 vs. 585) in preeclampsia were estimated without subgrouping. We found that 19 (95% CI: 15, 32) pregnant women were needed to receive supplements with calcium to prevent one episode of preeclampsia. However, the NNTs for supplement with vitamin D and calcium plus vitamin D ranged from benefits to harms, with the estimated NNTs of 17 (95% CI: −89, 12) and 23 (95% CI: −98, 14), respectively.

4. Discussion

We have performed a systematic review and network meta-analysis of calcium and vitamin D supplementation effects on preeclampsia and GH/PIH risk. Our finding from direct meta-analysis suggested that calcium supplementation could significantly reduce the risk of preeclampsia and GH/PIH by approximately 50% and 25%, respectively, when compared with placebo. Supplementation appeared more effective in high risk pregnancies than in low risk pregnancies, and in those who consumed the supplement for 18 weeks or shorter duration. The network meta-analysis indicated the best supplementation for lowering preeclampsia was vitamin D, followed by calcium and calcium plus vitamin D. The NNTs for these corresponding supplements would be 17, 19, and 23, respectively; however, only NNT for calcium supplement was beneficial, whereas the rest supplements could be either beneficial or harmful.

Although our diagnostics do not indicate any heterogeneity or little effect of small study effects, these results are based on very small numbers of participants. Our results are consistent with the updated Cochrane review [15], which found significant preventive effect of calcium supplementation on preeclampsia, especially in high risk women. Tang et al. also found the same effect of calcium supplementation in high risk, but not for low risk pregnancy [54]. In addition, effect of calcium supplement was significantly benefit in developing but not for developed countries, which was consistent to Imdad et al. [55], who found benefit of calcium supplement in developing countries where calcium intake was low. Therefore, the WHO has recommended prescribing calcium supplementation in routine antenatal care to those high risk pregnant women with low calcium intake for prevention of preeclampsia.

The findings of vitamin D and calcium plus vitamin D supplementation are also similar with the latest Cochrane review [19]. The effects of these supplementations might reduce the risk of preeclampsia, but further better-quality RCTs are still needed to confirm the effects.

4.1. Strengths and Limitations

Our study had a number of strengths. In comparison with earlier systematic reviews of observational studies, our meta-analysis included only RCTs, thus selection bias and confounding biases should be minimized. We compared effects of all supplementations on preeclampsia using network meta-analysis to indirectly compare efficacy between supplementations by borrowing data from common comparators. Neither publication bias nor inconsistency was detected. A ranking of interventions with their NNTs has also been calculated.

However, our study also had some limitations. Some relevant studies might be missing from our pooling because neither grey literature databases were used for identifying studies, nor non-English studies were considered. The number of included studies for vitamin D and calcium plus vitamin D were very small, and thus estimation of supplementation effects were imprecise. Different dosages of supplementations had been used, and given the small number of included studies we were unable to tease out a dosage effect. Although transitivity could not be directly assessed with aggregated meta-data, our study indirectly assessed transitivity assumption by extracting patient and methodological characteristics of included studies (i.e., dosage, duration of use, gestational age at start supplementation, gestational age at enrolment and delivery).

4.2. Summary of Evidence

Our meta-analysis has advantages over previous systematic reviews by integrating both direct and indirect comparisons of calcium, vitamin D, and calcium plus vitamin D supplementation in the entire network approach. Effects of calcium supplement on preeclampsia were robust and consistent for both direct and indirect meta-analyses. In addition, these effects were more beneficial if duration of receiving calcium supplementation was 18 weeks or shorter. As for our data, most included studies had mean gestational age at delivery of 38 weeks. This implies that calcium supplementation should be initiated at about 20 weeks or later. As for the pathophysiology of preeclampsia, abnormality of placenta might release secreted factors in mother's circulations, which resulted in clinical manifestation of preeclampsia occurring during 20 weeks of gestational age or after [56–58]. Increasing calcium concentration might play a role in decreasing smooth muscle contractility and increasing vasodilation, thus lowering risk of preeclampsia [9,59].

Until now, there has been no RCTs directly assessing the efficacy of supplementation on preeclampsia comparing calcium vs. vitamin D, and calcium plus vitamin D vs. vitamin D, but our network meta-analysis extrapolated these results. Vitamin D might be preferred for preventing preeclampsia. Possible explanations for this result might be as follows: First, adequate vitamin D intake might maintain calcium homeostasis, which in turn has an inverse relationship with blood pressure [10], or might directly suppress vascular smooth muscle cell proliferation [60]. Second, vitamin D might be a potent endocrine suppressor of renin biosynthesis and regulate the renin-angiotensin system,

which plays a critical role in the regulation of blood pressure [60]. Third, vitamin D might have immune-modulatory effect by balancing T helper cells [61].

Although supplementation of vitamin D with/without calcium ranked higher than calcium supplementation alone, this needs to be confirmed in head to head trials. However, the evidence was not enough to make a conclusive statement for using vitamin D in both developed and developing countries. If proven, applying this in routine care of pregnancy might be more difficult particularly in developing countries because of its greater investigation and prophylaxis cost when compared to calcium supplements. This suggests that calcium supplementation alone may remain the standard of choice for the prevention of preeclampsia and also in term of safeties when accessibility to addition of vitamin D to calcium is limited.

Currently, with existing evidence, vitamin D is still far from being recommended for prevention of preeclampsia according to Heaney's criteria [62]. Further research should focus on the recommended daily allowance of vitamin D for pregnant women, minimally clinical effective dosage of vitamin D, safety of vitamin D with different dosages, timing of initiation of supplementation in pregnancy, supplementation regimen (daily or weekly or single dose), supplementation alone or in combination with other nutrients, and to which type of pregnancy (low or high risk).

5. Conclusions

Our evidence suggests that calcium supplementation could reduce risk of preeclampsia. Vitamin D supplementation might also be beneficial, but this was based on evidence from a small number of studies examining vitamin D with short term assessment. Therefore, larger, well-designed RCTs are still required to determine the efficacy of vitamin D supplementation alone or in combination with calcium to reduce the risk of preeclampsia. Conversely, this network meta-analysis needs to be updated once more RCTs of vitamin D supplementation are available.

Supplementary Materials: The following are available online at www.mdpi.com/2072-6643/9/10/1141/s1, Table S1: Direct comparisons between supplementations on preeclampsia; Table S2: Direct comparisons between supplementations on gestational hypertension or pregnancy induced hypertension; Table S3: Risk of Bias Assessment; Table S4: Patient and methodological characteristics of included studies by treatment; Figure S1: Risk of bias assessment; Figure S2: Direct comparisons of supplementations on preeclampsia (a) Calcium vs. placebo by participants (b) Calcium vs. placebo by duration of calcium supplementation (c) Calcium vs. placebo by country setting (d) Vitamin D vs. placebo (e) Calcium plus vitamin D vs. placebo; Figure S3: Network of all possible interventions for prevention of preeclampsia; Figure S4: Rankogram of calcium, vitamin D, calcium plus vitamin D and placebo effects on preeclampsia; Figure S5: Comparison-adjusted funnel plot for the network meta-analysis.

Acknowledgments: Thanks to Stephen John Pinder for checking and improving the English of this manuscript. No funding source or any sponsor was involved for this research or preparation of the manuscript.

Author Contributions: Study concept and design: W.K., S.A.V., V.T. and A.T. Study selection and risk of bias assessment: W.K. and V.T. Data extraction: W.K. and S.A.V. Data analysis: W.K., S.A.V. and A.T. Interpretation of data: W.K., S.A.V., O.V., S.R., J.A., M.M. and A.T. Drafting the manuscript: W.K., S.A.V., O.V., S.R., J.A., M.M. and A.T. Critical revision of the manuscript for important intellectual content: W.K., S.A.V., O.V., S.R., J.A., M.M. and A.T. Final approval of the version to be published: All authors read and approved the final manuscript.

Conflicts of Interest: The authors report no conflicts of interest.

Appendix A. Search Terms and Search Strategy

Appendix A.1. PubMed Database

((((((((((calcium supplement*)) OR ("calcium carbonate")) OR ("calcium gluconate")) OR ("calcium acetate")) OR ("calcium citrate")) OR ("calcium lactate"))) OR ((((("vit* D supplement*")) OR ("cholecalciferol")) OR ("ergocalciferol")))) AND (((("Pregnant Women"[Mesh])) OR ("Pregnancy"[Mesh]))) AND ((((((((("Pre-Eclampsia"[Mesh])) OR ("Eclampsia"[Mesh])) OR (preeclampsia)) OR ("gestational hypertension")) OR ("gestational hypertensive disorder")) OR

("hypertensive disorder during pregnancy")) OR ("pregnancy induced hypertension")) OR (PIH)) OR ("pre-clamptic toxaemia"))

Appendix A.2. Scopus Database

((TITLE-ABS-KEY ("calcium supplement*" OR "calcium carbonate" OR "calcium gluconate" OR "calcium acetate" OR "calcium citrate" OR "calcium lactate")) OR (TITLE-ABS-KEY ("vit* D supplement*" OR "cholecalciferol" OR "ergocalciferol"))) AND (TITLE-ABS-KEY ("pre-Eclampsia" OR eclampsia OR preeclampsia OR "gestational hypertension" OR "gestational hypertensive disorder" OR "hypertensive disorder during pregnancy" OR "pregnancy induced hypertension" OR pih OR "pre-clamptic toxaemia")) AND (TITLE-ABS-KEY ("pregnant women" OR "pregnancy")).

Table A1. PICO Searching.

	Domain	Terms
1	Pregnancy	"pregnancy"[Mesh] ◈
2		"pregnant women"
3		1 OR 2
4	Calcium supplementation	calcium supplement*
5		"calcium carbonate"
6		"calcium gluconate"
7		"calcium acetate"
8		"calcium citrate"
9		"calcium lactate"
10		4 OR 5 OR 6 OR 7 OR 8 OR 9
11	Vitamin D supplementation	"vit* D supplement*"
12		"cholecalciferol"
13		"ergocalciferol"
14		11 OR 12 OR 13
15	Calcium or Vitamin D	10 OR 14
16	Preeclampsia	"pre-eclampsia"[Mesh] ◈
17		"eclampsia"[Mesh] ◈
18		"preeclampsia"
19		"gestational hypertension"
20		"gestational hypertensive disorder"
21		"hypertensive disorder during pregnancy"
22		"pregnancy induced hypertension"
23		PIH
24		"pre-eclamptic toxaemia"
25		16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24
26		3 AND 15 AND 25
27		systematic[sb] AND 26 ◈

◈ Option for Medline.

Appendix B

Appendix B.1. Data Extraction Form

Table A2. General information of the study.

Study ID	.....
Reviewer	.....
Date of review	(DD/MM/YYYY) .....
Study title	.....
First Authors	.....
Journal	..... Year .....

Table A3. Study Setting

Setting	**□ 1. Hospital Based**	**□ 2. Community Based**
Country of study	.....	

Table A4. General Characteristics of study.

Study Design	**□ 1. Randomized Controlled Trial**	**□ 2. Quasi-Experimental Design**
Period of the study	..... months	

Table A5. Participants.

Pregnant Women	**□ 1. Low Risk Women** **□ 2. High Risk Women**

Table A6. Intervention.

Calcium Supplementation		
Form	□ 1. Yes □ 2. No □ 1. Calcium carbonate □ 2. Calcium gluconate □ 3. Calcium acetate □ 4. Calcium citrate □ 5. Calcium lactate □ 6. Not specified □ 7. Other	
Dosage	..... g	Duration ..... weeks
Timing	□ 1. Single Dose □ 2. Daily □ 3. Weekly □ 4. Monthly □ 5. Other	
Started at	□ 1. First Trimester (0 to 13 Weeks) □ 2. Second Trimester (14 to 26 Weeks) □ 3. Third Trimester (27 to 40 Weeks) □ 4. No mention	
Co-Supplement	□ 1. Yes, specify ..... □ 2. No	
Vitamin D Supplementation		
Form	□ 1. Yes □ 2. No □ 1. Ergocalciferol □ 2 .Cholecalciferol □ 3. Not specified □ 4. Other	
Dosage	..... IU	Duration ..... weeks
Timing	□ 1. Single Dose □ 2. Daily □ 3. Weekly □ 4. Monthly □ 5. Other	

Table A6. *Cont.*

Started at	□ 1. First Trimester (0 to 13 Weeks) □ 2. Second Trimester (14 to 26 Weeks) □ 3. Third Trimester (27 to 40 Weeks) □ 4. No mention	
Co-Supplement	□ 1. Yes, specify ..... □ 2. No	
Calcium plus Vitamin D Supplementation		
Calcium Form	□ 1. Yes □ 2. No □ 1. Calcium carbonate □ 2. Calcium gluconate □ 3. Calcium acetate □ 4. Calcium citrate □ 5. Calcium lactate □ 6. Not specified □ 7. Other	
Dosage	..... g	Duration ..... weeks
Timing	□ 1. Single Dose □ 2. Daily □ 3. Weekly □ 4. Monthly □ 5. Other	
Vit D Form	□ 1. Ergocalciferol □ 2 .Cholecalciferol □ 3. Not specified □ 4. Other	
Dosage	..... IU	Duration ..... weeks
Timing	□ 1. Single Dose □ 2. Daily □ 3. Weekly □ 4. Monthly □ 5. Other	
Started at	□ 1. First Trimester (0 to 13 Weeks) □ 2. Second Trimester (14 to 26 Weeks) □ 3. Third Trimester (27 to 40 Weeks) □ 4. No mention	
Co-Supplement	□ 1. Yes, specify ..... □ 2. No	

Table A7. General baseline characteristics of participants.

Characteristics	Intervention *n* =	Control *n* =	Total *n* =
Mean Age (year)			
Mean Gestation age at enrolment (week) (mean, SD)			
SBP (mean, SD)			
DBP (mean, SD)			
Abnormal Proteinuria (%)			
BMI (mean, SD)			
Primigravida (%)			
Nulliparous (%)			
Gestational Diabetes Mellitus (%)			
Smoking (%)			
Mean total weight gain (mean, SD)			
% Withdraw (lost FU)			
Mean gestational age at delivery (mean, SD)			
Mean baseline calcium level (mean, SD)			
Mean baseline vitamin D level (mean, SD)			

Table A8. Type of Outcomes and Definitions.

Preeclampsia	□ 1. Yes □ 2. No	
	□ Preeclampsia	□ SBP ≥ 140 mmHg, DBP ≥ 90 mmHg and Proteinuria >2+
	□ Severe preeclampsia	□ SBP ≥ 160 mmHg, DBP ≥ 1100 mmHg and Proteinuria >2+
	□ Early onset preeclampsia	□ preeclampsia occur <34 weeks' gestation
	□ Late onset preeclampsia	□ preeclampsia occur ≥34 weeks' gestation
Eclampsia	□ 1. Yes □ 2. No	
GH or PIH	□ 1. Yes □ 2. No SBP ≥ 140 mmHg or DBP ≥ 90 mmHg	

Appendix B.2. Intervention and Outcomes

Table A9. Dichotomous outcomes for Preeclampsia.

Treatment	Preeclampsia			
	Yes	No	RR/OR	95% CI
Calcium				
Vitamin D				
Calcium + Vit D				
Placebo				

Table A10. Dichotomous outcomes for Eclampsia.

Treatment	Eclampsia			
	Yes	No	RR/OR	95% CI
Calcium				
Vitamin D				
Calcium + Vit D				
Placebo				

Table A11. Dichotomous outcomes for GH/PIH.

Treatment	GH/PIH			
	Yes	No	RR/OR	95% CI
Calcium				
Vitamin D				
Calcium + Vit D				
Placebo				

Appendix C. Cochrane "Risk of Bias" Assessment

Table A12. Risk of bias.

	Low (2)	High (1)	Unclear (0)	Comment
Adequate sequence generation	□	□	□	
Allocation concealment	□	□	□	
Blinding of participants and personnel	□	□	□	
Blinding of outcome assessment	□	□	□	
Incomplete outcome data addressed	□	□	□	
Selective outcome reporting	□	□	□	
Other sources of bias	□	□	□	

Criteria for Judging Risk of Bias in the "Risk of Bias Assessment" Tool

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Table A13. Random Sequence Generation.

Selection Bias (Biased Allocation to Interventions) Due to Inadequate Generation of a Randomized Sequence	
Criteria for judgment of "Low risk" of bias	Randomization was performed using any of following methods: Using a random number table; Simple or block or stratified randomization by using a computer random number generator with or without detailed description of generation process; Tossing Coin; Shuffling cards or envelopes; Throwing dice; Drawing of lots;
Criteria for judgment of "High risk" of bias	Systematic, non-random sequence generation was performed using any of the follow methods: Odd or even sequence generated by birth date; Sequence generated by some rule based on date (or day) of admission; Sequence generated by some rule based on hospital or clinic record number. Categorized with non-random approach using any of the following methods: by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
Criteria for judgment of "Unclear risk" of bias	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.

Table A14. Allocation Concealment.

Selection Bias (Biased Allocation to Interventions) Due to Inadequate Concealment of Allocations Prior to Assignment	
Criteria for judgment of "Low risk" of bias	If any of following was applied or mentioned Central allocation (including telephone, web-based and pharmacy-controlled randomization); Sequentially numbered drug containers of identical appearance; Sequentially numbered, opaque, sealed envelopes.
Criteria for judgment of "High risk" of bias	Authors used any of following Using an open random allocation schedule (e.g., a list of random numbers); Assignment envelopes were used without appropriate safeguards (e.g., if envelopes were unsealed or non-opaque or not sequentially numbered); Alternation or rotation; Date of birth; Case record number; Any other explicitly unconcealed procedure.
Criteria for judgment of "Unclear risk" of bias	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement–for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed

Table A15. Blinding of Participants and Personnel.

Performance Bias Due to Knowledge of the Allocated Interventions by Participants and Personnel during the Study	
Criteria for judgment of "Low risk" of bias	Any one of the following: Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; Incomplete blinding, such as blinding had to be uncovered because of characteristic side effect of intervention, but the outcome is not likely to be influenced by lack of blinding; No blinding, but the outcome is not likely to be influenced by lack of blinding.

Table A15. *Cont.*

Performance Bias Due to Knowledge of the Allocated Interventions by Participants and Personnel during the Study	
Criteria for judgment of "High risk" of bias	Any one of the following: Single blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding; No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding.
Criteria for judgment of "Unclear risk" of bias	Any one of the following: Insufficient information to permit judgment of 'Low risk' or 'High risk'; The study did not address this outcome.

Table A16. Blinding of Outcome Assessment.

Detection Bias Due to Knowledge of the Allocated Interventions by Outcome Assessors	
Criteria for judgment of "Low risk" of bias	Any one of the following: Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken; No blinding of outcome assessment, but the outcome measurement is not likely to be influenced by lack of blinding.
Criteria for judgment of "High risk" of bias	Any one of the following: Blinding of outcome assessment, but likely that the blinding could have been broken and the outcome measurement is likely to be influenced by lack of blinding; No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for judgment of "Unclear risk" of bias	Any one of the following: Insufficient information to permit judgment of 'Low risk' or 'High risk'; The study did not address this outcome.

Table A17. Incomplete Outcome Data.

Attrition Bias Due to Amount, Nature or Handling of Incomplete Outcome Data	
Criteria for judgment of "Low risk" of bias	Any one of the following: No missing outcome data; By checking the similarity between the remaining patients and loss to follow up patients, the reasons for missing outcome data unlikely to be related to preeclampsia such as migrating to another area; Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods.

Table A17. *Cont.*

Criteria for judgment of "High risk" of bias	Any one of the following: By checking the similarity between the remaining patients and loss to follow up patients, the reasons for missing outcome data likely to be related to preeclampsia such as diabetes mellitus, smoking status, BMI, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means), among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; Potentially inappropriate application of simple imputation.
Criteria for judgment of "Unclear risk" of bias	Any one of the following: Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g., number randomized not stated, no reasons for missing data provided); The study did not address this outcome.

Table A18. Selective Reporting.

Reporting Bias Due to Selective Outcome Reporting	
Criteria for judgment of "Low risk" of bias	Any of the following: The study protocol is available and all of the study's pre-specified outcomes (preeclampsia, maternal and fetal outcomes) which are of interest in the review have been reported in the pre-specified way; The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified.
Criteria for judgment of "High risk" of bias	Any one of the following: Not all of the study's pre-specified primary outcomes (preeclampsia) have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g., early onset preeclampsia, late onset preeclampsia) that were not pre-specified; One or more reported primary outcomes were not pre-specified One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for judgment of "Unclear risk" of bias	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.

Table A19. Other Bias.

Bias Due to Problems Not Covered Elsewhere in the Table	
Criteria for judgment of "Low risk" of bias	The study appears to be free of other sources of bias like baseline imbalance of important factors like obesity, or smoking by checking characteristics of participants between groups

Table A19. *Cont.*

Bias Due to Problems Not Covered Elsewhere in the Table	
Criteria for judgment of "High risk" of bias	There is at least one important risk of bias. For example, the study: Had a potential source of bias related to the specific study design used (e.g., problem in randomization, protocol violation, in cluster-randomized trials, there is loss of clusters (or) in cross-over trials, there is carry-over effect); or Had been claimed to have been fraudulent; or Had some other problem.
Criteria for judgment of "Unclear risk" of bias	There may be a risk of bias, but there is either: Insufficient information to assess whether an important risk of bias exists; or Insufficient rationale or evidence that an identified problem will introduce bias.

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Review

European Journal of Preventive Cardiology

European Journal of Preventive Cardiology
2017, Vol. 24(10) 1032–1042

DOI: 10.1177/2047487317705916
journals.sagepub.com/home/ejpc

Effects of education and income on cardiovascular outcomes: A systematic review and meta-analysis

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Abstract

Objective: Previous studies have reported discrepancy effects of education and income on cardiovascular diseases. This systematic review and meta-analysis was therefore conducted which aimed to summarize effects of education and income on cardiovascular diseases.

Methods: Studies were identified from Medline and Scopus until July 2016. Cohorts were eligible if they assessed associations between education/income and cardiovascular diseases, had at least one outcome including coronary artery diseases, cardiovascular events, strokes and cardiovascular deaths. A multivariate meta-analysis was applied to pool risk effects of these social determinants.

Results: Among 72 included cohorts, 39, 19, and 14 were studied in Europe, USA, and Asia. Pooled risk ratios of low and medium versus high education were 1.36 (95% confidence interval: 1.11–1.66) and 1.21 (1.06–1.40) for coronary artery diseases, 1.50 (1.17–1.92) and 1.27 (1.09–1.48) for cardiovascular events, 1.23 (1.06–1.43) and 1.17 (1.01–1.35) for strokes, and 1.39 (1.26–1.54) and 1.21 (1.12–1.30) for cardiovascular deaths. The effects of education on all cardiovascular diseases were still present in US and Europe settings, except in Asia this was present only for cardiovascular deaths. Effects of low and medium income versus high on these corresponding cardiovascular diseases were 1.49 (1.16–1.91) and 1.27 (1.10–1.47) for coronary artery diseases, 1.17 (0.96–1.44) and 1.05 (0.98–1.13) for cardiovascular events, 1.30 (0.99–1.72) and 1.24 (1.00–1.53) for strokes, and 1.76 (1.45–2.14) and 1.34 (1.17–1.54) for cardiovascular deaths.

Conclusion: Social determinants are risk factors of cardiovascular diseases in developed countries, although high heterogeneity in pooling. Data in Asia countries are still needed to update pooling.

Keywords

Cardiovascular diseases, cardiovascular death, education, income, meta-analysis, social determinants of health

Received 7 February 2017; accepted 30 March 2017

Introduction

Non-communicable diseases (NCD) are responsible for more than two-thirds of global mortality with a total of 52 million deaths projected by 2030.[1] The majority of diseases are cardiovascular diseases (CVD) followed by cancers, respiratory diseases, and diabetes. CVDs are a major public health problem accounting for about 30% of annual global mortality (17.5 million annually) and 10% of the global disease burden.[1]

The Framingham Heart Study,[2] WHO-MONICA project,[3] and INTERHEART[4] study provided evidence for the major risk factors of CVDs. Interventions that modify these risk factors are known to reduce cardiovascular morbidity and mortality. Despite much effort

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invested in primary and secondary prevention, CVD remains a major problem in industrialized and high income countries, and in low- and middle-income developing countries (LMICs).[1]

Many studies have identified additional risk factors for CVDs. Recently, the fifth epidemiological transition proposed that social upheaval,[5] a breakdown in existing social and health structures, leads to increased CVD morbidity and mortality. Since then, many social determinants of health (SDH) have been increasingly considered. Many studies have shown that SDH indirectly influence CVD by impacting on behavioral and metabolic cardiovascular risk factors (CVRFs), psychosocial factors, and environmental living conditions.[6,7] Some landmark[8–10] and numerous other epidemiological studies[11–14] show an inverse relationship between SDH and CVD morbidity and mortality.

Some evidence shows association between education and CVRFs, i.e. those with low education were more likely to develop CVRFs (e.g. hypertension, diabetes, dyslipidemias, overweight, etc.), and have less healthy dietary habits.[15–17] Evidence also showed that lower education is associated with atherosclerosis, ischemic heart disease (IHD), cerebrovascular diseases, CVD mortality and all-cause mortality.[15,18] Similar to education, an inverse relationship of income on IHD, coronary events, pre-hospital coronary death and CVD mortality has also been reported.[19–21] These effects of education and income are more consistent in developed countries, but the results are still inconclusive in LMICs.[22]

Several narrative and systematic reviews[23–28] assessed the relationship between socioeconomic status (SES) and CVDs, including myocardial infarction (MI), stroke, heart failure (HF), and death. Two meta-analyses have reported the effects of education and income on MI[23] and CVD mortality.[27] In both studies, education and income were roughly categorized as low and high and SES classes were not uniformly classified and pooled, resulting in inability to assess SES gradients. Only a few studies included participants from LMICs. We therefore conducted a systematic review and meta-analysis to pool the effects of low to high education and income on various cardiovascular outcomes by including more studies conducted in developing countries.

Methods

The review protocol has been registered with the international prospective register of systematic review (PROSPERO number CRD42016046615).[29]

Search strategy

Relevant studies were identified from Medline and Scopus databases since inception to 31 July 2016. Titles and abstracts were screened, and full articles were retrieved if the decision to include based on title and abstract could not be made. Reference lists were checked for studies overlooked by our searching. The search terms used and search strategies for both databases are described in the online Supplementary Material, Appendix A.

Selection of studies

Retrospective/prospective cohorts published in English were selected if they met following criteria: (a) assessed associations between education/income and cardiovascular outcomes in general adults or specific diseases; (b) measured education or income; (c) had at least one outcome of interest (i.e. coronary artery diseases (CADs), cardiovascular events (CVEs), strokes and cardiovascular deaths); (d) had contingency data between education/income and cardiovascular outcomes, or a beta-coefficient. Studies were excluded if data for education and income were combined; or income was based on ownership of car/house/health insurance/zip-code. For missing data, we made three attempts to contact authors to request additional data.

Study factors

Education and income were our study factors, which were reported differently across studies. To standardize data for pooling across studies, they were re-categorized into three groups as low, medium, and high for education years $\leq$9 (i.e. illiteracy/no education/basic/primary education), 10–12 (i.e. secondary/high school/intermediate/technical/apprenticed/trade/vocation), and >12 years (i.e. university/college/associates/master/professional/doctor of philosophy (PhD)), respectively. Income expressed in other currencies was converted to US currency/year using the reported exchange rates or the online exchange converter at the time of retrieval/identify.[30] Salary income was re-categorized as low, medium, and high for income $\leq$20,000, 20,001 to 40,000, and >40,000 US$/year, respectively. If original studies reported income as quartiles, the 1st, 2nd, and 3rd + 4th quartiles were re-classified as low, medium, high incomes, respectively. If the income was reported as quintiles, the 1st + 2nd, 3rd, and 4th + 5th quintiles were classified as low, medium, and high, respectively.

Outcomes

Outcomes of interest were CVDs including CAD (e.g. acute MI, IHD, coronary heart disease (CHD)), CVE (e.g. HF, hospital admission due to cardiac causes, revascularization and composite CVDs (e.g. IHD or

stroke)), strokes (ischemic or hemorrhagic strokes), and cardiovascular deaths. These were defined according to original studies.

Data extraction

Two reviewers (WK and SAV) independently extracted general characteristics of studies/patients (e.g. country, age, gender, body mass index (BMI), smoking, alcohol consumption, diabetes, hypertension, etc.). Cross-tabulated data between education/income groups and individual outcomes were extracted for pooling. Summary statistics (e.g. relative risk (RR), or hazard ratio (HR)) along with 95% confidence interval (CI) were extracted instead if frequency data were not reported. Data were computerized and validated, any disagreements were resolved by consensus.

Risk of bias assessment

Quality of studies were independently assessed by two reviewers (WK and SAV) using the Newcastle and Ottawa risk of bias criteria (Supplementary Material, Appendix B). Three domains were evaluated, i.e. selection of study groups, comparability of groups and ascertainment of exposure and outcome. Each domain was graded by giving stars if it was low risk of bias. A total grade of seven or more stars was regarded as indicating higher quality or lower risk of bias.

Statistical analysis

RRs of each outcome between low versus high (RR_1) and medium versus high (RR_2) education/income groups were calculated from frequency data where frequency data were available. These were then combined with reported summary statistics if frequency data were not available. Multivariate random-effect meta-analysis[31] was applied for pooling two RRs simultaneously. Variance-covariance between RR_1 and RR_2 was assumed to be zero for those studies reporting summary RRs. Heterogeneity was assessed using Cochrane's Q test and I^2 statistic. Heterogeneity was present if the p-value of the Q test was <0.1 or $I^2 \geq 25\%$.

Subgroup analyses were performed to explore potential sources of heterogeneity by fitting each of co-variables (i.e. country, country income level,[32] number of co-variables adjustment, age group, BMI, sex, diabetes, obesity, hypertension, high physical activity, smoking, alcohol drinking, dyslipidemia, and chronic kidney disease) in a meta-regression model.

Finally, exploration of publication bias was visualized using a funnel plot and Egger's test.[33] If any of these indicated asymmetry, a contour-enhanced funnel plot[34] was constructed to distinguish whether asymmetry was due to publication bias or heterogeneity.

All analyses were performed using STATA[35] version 14.1. Values of $p < 0.05$ were considered statistically significant, except for the test of heterogeneity where $p < 0.10$ was used.

Results

We identified 354 studies from Medline and 1335 studies from Scopus databases with 11 additional studies identified from reference lists. Of these 1700 studies, 115 were duplicates, leaving 1585 to be screened. After screening titles and abstracts, 1399 studies did not answer our primary question, leaving 72 studies for inclusion. Reasons for exclusion of the studies are presented in Figure 1 following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guideline.[36]

General characteristics of included studies

Characteristics of the 72 included cohorts published between 1982–2016 are described, see Supplementary Material, Table 1. Among them, 14, 39 and 19 studies were conducted in Asia, Europe, and the USA respectively. Most studies were from high-income countries (93.1%); mean age and mean BMI ranged from 38.5–78 years and 23.02–30.33 kg/m^2, respectively. Percentages of males, diabetes, smoking or hypertension varied from 35.9–78%, 1.3–42%, 7.28–72.64%, and 6.25–72.5% respectively. Among 72, 33, 10, and 29 studies assessed association effects of education, income, and both on cardiovascular outcomes, with a sample size ranged from 128–4,157,202.

Risk of bias assessment

Results of "risk of bias" assessment of the included studies are shown in Supplementary Material, Table 2. Total stars ranged from 5–9 with a median of seven. Among the included studies, 45 out of 72 (62%) had a low risk of bias and 27 out of 72 (38%) had a high risk of bias.

Education and cardiovascular outcomes

A total of 62 studies assessed the association between education and cardiovascular death ($n = 35$ and 31 for low and medium vs high), CAD ($n = 21$ and 18 for low and medium vs high), CVE ($n = 13$ and 15 for low and medium vs high) and stroke ($n = 15$ and 13 for low and medium vs high). Among these, only a few studies assessed relative effects of education without adjusting co-variables, or frequency data were available (three in

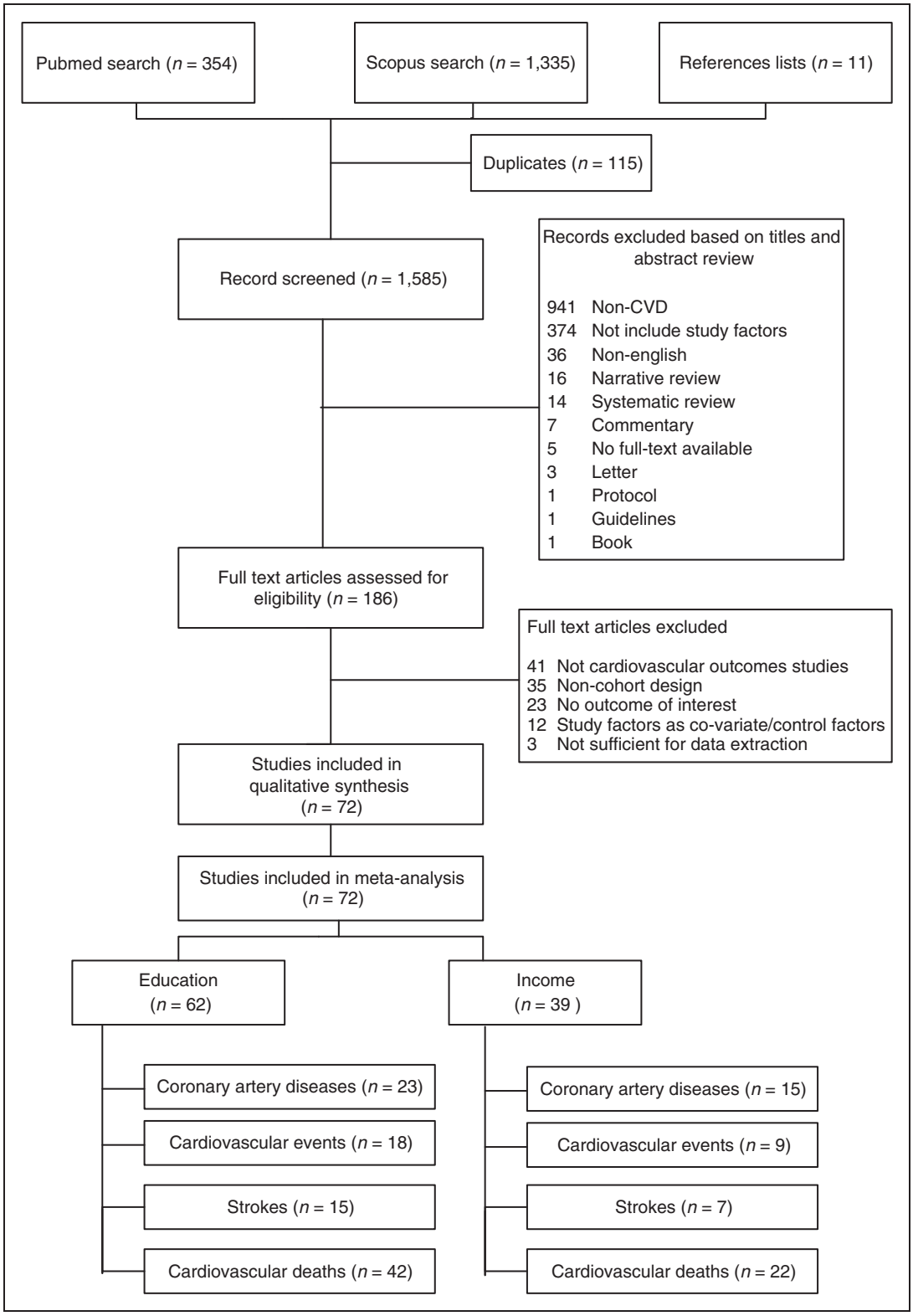

Figure 1. Flow diagram for selection of studies.
CVD: cardiovascular disease.

Table 1. Estimations of pooled effects of education and income on cardiovascular outcomes (co-variate adjusted studies only).

	Coronary artery diseases				Cardiovascular events			
	n	RR (95% CI)	Q *p*-value	I^2 (%)	*n*	RR (95% CI)	Q *p*-value	I^2 (%)
Education								
Medium vs high	15	1.21 (1.06–1.40)	0.005	96	12	1.27 (1.09–1.48)	0.003	83
Low vs high	17	1.36 (1.11–1.66)	0.002	94	13	1.50 (1.17–1.92)	0.001	99
Income								
Medium vs high	10	1.27 (1.10–1.47)	0.001	95	7	1.05 (0.98–1.13)	0.131	99
Low vs high	10	1.49 (1.16–1.91)	0.002	98	6	1.17 (0.96–1.44)	0.117	97
	Strokes				Cardiovascular deaths			
	n	RR (95% CI)	Q *p*-value	I^2 (%)	*n*	RR (95% CI)	Q *p*-value	I^2 (%)
Education								
Medium vs high	12	1.17 (1.01–1.35)	0.034	99	28	1.21 (1.12–1.30)	<0.001	98
Low vs high	13	1.23 (1.06–1.43)	0.005	83	34	1.39 (1.26–1.54)	<0.001	98
Income								
Medium vs high	6	1.24 (1.00–1.53)	0.049	99	12	1.34 (1.17–1.54)	<0.001	96
Low vs high	6	1.30 (0.99–1.72)	0.061	98	21	1.76 (1.45–2.14)	<0.001	99

CI: confidence interval; Q *p*-value: *p*-value for Q test for heterogeneity: RR: relative risk.

cardiovascular deaths[37–39] and CADs,[37,40,41] two in CVEs,[38,39] and two in strokes).[37,40] For consistency, only studies with adjusted relative education effects were pooled. Effects of education on outcomes were heterogeneous across studies with the I^2 ranging from 83–99% (Table 1). Multivariate meta-analysis was applied indicating significant educational effects on all outcomes (Table 1 and Figure 2). The strongest education effect was on CVE, where low and medium education increased risk of CVE by 50% and 27% compared to high education. A similar trend was observed for cardiovascular deaths, in which the risks for low and medium vs high education were 39% and 21%, respectively. Additionally, patients with low education showed 36% higher risk, and patients with medium education showed 21% higher risks for CAD. Furthermore, low and medium education levels were associated with 23% and 17% higher risks, respectively for developing stroke when compared to high education level.

Sources of heterogeneity were next explored by meta-regression or subgroup analyses (Table 2 and Supplementary Material, Tables 3–6). Geographical regions were grouped as Asia, Europe, and USA but few studies in the Asian setting were available for most outcomes. Effects of both low/medium education still remained for all four cardiovascular outcomes after pooling within Europe and USA, but not for Asia, which was likely due to the small numbers of studies (Table 2).

We performed subgroup analyses by co-variables including number of adjusted variables, age ($\leq$60 vs >60 years), BMI (<25 kg/m^2 vs $\geq$25 kg/m^2), percentage of males, diabetes, and smoking (Supplementary Material, Tables 3–6); and none of these was identified as a source of heterogeneity. However, education levels were associated with all four CVD outcomes in the subgroup younger than 60 years (Supplementary Material, Tables 3–6). Risk of cardiovascular death and CAD outcomes was higher in studies comprising a higher percentage of male participants. Likewise, risk of CVD (except CAD) was higher in studies with a higher proportion of diabetic participants. Association between BMI and CVE was detected in the BMI subgroup $\geq$25 kg/m^2 (Supplementary Material, Tables 3–6).

There was no evidence of publication bias using Egger's test except for low versus high education level on CVD outcomes (Egger's test: $\beta = 2.33$, $p = 0.008$), for which funnel plots showed asymmetry (Supplementary Material, Figures 1 and 2). Contour-enhanced funnel plot showed that some studies fell in both non-significant and significant areas, so asymmetry was more likely due to heterogeneity (Supplementary Material, Figures 3 and 4). No individual study significantly changed the overall estimates based on results of the sensitivity analysis.

Income and cardiovascular outcomes

Thirty-nine studies assessed income effects on cardiovascular death ($n = 22$ and 13 for low and medium vs high), CAD ($n = 13$ and 14 for low and medium vs high), CVE (both $n = 8$ for low and medium vs high) and stroke (both $n = 7$ for low and medium vs high).

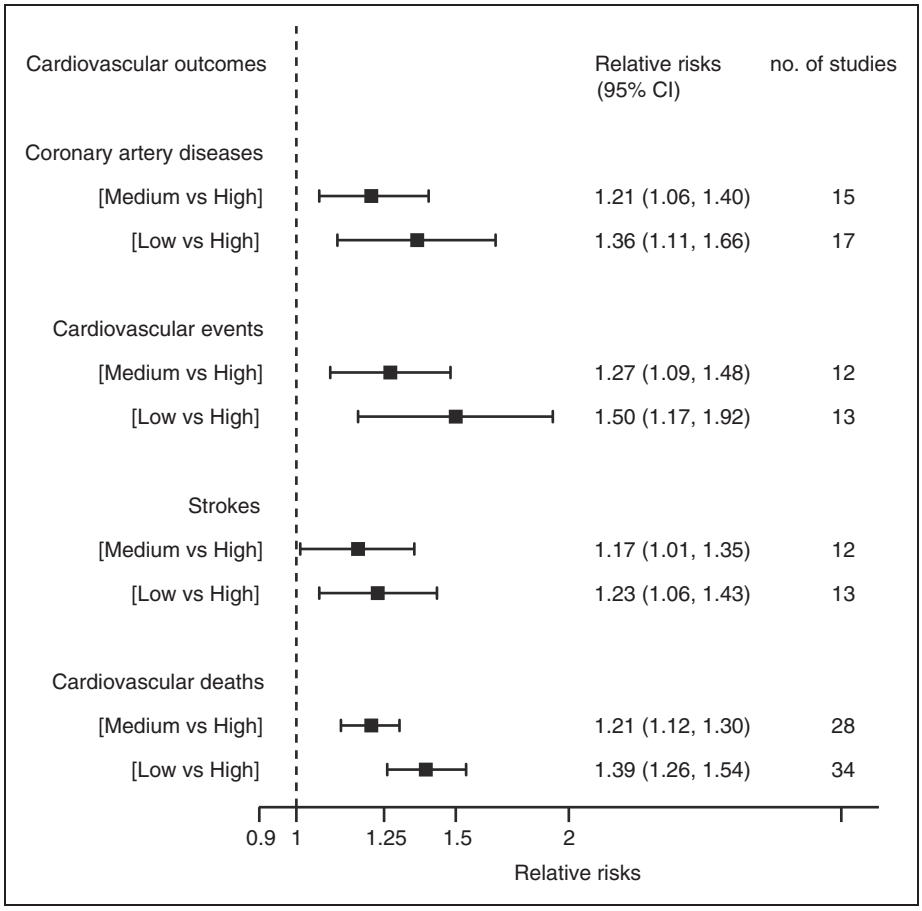

Figure 2. Pooling effects of educations on cardiovascular outcomes (co-variate adjusted studies only).
CI: confidence interval.

Five studies (1, 3, 2, and 1 for cardiovascular deaths,[40] CADs,[40–42] CVEs,[43,44] and strokes)[40] reported unadjusted relative effects of income were excluded. Effects of income on these outcomes were highly heterogeneous across studies, i.e. I^2 95% to 99% (Table 1 and Figure 3). The largest income effect was observed for cardiovascular death, with 76% and 34% higher risk of cardiovascular death for low and medium versus high income, respectively. Comparable effects were seen on CAD, with 49% and 27% higher risks, respectively. Furthermore, low income patients showed 17% higher risk, and medium income patients showed 5% higher risk for CVE. Additionally, low and medium incomes were associated with about 30% and 24% higher risks of developing stroke compared to high income.

Sources of heterogeneity were explored by meta-regression or subgroup analyses (Table 2 and Supplementary Material, Tables 3–6). By geographical region, European studies showed income effects similar to the overall pooled effect (Table 2). Subgroup analyses were performed by age groups indicating low income was associated with higher risk for cardiovascular death, CAD and CVE, in the studies with participants aged $\leq$60 years (Supplementary Material, Tables 3–6).

No publication bias was identified by Egger's test except for medium versus high income level groups with CAD outcome (Egger's test: $\beta = 2.98$, $p = 0.009$), but funnel plots showed asymmetry (Supplementary Material, Figures 5 and 6). Contour-enhanced funnel plots suggested that asymmetry was more likely due to heterogeneity (Supplementary Material, Figures 7 and 8). Overall estimates were similar to the sensitivity analyses.

Discussion

We performed a systematic review and meta-analysis to pool the effects of education and income on CVD outcomes. Our findings indicate that groups with low to medium education and income are at higher risk of CAD, CVE, stroke and cardiovascular death than those with high education and income. The pooled RRs for low and medium versus high education were 1.36 and 1.21 respectively for CAD, 1.50 and 1.27

Table 2. Pooled education and income effects on cardiovascular outcomes by regions.

		Education				Income			
		n	RR (95% CI)	Q *p*-value	I^2	*n*	RR (95% CI)	Q *p*-value	I^2
Cardiovascular deaths									
Asia	Medium vs high	2	1.12 (0.78–1.60)	0.540	5	0	NA	NA	NA
	Low vs high	8	1.34 (1.04–1.72)	0.024	99	4	1.69 (1.07–2.67)	0.024	96
Europe	Medium vs high	15	1.17 (1.06–1.29)	0.001	99	12	1.40 (1.18–1.67)	<0.001	97
	Low vs high	19	1.32 (1.17–1.49)	<0.001	91	14	1.89 (1.47–2.44)	<0.001	99
USA	Medium vs high	14	1.30 (1.14–1.49)	<0.001	72	1	NA	NA	NA
	Low vs high	8	1.69 (1.28–2.22)	<0.001	95	4	NA	NA	NA
CAD									
Asia	Medium vs high	3	1.03 (0.85–1.25)	0.750	28	0	NA	NA	NA
	Low vs high	4	1.03 (0.79–1.33)	0.839	45	0	NA	NA	NA
Europe	Medium vs high	11	1.04 (0.72–1.50)	0.852	99	11	1.39 (1.18–1.63)	<0.001	92
	Low vs high	15	1.24 (0.97–1.60)	0.086	96	12	1.74 (1.31–2.32)	<0.001	98
USA	Medium vs high	4	1.21 (0.97–1.51)	0.085	75	3	NA	NA	NA
	Low vs high	2	1.51 (0.93–2.45)	0.099	47	1	NA	NA	NA
CVE									
Asia	Medium vs high	2	1.47 (0.82–2.63)	0.191	61	2	NA	NA	NA
	Low vs high	4	1.85 (0.93–3.70)	0.081	96	2	NA	NA	NA
Europe	Medium vs high	8	1.26 (1.06–1.49)	0.090	76	5	1.05 (0.95–0.37)	0.368	99
	Low vs high	9	1.36 (1.07–1.72)	0.011	95	5	1.24 (0.98–1.58)	0.080	98
USA	Medium vs high	5	1.07 (0.69–1.66)	0.758	78	1	NA	NA	NA
	Low vs high	0	NA	NA	NA	1	NA	NA	NA
Strokes									
Asia	Medium vs high	4	1.22 (0.91–1.65)	0.192	87	0	NA	NA	NA
	Low vs high	5	1.27 (1.07–1.50)	0.006	34	0	NA	NA	NA
Europe	Medium vs high	6	1.46 (1.23–1.72)	<0.001	87	5	1.37 (1.24–1.52)	<0.001	70
	Low vs high	7	1.61 (1.28–2.02)	<0.001	76	5	1.54 (1.33–1.79)	<0.001	64
USA	Medium vs high	3	0.98 (0.81–1.19)	0.848	89	2	0.89 (0.62–1.27)	0.514	49
	Low vs high	3	0.99 (0.83–1.20)	0.957	53	2	0.91 (0.58–1.41)	0.661	78

CAD: coronary artery disease; CI: confidence interval; CVE: cardiovascular event; NA: not available or insufficient data; Q *p*-value: *p*-value for Q test for heterogeneity: RR: relative risk.

respectively for CVE, 1.23 and 1.17 respectively for stroke, and 1.39 and 1.21 respectively for cardiovascular death. The pooled RRs for low and medium versus high income for these corresponding outcomes were 1.49 and 1.27, 1.17 and 1.05, 1.30 and 1.24, and 1.76 and 1.34, respectively.

Direct or indirect mechanisms linking education and income with CVD have been described showing behavioral risk factors,[45] lifestyle or living environment conditions,[46] health literacy,[47] and psychological factors[48] play important roles. Those with low education or low income had a higher prevalence of risk behaviors (smoking, obesity, physical inactivity, unhealthy diet, etc.), were more likely to have poor polluted environment, poor health literacy (ability to read/understand comprehend medical information, lacking awareness of impact of lifestyle behavior, poor adherence/incorrect medication, ignorance of medical checkups), and had higher prevalence of depression with poorer coping in response to cumulative stress. Consequently, mortality was high, potentially due to delayed access to medical care, poor understanding in disease progress management, and lack of post-disease cardiac rehabilitation.[49]

Moreover, education and income have mutual causal influences on CVD morbidity and mortality and one should not rely on single, potentially biased parameters.[50] Combined effects of education and income had been studied previously,[51] and persons with low income and education had the highest risk of incident CHD, when compared with high education/low income, low education/high income, and high education/high income. However, some researchers have suggested education and income should not be

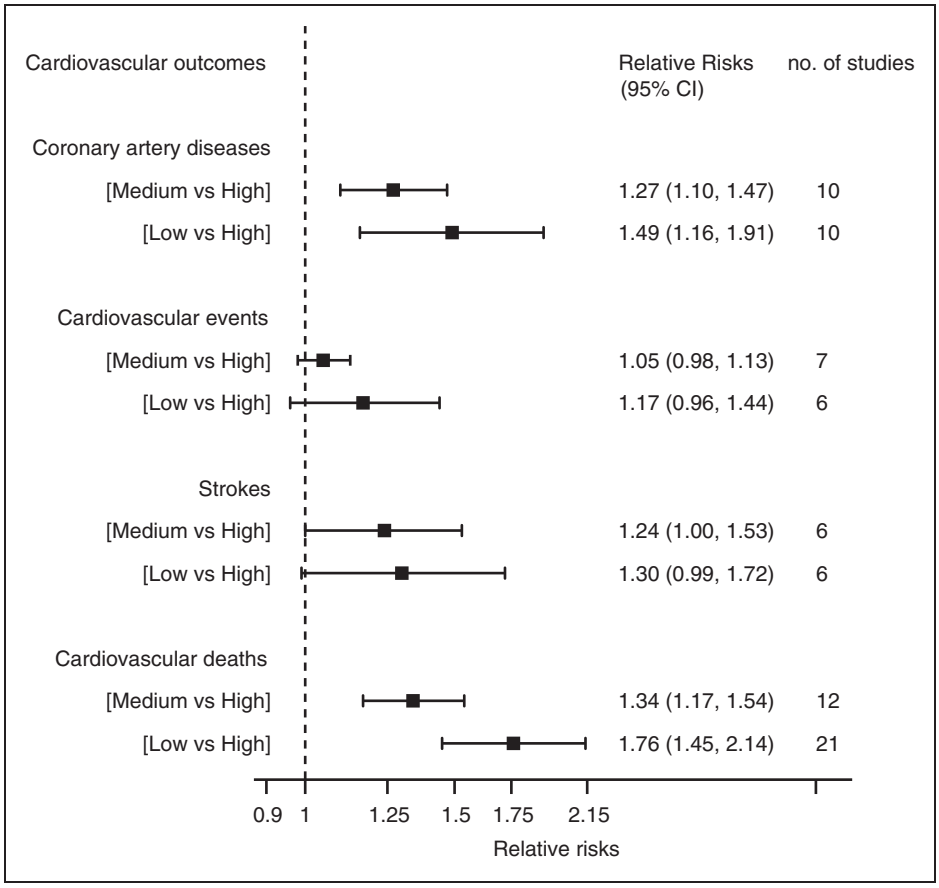

Figure 3. Pooling effects of incomes on cardiovascular outcomes (co-variate adjusted studies only).
CI: confidence interval.

combined and should not be interchangeable,[52] because they may affect CVD outcomes through different, potentially independent, causal pathways. For example, Ahmed et al.[53] found low income was a significant independent predictor of HF regardless of education level in community-dwelling older population age ≥65 years population. To test this hypothesis, individual patient data containing education and income variables are required, and mediation analysis applied.

Many studies[52,54] assessed education/income effect by comparing highest and lowest strata, which could not demonstrate dose-response effects.[10,55,56] To increase comparability across the studies and exposure gradient, the medium-level education and income categories were maintained. This confirmed the social gradient effect of education and income. Although there was high heterogeneity in the results, statistical significance was seen, except for effects of income on CVE and stroke outcomes. This may result from different definitions and classifications of education and income categories between individual studies, and between different geographical regions, economies, educational systems, and cultures. Differences in study periods over time could lead to variability in scales used to classify the exposure.

Strengths and limitations

Our meta-analysis has some strengths. We believe, it is the first meta-analysis assessing levels of education and income effects on major CVD outcomes. To increase comparability across studies and study social gradient effects, three strata of education/income were categorized into three groups to yield more details than previously.[23,27] Effects of education/income were simultaneously pooled using multivariate meta-analyses. In addition, only cohort studies providing more reliable effects of education and income on CVD outcomes were included. This review followed PRISMA guidelines.[36]

However, our study also has some limitations. Pooled estimates were affected by high heterogeneity, from differences in characteristics of the study populations, differences in definitions and classifications of

education and income in both developed and developing countries, and differences in measurement timing of education and income categories across studies. Although many efforts were made to explore the heterogeneity, we could not identify sources. We also did not have access to primary data and many studies did not adjust and report confounding variables, so estimated risks might be confounded.

Clinical implications and further research

Braveman et al.[52] explained educational influence on general and health-related knowledge, health literacy, and problem-solving skills, which can change health outcome. The results of our meta-analysis provide some evidence of effects of education and income on CVD outcomes. However, whether education or income is directly associated with CVD outcomes,[50] or education is indirectly associated with CVD outcomes through income as mediator,[57] or both education and income are indirectly associated with CVD outcomes through other risk factors such as BMI,[58] diabetes, or smoking as mediators has not been clearly answered in studies. Further research should focus on the causal pathway between education and income on CVD outcomes with more advanced statistical models, such as mediation/moderation analysis.[59]

Conclusion

In conclusion, low/medium education and income increase the risks of CAD, CVE, stroke and cardiovascular death. Further studies should be conducted to assess causal pathway of education/income on cardiovascular outcomes to confirm our findings, especially in Asian countries.

Acknowledgements

The authors wish to express thanks to Stephen J Pinder for checking and improving the English of this article.

Author contribution

WK, SAV, and AT contributed to the conception and design, data analysis, and interpretation of data, WK and SAV contributed to study selection, risk of bias assessment, and data extraction, WK, SAV, JA, MM, and AT contributed to drafting the manuscript, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. All authors gave final approval.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Sleep Medicine Reviews 36 (2017) 96–106

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Performance of screening questionnaires for obstructive sleep apnea during pregnancy: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 16 March 2016
Received in revised form
3 November 2016
Accepted 7 November 2016
Available online 15 November 2016

Keywords:
Berlin questionnaire
Epworth sleepiness scale
Pregnancy
Obstructive sleep apnea
Systematic review

SUMMARY

This review aims to evaluate the performance of obstructive sleep apnea (OSA) screening questionnaires during pregnancy. A systematic review and meta-analysis was performed using MEDLINE Scopus, CINAHL, and the Cochrane library. A bivariate meta-analysis was applied for pooling of diagnostic parameters. Six of the total 4719 articles met the inclusion criteria. The Berlin questionnaire (BQ, N = 604) and Epworth sleepiness scale (ESS, N = 420) were the most frequently used screening tools during pregnancy. The pooled prevalence of OSA during pregnancy was 26.7% (95%CI: 16.9%, 34.4%, $I^2 = 83.15\%$). BQ performance was poor to fair with pooled sensitivity and specificity of 0.66 (95%CI: 0.45, 0.83; $I^2 = 78.65\%$) and 0.62 (95%CI: 0.48, 0.75; $I^2 = 81.55\%$), respectively. BQ performance was heterogeneous depending on type of reference test and pregnancy. Sensitivity increased if diagnosis was based on polysomnography (0.90), and respiratory disturbance index (0.90). However, sensitivity decreased if screening was performed in early pregnancy (≤20 weeks gestation: 0.47), and high-risk pregnancy (0.44). Performance of ESS was poor with pooled sensitivity and specificity of 0.44 (95%CI: 0.33, 0.56; $I^2 = 32.8\%$) and 0.62 (95%CI: 0.48, 0.75; $I^2 = 81.55\%$), respectively. In conclusion, BQ and ESS showed poor performance during pregnancy, hence a new OSA screening questionnaire is needed.

Registration: PROSPERO registration CRD42015025848.

Introduction

Obstructive sleep apnea (OSA) is a significant medical condition occurring from repetitive upper airway collapse during sleep resulting in intermittent oxygen desaturation, arousals, and sympathetic activation [1]. The prevalence of OSA in the general population varies from approximately 2%–26% worldwide [2,3]. However, it has been estimated that up to 93% of women and 82% of men with moderate to severe OSA remain undiagnosed [4]. A greater proportion of under-diagnosis of OSA in women is probably the result of "non-classical" presentations of OSA especially in premenopausal women [5,6]. Challenges increase when women become pregnant as physiologic and hormonal changes predispose to the development of new-onset sleep-disordered breathing (SDB) or exacerbation of pre-existing SDB [7,8].

However, the prevalence of SDB during pregnancy remains uncertain across the world, and also depends greatly on various factors including the population studied, ethnicity, type of pregnancy (low versus high risk), period of pregnancy, type of diagnostic test, and use of classification cut points [9–14]. Based on previous studies using objective sleep test at a single time point, the prevalence of SDB in high-risk pregnancy ranged from 20% to 35%. This finding is similar to that observed in Thai pregnant women, a prevalence much higher than that reported

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http://dx.doi.org/10.1016/j.smrv.2016.11.003

Abbreviations

AASM	American academy of sleep medicine
AHI	apnea-hypopnea index
ANC	antenatal care
ASA checklist	American society of anesthesiologist's checklist
AUROC	area under the receiver operator curve
BMI	body mass index
BQ	Berlin questionnaire
CI	confidence interval
DOR	diagnostic odds ratio
EDS	excessive daytime sleepiness
ESS	Epworth sleepiness scale
FN	false negative
FP	false positive
GA	gestational age
GDM	gestational diabetes
GHT	gestational hypertension
HSROC	hierarchical summary receiver operating curve
LR+	positive likelihood ratio
LR−	negative likelihood ratio
MAP index	multivariate apnea prediction index
MeSH	medical subject heading
OSA	obstructive sleep apnea
PRISMA	preferred reporting items for systematic reviews and meta-analysis
PROSPERO	the international prospective register of systematic reviews
PSG	polysomnography
PSQI	Pittsburgh sleep quality index
QUADAS-2	quality assessment of diagnostic accuracy studies
RDI	respiratory disturbance index
SDB	sleep-disordered breathing
SDQ	sleep disorder questionnaire
SROC	summary receiver operating curves
STOP	snoring, tiredness, observed apnea, high blood pressure questionnaire
STOP-BANG	snoring, tiredness, observed apnea, high blood pressure - body mass index, age, neck circumference, and gender questionnaire
TN	true negative
TP	true positive

in general non complicated pregnancies [15]. Moreover, prevalence of SDB increases as a pregnancy progresses from the 1st trimester (30%) to the 3rd trimester (47%) in a study with serial screening [7].

Data from meta-analyses also indicate that SDB during pregnancy is associated with adverse maternal and fetal outcomes including gestational hypertension (GHT)/pre-eclampsia, gestational diabetes (GDM) and low infant birth-weight [16,17]. Early screening for OSA in pregnancy may help in reducing these adverse outcomes. However, currently there is no standard guideline for OSA screening during pregnancy despite its potential impact. Although in-laboratory polysomnography (PSG) is the gold standard diagnostic test, long waiting periods for appointments, particularly considering the short time-window to perform the test early during the pregnancy, and the discomfort induced by the sleep test may lead to absence of investigation [18]. Thus, simple and accurate screening strategies should be investigated. Risk stratification for the probability of OSA in pregnant women will also help in prioritizing the need for further diagnostic sleep testing given the limited resources in many places throughout the world. Early diagnosis and treatment of OSA in pregnancy should be implemented given the potential benefit on pregnancy outcomes [19,20].

The Berlin and STOP-BANG questionnaires have been developed and used to identify those at high risk of OSA in non-pregnant populations with fair to good performance [21,22]. For example, the Berlin questionnaire has a sensitivity and specificity ranging from 68% to 86% and 46%–95% [21], respectively, with corresponding pooled values of 72% (95%CI: 66–78%) and 61% (95%CI: 55–67%) [23,24].

Validation studies assessing the performance of the Berlin and STOP-BANG questionnaires during pregnancy have shown inconsistent results. Furthermore, the validity of the tests greatly depends on the severity of SDB itself and the trimester of pregnancy [9–15].

Considering the urgent need for a simple and feasible screening tool for OSA during pregnancy, a systematic review and meta-analysis were performed to clarify the performance of OSA questionnaires when applied to pregnant women. This study aimed to determine the sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR−), and area under the receiver operator curve (AUROC) of available tests and the prevalence of OSA during pregnancy from existing studies.

Methods

Search strategy and study location

Our study protocol was registered with the International prospective register of systematic reviews (PROSPERO) (registration number: CRD42015025848). In order to include all available evidence, a systematic search of the literature was performed through MEDLINE (from 1996 to January 2016), Scopus (from 1980 to January 2016), CINAHL, and Cochrane library. Search terms were built according to the research question which was modelled on the PICO principle, i.e., patient, intervention, comparator, and outcome. These included: pregnancy(MeSH), "pregnant women", parturient, gestation*, obstetric*; "sleep questionnaire", Berlin, STOP-BANG "Epworth sleepiness scale" or ESS, "Pittsburgh sleep quality index", PSQI, screening, validation, prevalence, predictors; "sleep test", polysomnography, PSG, Watch-PAT; and obstructive sleep apnea (MeSH) sleep apnea, obstructive(MeSH), "sleep apnea", OSA, "sleep disordered breathing", SDB, snoring. Details of the search strategy are described in the Appendix.

Inclusion and exclusion criteria

Any type of observational study (cross-sectional, cohort, or case-control) or randomized-controlled trial published in any language was included in the review if it met all the following criteria: 1) studied in women during pregnancy 2) used at least one of the OSA screening questionnaires (e.g., Berlin questionnaire, STOP-BANG questionnaire, ESS, etc.), and 3) had outcome of interest as OSA/SDB by objective sleep tests including PSG, Watch-PAT [25], or any type 3 home monitoring.

Studies were excluded if they: 1) were reviews or case reports 2) provided insufficient data for pooling despite several attempts to contact authors; or 3) were multiple publications of the same original study.

All citations were then combined and duplicates were excluded. The literature search results were evaluated independently by two reviewers (VT and PN) to locate eligible studies for inclusion. Irrelevant studies were excluded at the first step of the abstracts reviews. The full-text articles of the remaining studies were then retrieved and reviewed thoroughly to determine eligibility. Disagreement between the 2 reviewers was resolved by a third party (AT).

Data extraction

Data from the included studies were extracted using standardized data extraction forms. General characteristic of studies and subjects were extracted. For data used for pooling, cross-tabulated numbers of studied sleep questionnaires and standard tests including true positive (TP), false positive (FP), false negative (FN), and true negative (TN) were extracted from individual studies. Additionally, usage of cut-off thresholds for sleep questionnaires and the standard test were also extracted.

Studied questionnaires

The Berlin questionnaire consists of 10 self-administered questions with 3 categories regarding risk factors of OSA as follows: snoring component, daytime sleepiness, and obesity (BMI $\geq$30 kg/m^2) or chronic hypertension. Being positive for 2 out of 3 categories is considered as high risk for OSA [21]. The ESS is used to assess daytime sleepiness, consisting of 8 questions regarding propensity to doze off in certain situations. Total ESS scores range from 0 to 24, and a score $\geq$10 is defined as excessive daytime sleepiness [26]. Details of all other questionnaires are shown in Table S1.

Reference test

The outcome of interest was OSA/SDB diagnosed by performing PSG, Watch-PAT, or any type 3 home monitoring. The diagnosis of OSA/SDB was, according to the original studies, based on an apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) $\geq$5 [18].

Assessment of methodological quality

Methodological quality of each study was assessed independently by 2 reviewers (VT and PN) based on the QUADAS-2 (quality assessment of diagnostic accuracy studies). The QUADAS-2 tool assesses risk of bias (internal validity) and applicability (external validity) with several domains consisting of patient selection, index test, reference standard, and the flow and timing between index test and reference standard. Each domain is graded as low, high, or unclear risk of bias [27].

Statistical analysis

A bivariate meta-analysis with a random-effect model was applied for pooling diagnostic parameters (i.e., sensitivity, specificity, likelihood ratio positive/negative (LR+/LR−), and diagnostic odds ratio (DOR) using metandi and midas commands in STATA [28]. Hierarchical summary receiver operating curves (HSROC) analysis was applied to construct summary receiver operating curves (SROC) and assess threshold effects [29,30]. Pre-test probability (i.e., prevalence of OSA) and positive predictive value were pooled using the user-provided pmeta command in STATA. In addition, a post-test probability was performed for further estimation based on Bayes' theorem and depicted visually with Fagan's nomogram [31]. Heterogeneity was considered present if $I^2 > 25\%$ or Q test <0.1. Exploration of sources of heterogeneity was performed by fitting the co-variables one by one on diagnostic odd ratios (DOR) incorporating both sensitivity and specificity in a meta-regression, and subgroup and sensitivity analyses were carried out accordingly [32,33]. Publication bias was assessed using Deek's funnel plot [34]. Threshold effects from a different cut-off point in each diagnostic test were also assessed.

Results

Our extensive search yielded 4915 citations, as shown in the PRISMA flow diagram in Fig. 1 [35]. After thorough screenings, 31 studies were included in the qualitative assessment, but only 6 studies were eligible for the meta-analysis [9–14]. Characteristics of included studies are summarized in Table 1, and reasons for exclusion of studies are summarized in Table S2 [15,19,20,36–57].

Among the 6 studies, 4 studies enrolled subjects through outpatient antenatal care services (ANC) [9,11–13], whereas 1 study enrolled subjects during obstetric admission [10] and 1 study enrolled subjects both during in-patient and ANC visits [14].

Screening of subjects was performed during the 2nd or 3rd trimesters in 4 studies [9,10,12,14]; gestational age (GA) $\leq$20 weeks in 1 study [13]; and at all trimesters in 1 study [11]. One study serially screened subjects with questionnaires during 2nd and 3rd trimesters, but validation PSG was performed only during 3rd trimester [12].

Pregnant women were recruited from the general ANC services in 3 studies [9,12,14]. The other 2 studies included pregnant women during their ANC visit with conditions considered to be high risk for either OSA or obstetric complications, e.g., chronic hypertension, pre-gestational diabetes, GDM, obesity, or a prior history of pre-eclampsia [11,13]. One study enrolled pregnant women who were admitted to the hospital with conditions, e.g., preterm labor, GDM, preeclampsia, preterm premature rupture of membranes, chronic hypertension, trauma, GHT, pregestational diabetes, and urinary tract infection, and thus was considered as a high risk pregnancy study [10].

A total of 604 singleton pregnant women from 6 studies were included in the meta-analysis. Mean age ranged from 26.6 to 33.5 years with their mean gestational age ranging from 16.5 to 32.3 weeks. The prevalence of OSA (either AHI or RDI $\geq$5 events/hour) in overall and low risk pregnancy studies ranged from 12% to 35%, and ranged from 20% to 31.9% in high risk pregnancy studies.

Obstructive screening questionnaire characteristics

Among the 6 included studies [9–14], 5 questionnaires had been used for OSA screening, namely the Berlin questionnaire, STOP-BANG questionnaire, STOP questionnaire, ESS, and American Society of Anesthesiologist's checklist (ASA) [21,22,26,58–60]. Two clinical prediction scores for OSA including multivariate apnea prediction index (MAP index) and the Flemons index were used in 3 studies [61,62]. However, results from the MAP index, and Flemons index were not reported and there were insufficient 2 $\times$ 2 contingency table data for pooling [9,12,14].

In terms of questionnaire performance, 6 studies used Berlin questionnaire, 3 studies used ESS, 2 studies used STOP-BANG questionnaire, 1 study used STOP questionnaire, and 1 study used ASA checklist. Given the limited data, the meta-analysis was performed only for the Berlin and ESS questionnaires. The qualitative descriptions of reported results of these questionnaires are shown in Table 2 and Table S3.

Reference tests

All 6 studies administered at least one of the OSA screening questionnaires, which were validated against reference sleep

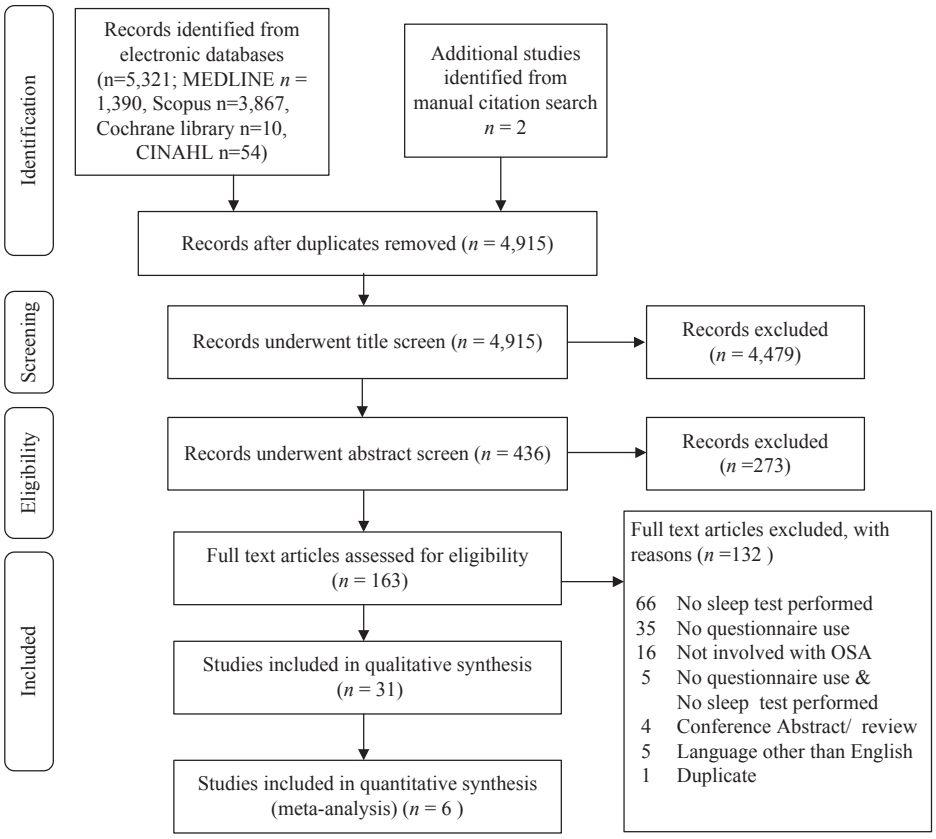

Fig. 1. PRISMA[34] flow chart of selection of studies. Abbreviations: OSA = obstructive sleep apnea; PRISMA = preferred reporting items for systematic reviews and meta-analysis.

tests. PSG, considered as the gold standard for OSA diagnosis was performed in only 2 studies [9,12] whereas either Watch-PAT (2 studies) [11,13], or ApneaLink (2 studies) were performed in the other studies [10,14]. However, only Watch-PAT has been validated against PSG for the diagnosis of OSA during pregnancy [63].

The 2 studies which performed PSG, used respiratory scoring criteria according to the American academy of sleep medicine scoring manual, 2007 [9,12]. Specifically, apnea was defined as a reduction of thermistor signal of at least 90% from baseline lasting ≥10 s, and hypopnea (alternative rule) was defined as a reduction in nasal pressure transducer signal of at least 50% from baseline which is associated with either oxygen desaturation ≥3% or arousal. Respiratory effort related arousal (RERA) was defined as a sequence of breaths lasting ≥10 s characterized by increasing respiratory effort or nasal airflow flattening leading to arousal [18].

One of the 2 studies using ApneaLink defined apneas and hypopneas as the reduction of airflow by 0–20% lasting ≥10 s, and reduction of airflow by 50% lasting ≥10 s, respectively [14]. The other ApneaLink study did not specify the criteria used [10].

Scoring of the Watch-PAT studies was based on the automatic algorithm provided by the manufacturer's propriety software based on heart rate and finger plethysmography [11,13].

Tabulation of AHI consisted of numbers of apneas and hypopneas divided by total sleep time (hours). Additionally, respiratory disturbance index (RDI) was defined as numbers of apneas, hypopneas, and RERAs divided by total sleep time (hours) [18].

Four studies diagnosed OSA based on AHI ≥5 events/hour cut-off threshold, the other 2 studies used a RDI ≥5 events/hour as the diagnostic cut-off threshold for OSA. Additionally, result based on a RDI ≥10 events/hour cut-off was also reported in 1 study [12].

Risk of bias assessment

A summary of methodological quality assessment according to the QUADAS-2 tool is shown as a percentage for each domain in Figs. 2 3 and Table S4. Details of the assessment criteria are shown in the Appendix. The agreement among independent reviewers was excellent with κ-statistics of 0.96.

For the patient selection domain, a high risk of bias was documented in 4 studies: convenience sampling in all studies [9,11,12,14] and selection of subsets of subjects at either end of the SDB risk spectrum in 1 study [12]. A high risk of bias for applicability for patient selection was documented in 3 studies due to selection of high risk pregnant women [10,11,13]. This resulted in spectrum bias, i.e., selection of the subjects at either the high or low risk ends of the spectrum of the condition. Risk of bias for the index test domain was high in 1 study because the criteria for diagnosis were not pre-specified [14]. Also, the blinding of the index test interpretation was unclear in 2 studies [10,13]. Concerns regarding applicability of the index test were high in 2 studies due to differences in body mass index (BMI) cut-off threshold for obesity, and timing of measurements during pregnancy [11,14]. A cut-off threshold of BMI ≥30 kg/m^2 was used in 4 studies [9,10,12,13], whereas a cut-off threshold of 27.5 kg/m2 was used in 1 Asian study [11], and ≥35 kg/m^2 in another study [14]. Pre-pregnancy BMI was used in 2 studies [11,13], early pregnancy BMI was used in 1 study [9], and pregnancy BMI was used in 3 studies [10,12,14].

Table 1
Characteristics of the included studies.

Author, year/questionnaire	Study characteristics	Patient characteristics			Diagnosis	OSA	
		Age mean (SD), y	GA mean (SD), wk	BMI mean (SD), kg/m^2	Sleep test/criteria	Prevalence	Severity
Tantrakul et al. 2015 [11] Berlin STOP-BANG ESS	**Study design:** Cross sectional study **Patients:** Singleton pregnancy **N = 72** **Setting:** high risk ANC clinic **Pregnancy risk:** High **GA:** Any **Country:** Thailand	33.1 (5.2)	22.8 (9.2)	**Pre-pregnancy** 24.2 (5.3) **Pregnancy** 26.9(5.3)	Watch-PAT200 AHI ≥5 Automated analysis on PAT software algorithm	31.9%	**Median (IQR) AHI overall** 2.4(8.0)
Lockhart et al. 2015 [14] STOP STOP-BANG ESS ASA -checklist	**Study design:** Prospective Cohort **Patients:** Volunteer singleton pregnancy **N = 248 setting:** OPD and IPD ANC service **Pregnancy risk:** General **GA:**≥27 weeks **Country:** USA	28 (6.3)	32 (3.1)	**Pre-pregnancy** n/a **Pregnancy median (IQR)** 31(27–36)	ApneaLink AHI ≥5 Apnea = reduction of airflow to 0–20% lasting ≥10 s; Hypopnea = reduction of airflow to 50% lasting ≥10 s	12%	n/a
Wilson et al. 2013 [12] Berlin MAP Index	**Study design:** Prospective Cohort **Patients:** Singleton pregnancy **N = 43** **Setting:** ANC clinic **Pregnancy risk:** General **GA:**2nd-3rd trimesters **Country:** Australia	33.5 (5.1)	22.3 (4.0)	**Pre-pregnancy** 32.2(8.0) **Pregnancy** 37.5(7.9)	PSG RDI≥5 RDI≥10 Scoring based on AASM 2007 criteria, alternative hypopnea rule (defined as reduction of nasal pressure signal at least 50% lasting ≥10 s with either oxygen desaturation ≥3% or arousal)	35%	**Median (IQR)AHI Without OSA:** 1.5 (0.6–2.7) **With OSA:** 6.2 (4.9–13.2)
Fung et al. 2013 [9] Berlin MAP Index	**Study design:** Prospective Cohort **Patients:** Convenient sample of singleton pregnancy **N = 41** **setting:** ANC clinic **Pregnancy risk:** General **GA:** 2nd trimester with 3rd trimester follow-up **Country:** Australia	31.2 ?	21.4 (2.4)	**Pre-pregnancy** 26.1(6.4) **Pregnancy** n/a	PSG RDI≥5 Scoring based on AASM 2007 criteria, alternative hypopnea (defined as reduction of nasal pressure signal at least 50% lasting ≥10 s with either oxygen desaturation ≥3% or arousal)	34%	**Median (IQR)RDI Without OSA:** 1.4 (0.6–2.6) **With OSA:** 6.2 (4.9–11.7)
Facco et al. 2012 [13] Berlin ESS	**Study design:** Prospective Cohort **Patients:** Singleton pregnancy **N = 100** **setting**: ANC Clinic **Pregnancy Risk:** High risk for OSA **GA:** 6–20 week **Country:** USA	33.0 (6.5)	16.5 (3.7)	**Pre-pregnancy** 31.9 (9.1) **Pregnancy** n/a	Watch-PAT100 AHI ≥5 Automated analysis on PAT software algorithm	28%	**Median (IQR)AHI Overall** 1.5 (0.5–6.0)
Olivarez et al. 2010 [10] Berlin	**Study design:** Prospective Cohort **Patients:** Singleton pregnancy **N = 100** **setting**: antepartum obstetric admission **Pregnancy risk:** High **GA**: ≥26 weeks **Country:** USA	26.6 (7.1)	32.3 (3.5)	**Pre-pregnancy** n/a **Pregnancy** 27.5 (7.2)	ApneaLink AHI ≥5 Apnea and hypopnea definitions were not specified	20%	n/a

Abbreviations: AASM = American academy of sleep medicine; AHI = apnea-hypopnea index; ANC = antenatal care; ASA checklist = American society of anesthesiologist's checklist; BMI = body mass index; ESS = Epworth sleepiness scale; GA = gestational age; IQR = interquartile range; IPD = in-patient department; MAP index = multivariate apnea prediction index; n/a = not applicable; OPD = out-patient department; OSA = obstructive sleep apnea; RDI = respiratory disturbance index; SD = standard deviation.

In terms of reference test, a high risk of bias was documented in 4 studies due to the fact that the testing was performed either with Apnea-Link or Watch-PAT instead of standard PSG [9,11,13,14]. An unclear risk of bias was present in 1 study due to unclear information on previous knowledge of the result of the test prior to study interpretation. Applicability of the reference test was rated high bias in 2 studies using ApneaLink because the criteria used for hypopnea scoring was not according to the American academy of sleep medicine sleep scoring manual [10,14].

Appropriate timing between questionnaire (index test) administration and sleep testing (reference standard) is considered to be under 2 weeks, see Appendix. Risk of bias assessment in the flow

Table 2
Diagnostic data and performance of Berlin questionnaire and Epworth sleepiness scale for screening of OSA during pregnancy.

Questionnaire/study	TP	FP	FN	TN	Sensitivity (95%CI)	Specificity (95%CI)	LR+ (95%CI)	LR− (95%CI)
Berlin								
Tantrakul et al. 2015 [11]	13	6	10	43	0.57 (0.34, 0.77)	0.88 (0.75, 0.95)	4.62 (2.01, 10.6)	0.50 (0.31, 0.80)
Lockhart et al. 2015 [14]	22	85	8	133	0.73 (0.54, 0.88)	0.61 (0.54, 0.68)	1.88 (1.43, 2.47)	0.44 (0.24, 0.80)
Wilson et al. 2013 [12]	13	19	2	9	0.87 (0.60, 0.98)	0.32 (0.16, 0.52)	1.28 (0.92, 1.76)	0.41 (0.1, 1.68)
Fung et al. 2013 [9]	13	13	1	14	0.93 (0.66, 1.00)	0.52 (0.32, 0.71)	1.93 (1.27, 2.93)	0.14 (0.02, 0.94)
Facco et al. 2012 [13]	11	23	17	49	0.39 (0.15, 0.59)	0.68 (0.56, 0.79)	1.23 (0.69, 2.18)	0.89 (0.64, 1.25)
Olivarez et al. 2010 [10]	7	29	13	51	0.35 (0.15, 0.50)	0.64 (0.52, 0.74)	0.97 (0.50, 1.88)	1.02 (0.71, 1.46)
ESS								
Tantrakul et al. 2015 [11]	9	19	14	28	0.39 (0.20, 0.61)	0.60 (0.44, 0.74)	0.97 (0.52, 1.79)	1.02 (0.68, 1.53)
Lockhart et al. 2015 [14]	15	88	11	119	0.58 (0.37, 0.77)	0.57 (0.50, 0.64)	1.36 (0.94, 1.96)	0.74 (0.46, 1.17)
Facco et al. 2012 [13]	10	17	18	55	0.36 (0.19, 0.56)	0.76 (0.65, 0.86)	1.51 (0.79, 2.89)	0.84 (0.62, 1.14)

Abbreviations: CI = confidence interval; ESS = Epworth sleepiness scale; FN = false negative; FP = false positive; LR- = likelihood ratio negative; LR+ = likelihood ratio positive; OSA = obstructive sleep apnea; TN = true negative; TP = true positive.

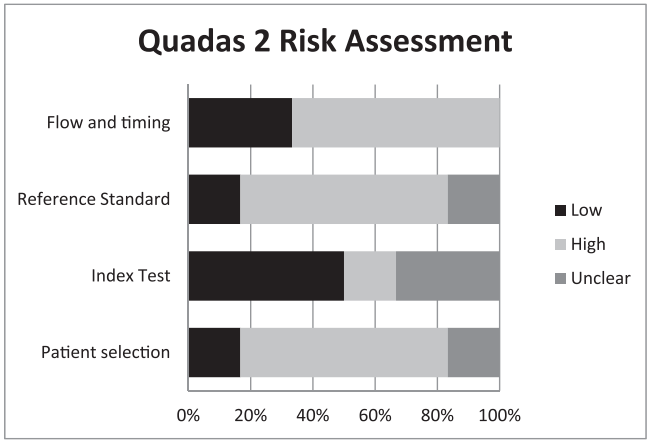

Fig. 2. Quality assessment for diagnostic test of the included studies according to the QUADAS-2 tool: proportion of studies with low, high, or unclear RISK of BIAS.

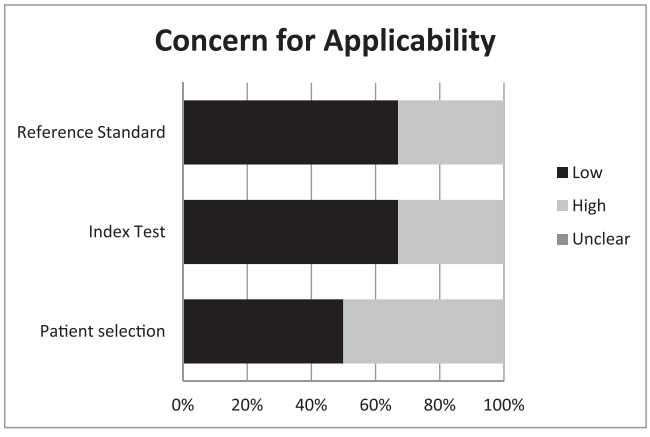

Fig. 3. Quality assessment for diagnostic test of the included studies according to the QUADAS-2 tool: proportion of studies with low, high, or unclear concerns regarding applicability.

and timing domain were high in 4 studies. The reasons were inappropriate interval between index test and reference standard (>2 weeks) in 2 studies [9,12]; not all subjects underwent the objective sleep testing in 2 studies [12,14]; not all subjects underwent the same type of recording in 1 study [9]; and not all subjects were included in the analysis in 3 studies [12–14]. Verification bias occurred if not all of the included subjects were subjected to an objective nocturnal sleep test [64–66].

High risk of bias and applicability occurred because of differences in methodology, especially the diagnostic measure of OSA and pregnancy risks. However, these factors were also included in the meta-regression to clarify the potential effect on questionnaire performance.

Performance of Berlin questionnaire

Among 6 included studies (n = 604), the overall pooled prevalence of OSA was 26.7% (95%CI: 16.9%, 34.4%). When categorized into low and high risk pregnancy, the pooled prevalence was approximately 23.5% (95%CI: 12.8%, 34.2%, I^2 = 82.7%, p < 0.001) and 29.6% (95%CI: 22.8%, 36.4%, I^2 = 0, p = 0.59), respectively.

The sensitivity and specificity of the Berlin questionnaires varied highly across studies, i.e., ranging from 0.35 to 0.93 and 0.32 to 0.88, respectively (see Fig. 4). The pooled sensitivity and specificity were 0.66 (95%CI: 0.45, 0.83; I^2 = 78.65 and Q test $p < 0.001$) and 0.62 (95%CI: 0.48–0.75; I^2 = 81.55 and Q test $p < 0.001$), respectively.

The LR+ and LR− were heterogeneous ranging from 0.97 to 4.62 and 0.14 to 1.02, respectively. The pooled LR+ and LR− were 1.75 (95%CI: 1.28–2.38; I^2 = 28.85 and Q test $p = 0.02$) and 0.54 (95%CI: 0.33, 0.90 I^2 = 69.91 and Q test $p = 0.01$), respectively (see Figure S1).

The DORs varied greatly across studies and ranged from 0.95 to 14.0, leading to a pooled DOR of 3.23 (95%CI: 1.54–6.77; I^2 = 96.49 and Q test $p < 0.001$), see Figure S2). This suggests that the odds of having OSA are 3 times higher in those with a positive Berlin questionnaire than those with a negative Berlin questionnaire. In addition, the SROC was estimated and graphed, which yielded an area under the curve (AUC) of 0.68 (95%CI 0.08–0.98), see Fig. 5.

Finally, the post-test probability was estimated using Fagan's nomogram (see Fig. 6), which yielded a post-test probability of 38% given a pre-test probability of 26% and LR+ of 1.75. This suggests that the overall probability of OSA occurrence is 38% if a pregnant woman has a positive Berlin questionnaire result.

Assessment of heterogeneity

Across studies, the Berlin questionnaire showed extremely high heterogeneity for the DOR with an I^2 of 91.0% (95%CI: 83%, 100%). The estimated threshold effect was −0.02 (95%CI: −0.70, 0.66), which suggests that the threshold cutoff of the Berlin score was only minimally influenced by heterogeneity.

Other sources of heterogeneity were explored with meta-regression, as shown in Figure S3. Results showed that

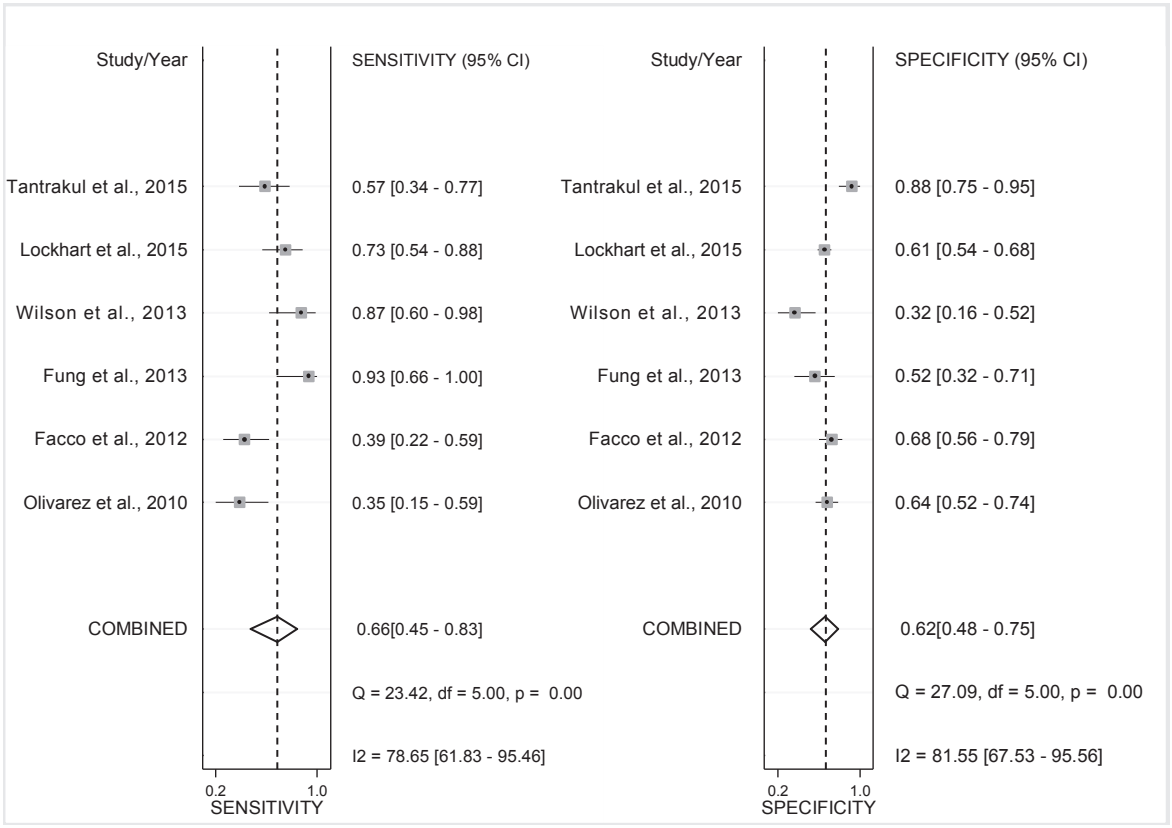

Fig. 4. Forest plot for Berlin questionnaire in screening OSA during pregnancy. Abbreviations: CI = confidence interval; df = degree of freedom; OSA = obstructive sleep apnea.

differences in the performances of the Berlin questionnaire (i.e., sensitivity and specificity) were accounted for by the use of PSG (yes/no), RDI vs AHI for OSA diagnosis, and risk of pregnancy (low vs high).

Accordingly, subgroup analyses were performed, which revealed improvements in sensitivity among those studies which used PSG and RDI as the reference tests, with a pooled sensitivity of 0.90 (95%CI:0.78–1.00), 0.90 (95%CI:0.78–1.00), respectively (See Table 3). In addition, the sensitivity was also higher in pregnant women in general ANC clinic and when the GA was above 20 weeks, with pooled sensitivities of 0.81 (95%CI: 0.71, 0.91) and 0.74 (95%CI: 0.56–0.93), respectively.

Publication bias assessment

Publication bias was assessed based on the DOR using Deek's funnel plot and test, see Figure S4. The funnel is symmetrical and this corresponded with Deek's test (coefficient = 11.47, SE = 19.01, *p*-value of 0.60) suggesting that a study size effect (publication bias) was unlikely.

ESS performance

Meta-analysis of ESS performance was analyzed from only 3 studies (N = 420), see Table 2. The sensitivity and specificity of ESS across different studies ranged from 0.36 to 0.58 and 0.58 to 0.76, respectively. The pooled sensitivity was 0.44 (95%CI: 0.33, 0.56; $I^2 = 32.8\%$ and Q test $p = 0.23$), with a pooled specificity of 0.62 (95%CI: 0.57, 0.67; $I^2 = 76.9\%$ and Q test $p = 0.013$). The pooled LR+ was 1.29 (95%CI: 0.973, 1.71; $I^2 = 0\%$ Q test $p = 0.56$), and the pooled LR-was 0.86 (95%CI: 0.70, 1.07; $I^2 = 0\%$ and Q test $p = 0.55$). The pooled DOR was 1.53 (95%CI: 0.89, 2.60; $I^2 = 0\%$ and Q test $p = 0.56$). These results indicate a low heterogeneity.

Discussion

We performed a systematic review and meta-analysis of how screening questionnaires for OSA performed during pregnancy. Our findings indicated that the Berlin questionnaire has poor to fair performance with a pooled sensitivity, specificity, LR+, and LR− of 0.66, 0.62, 1.75, and 0.68, respectively. Using the Berlin questionnaire could change the pre-test probability of being recognized with OSA from 26% to 38%. The ESS had a very poor predictive value.

A Fagan plot obtained using the Berlin questionnaire to detect OSA during pregnancy showed that it did not help clinical decision making either on treatment threshold (confirmation) or test threshold (exclusion). There was a high degree of heterogeneity in the usage of the Berlin questionnaire, but only a small threshold effect from a hierarchical SROC curve analysis. We attempted to explore the source/s of the noted heterogeneity using meta-regression analysis. The results showed a higher sensitivity of the Berlin questionnaire. This analysis indicated improvement in the sensitivity of the Berlin questionnaire if the reference test was a PSG, and looking at RDI. The sensitivity was also higher in the general pregnancy population compared to high risk pregnancy, and if it was performed after 20 weeks of gestation.

The explanation for the poor discriminative values of the conventional OSA screening questionnaires during pregnancy might be

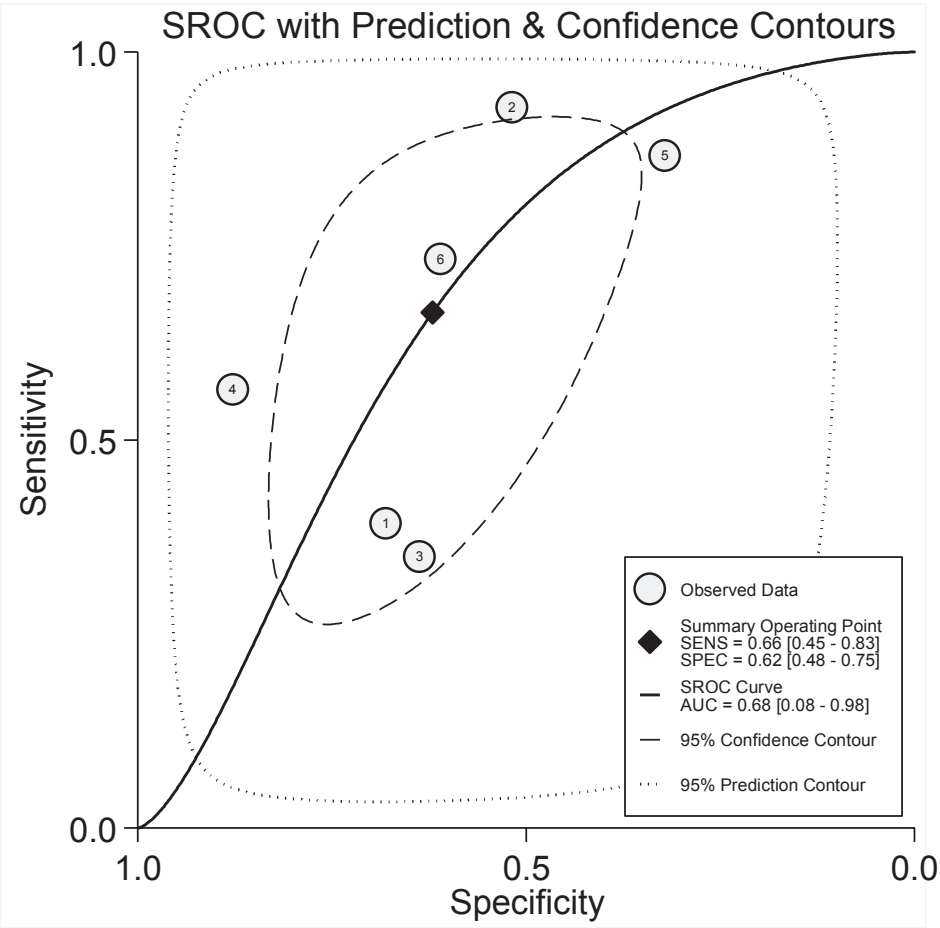

Fig. 5. Summary receiver operator curve (SROC) of Berlin questionnaire for diagnosis of OSA during pregnancy. Abbreviations: AUC = area under the curve; SENS = sensitivity; SPEC = specificity; SROC = summary receiver operator curve.

related to the facts that 1) both OSA and pregnancy lead to similar sleep complaints; 2) that there is a continuous change in symptomatology and the severity of the sleep-disordered-breathing with progression of pregnancy; 3) that the standard and threshold to diagnose SDB during pregnancy has not been defined; 4) finally, that the optimal timing of the questionnaire administration has not been standardized.

The Berlin questionnaire and ESS were the most frequently used screening tools during pregnancy. There are several other available OSA screening questionnaires such as the Nordic sleep questionnaire, and sleep disorder questionnaire, but they have not been tested or validated on pregnant women [23,24]. The majority of pregnant women experienced poor sleep quality, insufficient nocturnal sleep and daytime sleepiness. Sleep disruption occurs from early pregnancy and increases, particularly during the third trimester [8,67–69]. Our result showed higher sensitivity of the Berlin questionnaire after 20 weeks gestational age. Our findings indicate that more sensitive and specific sleep questionnaires in pregnancy are needed.

The ESS was of very little help in suggesting OSA during pregnancy. Excessive daytime sleepiness (EDS) is highly prevalent (31.0%–45.5%) even in early pregnancy and increased significantly as pregnancy progressed, probably due to the increase in progesterone and sleep disruption from pregnancy per se [70,71]. EDS (ESS≥10) is not associated with GDM and GHT. However, an ESS score >16 was associated with GDM [70,71]. There is a correlation between an increasing ESS score and the other symptoms of SDB such as loud snoring, and apnea; such findings raise the question of the optimal cut-off threshold for ESS in pregnant women. In addition, ESS had been found to be poorly predictive of OSA in non-pregnant population, so it is not surprising that it does not predict OSA in pregnancy [72,73]. Given that ESS is a better predictor of depression compared to other health outcomes, it might be worth looking at this association in pregnancy cohorts [74–76].

Worsening of OSA severity and symptoms occurred as pregnancy progressed and the prevalence of OSA increased from early pregnancy to 3rd trimester [7,69]. During the 3rd trimester, the incidence of new-onset SDB was reported at 20%, in association with twin pregnancy and new-onset of self-reported frequent snoring [7]. Pregnancy-onset snoring was also reported to be associated with pre-eclampsia [49]. This finding highlights the potential for SDB to impact adversely on maternal and fetal outcomes during pregnancy. However, there is still a lack of evidence for SDB during pregnancy, particularly with respect to the role of screening for SDB and potential benefits of treatment, which highlights the urgent need for more research in this area.

Recently, the STOP-BANG questionnaire has become more popular, given its simplicity and greater consistency across different AHI severity, when compared to the Berlin questionnaire [22,72,77]. But whether this remains true in pregnancy population needs further study. A recent review also pointed out that the current OSA

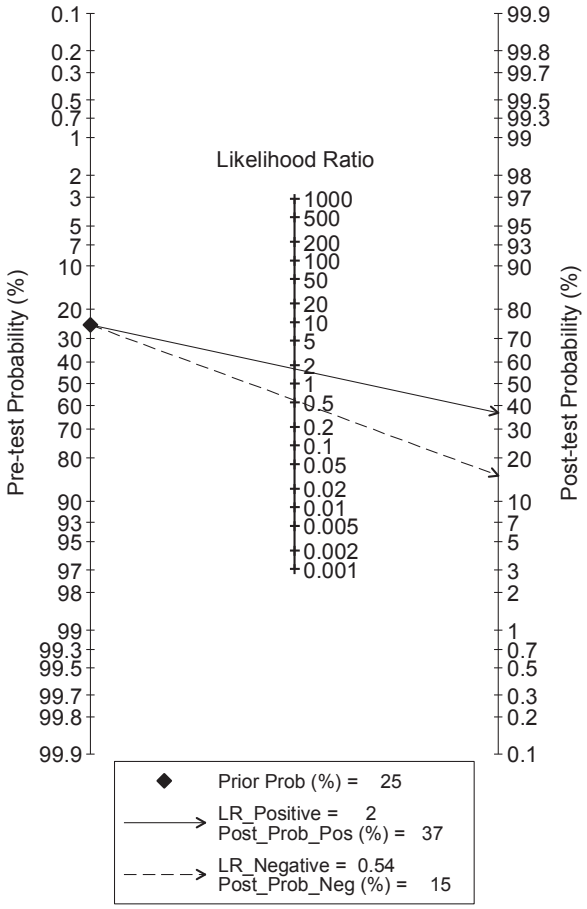

Fig. 6. Fagan plot of Berlin questionnaire for diagnosis of OSA during pregnancy. Abbreviations: LR_negative = likelihood ratio negative; LR_positive = likelihood ratio positive; OSA = obstructive sleep apnea; Post_Prob_neg = posterior probability negative; Post_Prob_Pos = posterior probability positive; Prior Prob = prior probability.

screening tools may not perform well in pregnancy. However, this article was not a systematic review or meta-analysis [78].

Interestingly, from our review the performance of OSA screening questionnaire from all the included studies was compared against the diagnosis of OSA with either AHI or RDI≥ 5 events/hour. There were not enough data available on moderate to severe OSA in pregnancy. The majority of SDB during pregnancy were mild as reported in a high risk cohort [7]. However, even mild SDB during pregnancy might be important as adverse outcomes have been reported [9,79].

In contrast to the non-pregnant population, OSA screening questionnaires were mostly performed based on the diagnosis of moderate to severe severity (AHI ≥15 events/hour) [23,24], given the unclear impact of mild OSA and its treatment on the cardiovascular outcomes [80,81].

There were some limitations in our study. First, there was only a small number of available studies. Second, presence of verification and spectrum biases in some of the included studies might have caused overestimation of questionnaire performance, particularly for sensitivity [64–66]. Third, there was a high degree of heterogeneity among studies regarding recruited population, and diagnosis measures, therefore caution must be taken in generalization of the results.

In conclusion, with the complexity and the dynamic change of OSA and pregnancy, screening for this condition during pregnancy is complicated. Current OSA screening questionnaires perform poorly during pregnancy. There is a need for tools that take into account the changes over time of the symptoms of OSA, and pregnancy. New screening tools and strategies specific to pregnancy that enable us to serially screen and monitor for OSA throughout pregnancy should be developed.

Practice points

- Diagnosis of OSA during pregnancy is challenging despite its adverse effect on maternal and fetal outcomes.
- Early diagnosis and treatment of OSA during pregnancy may have potential benefits on pregnancy outcomes.
- Current conventional OSA screening questionnaires perform poorly in pregnancy. And there is no standard guideline for screening and treatment of OSA during pregnancy.

Research agenda

- There is an urgent need for a simple and accurate screening tool for OSA during pregnancy.
- As pregnancy progresses, there are dynamic changes of OSA and pregnancy. Hence a specific screening tool that can successively screen for OSA throughout pregnancy should be developed and validated.

Table 3
Meta-regression and subgroup analyses for Berlin questionnaire during pregnancy.

Factors	Conditions	No. of studies	I^2	Sensitivity (95%CI)	*p*-value	Specificity (95%CI)	*p*-value
All studies		6	96.5	0.67 (0.45, 0.83)		0.62 (0.48, 0.74)	
Risk of pregnancy	High	3	83%	0.44(0.32, 0.56)	<0.001	0.74(0.62, 0.85)	0.35
	General	3		0.81(0.71, 0.91)		0.51(0.35, 0.67)	
Reference sleep test	PSG	2	79%	0.90(0.78, 1.00)	0.03	0.42(0.23, 0.60)	0.03
	Non-PSG	4		0.52(0.37, 0.67)		0.70(0.60, 0.79)	
Respiratory index	AHI	4	79%	0.52(0.37, 0.67)	0.03	0.70(0.60, 0.79)	0.03
	RDI	2		0.90(0.78, 1.00)		0.42(0.23, 0.60)	
Early pregnancy (GA ≤20 weeks)	Yes	2	58%	0.47(0.17, 0.78)	0.15	0.78(0.65, 0.90)	0.38
	No	4		0.74 (0.56, 0.93)		0.54(0.42, 0.66)	

Abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; GA = gestational age; OSA = obstructive sleep apnea; PSG = polysomnography; RDI = respiratory disturbance index.

Conflicts of interest

None of the authors had a conflict of interest or financial support.

Authors' contribution

Study concept and design: VT, PN, CG, WK, AT. Study selection and risk of bias assessment: VT, PN, WK. Data extraction: VT, PN. Data analysis: VT, AT. Interpretation of data: VT, PN, CG, MM, PP, WK, JA, AT. Drafting the manuscript: VT, PN, CG, MM, PP, JA, AT. Critical revision of the manuscript for important intellectual content: VT, PN, CG, MM, PP, JA, AT. Final approval of the version to be published: all authors read and approved the final manuscript.

Acknowledgments

This study is a part of Dr. Visasiri Tantrakul's training in Ph.D. program for Clinical Epidemiology, Faculty of Medicine, Ramathibodi Hospital and Faculty of Graduate Studies, Mahidol University, Bangkok, Thailand. All authors declare that no funding source or any sponsor was involved in this study and manuscript preparation for publication. We would like to thank Mr. Stephen Pinder for checking and improving the English of our manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2016.11.003.

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BMJ Open

Consumption of fruits and vegetables and associations with risk factors for non-communicable diseases in the Yangon region of Myanmar: a cross-sectional study

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To cite: Kjøllesdal M, Htet AS, Stigum H, *et al*. Consumption of fruits and vegetables and associations with risk factors for non-communicable diseases in the Yangon region of Myanmar: a cross-sectional study. *BMJ Open* 2016;**6**: e011649. doi:10.1136/bmjopen-2016-011649

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-011649).

Received 23 February 2016
Revised 28 June 2016
Accepted 6 July 2016

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ABSTRACT

Objectives: To explore the intake of fruits and vegetables in the Yangon region, Myanmar, and to describe associations between intake of fruits and vegetables (FV) and established risk factors for non-communicable diseases.

Design: 2 cross-sectional studies, using the STEPs methodology.

Setting: Urban and rural areas of the Yangon region of Myanmar.

Participants: 1486, men and women, 25–74 years, were recruited through a multistage cluster sampling method. Institutionalised people, military personnel, Buddhist monks and nuns were not invited. Physically and mentally ill people were excluded.

Results: Mean intake of fruit was 0.8 (SE 0.1) and 0.6 (0.0) servings/day and of vegetables 2.2 (0.1) and 1.2 (0.1) servings/day, in urban and rural areas, respectively. Adjusted for included confounders (age, sex, location, income, education, smoking and low physical activity), men and women eating ≥2 servings of fruits and vegetables/day had lower odds than others of hypertriglyceridaemia (OR 0.72 (95% CI 0.56 to 0.94)). On average, women eating at least 2 servings of fruits and vegetables per day had cholesterol levels 0.28 mmol/L lower than the levels of other women. When only adjusted for sex and age, men eating at least 2 servings of fruits and vegetables per day had cholesterol levels 0.27 mmol/L higher than other men.

Conclusions: A high intake of FV was associated with lower odds of hypertriglyceridaemia among men and women. It was also associated with cholesterol levels, negatively among women and positively among men.

Strengths and limitations of this study

- Our study had a high response rate.
- Research was carried out in a population in which knowledge about risk factors for non-communicable diseases is scarce.
- The questions on fruit and vegetable consumption were brief, including few details which could have enhanced the interpretation.
- Data collection was confined to one area of the country, thus making it difficult to make nationwide implications.

INTRODUCTION

Dietary factors contribute to a large share of the global burden of disease. Lim *et al*[1] estimate that in 2010, 10% of all deaths (12.5 million) were attributable to such risk factors. The number of deaths attributed to a diet low in fruits and vegetables (FV) alone was ~6.6 million.[1] The protective effects of FV in the diet may be because of their high content of vitamins and minerals, as well as fibre, acting through mechanisms such as lowering blood pressure (BP), reducing antioxidant stress, improving lipoprotein profile and increasing insulin sensitivity.[2]

The WHO has recommended a daily intake of ≥5 portions (400 g) of FV.[3] However, many people have lower intakes, both in high-income and low-income countries.[4] A study from 52 low-income and middle-income countries reported low intakes of FV, defined as <400 g/day, which varied from 37% among men in Ghana to 99% for women and men in Pakistan.[5] In many Southeast Asian countries, large proportions of the population had a low intake.[5] In Myanmar, the proportions were 83%

among men and 85% among women.[5] A low intake of FV was more common with increasing age and in lower income groups in many countries, and with rural settlement in some.[5]

A low intake of FV is associated with non-communicable diseases (NCDs), such as cardiovascular diseases (CVDs), cancer and diabetes,[1 3] as well as with its risk factors.[3 6 7] Most studies are conducted in Western countries, and little is known about the association between the intake of FV and NCD risk factors in developing countries.[8]

Ischaemic heart disease and stroke are now the two leading causes of death in Southeast Asia, with 22% of all deaths attributable to them, which leads to 10% of the disability-adjusted life years (DALYs).[9] Diabetes is the eighth leading cause of death in this region.[9] The high prevalence of, and mortality from these diseases, makes prevention an urgent task. Estimations of the occurrence of risk factors, and of associations between distal and more proximal factors, could help in directing the efforts of NCD prevention in a country. Based on previous studies, increasing the intake of FV could potentially be a means to reduce the risk of NCDs. Nonetheless, more knowledge is warranted on the association between the intake of FV and NCDs in this region, and about the differences in intake of FV in various sociodemographic groups.

Therefore, we first aim to explore the intake of FV and its relation with sociodemographic factors, and second, to describe associations between the intake of FV and established risk factors for NCDs; BP, body mass index (BMI), waist hip ratio (WHR), lipid profiles and blood glucose among women and men aged 25–74 years in the Yangon region of Myanmar.

METHODS

Two regional, cross-sectional studies focusing on the risk factors for NCDs were conducted in urban and rural areas of Yangon, Myanmar from September to November 2013 and September to November 2014, respectively. The studies followed the WHO STEPs-wise approach for the surveillance of risk factors for chronic disease.[10] The approach consists of three STEPs: (1) questionnaire survey based on sociodemographic characteristics, lifestyle-related habits and history of hypertension and diabetes; (2) Physical measurements including BP, body height, weight, waist and hip circumference; and (3) laboratory investigation for fasting lipid profiles (total cholesterol (TC), triglycerides (TG)) and fasting blood glucose (FBG) from venous blood sample.

Sampling

Men and women aged 25–74 years were included in the study. Institutionalised people, military personnel, Buddhist monks and nuns were not invited to the study. People who were physically and mentally ill were excluded. Based on the WHO sample size calculator for the STEP survey,[10] we estimated that with a level of confidence of 1.96, a margin of error of 0.05, a design effect of 1.5 and an expected response rate of 80%, that we would need a sample size of 500 in each of the two studies for many of the risk factors, which has a prevalence of around 10%, for example, hypertension and low levels of physical activity, or alternatively around 90%, like a low intake of FV.[11] Other risk factors would require a sample size of ∼1000, with a prevalence of around 20–25%, for example, smoking and overweight.[11] Based on these numbers and practical limitations, we considered a sample of 800 to be sufficient in each survey. Calculations were separately carried out for the urban and rural survey, with the aim to be able to compare men and women (number of sex/age estimates=2).

A multistage cluster sampling method was performed. First, six urban townships and six rural townships were randomly selected. Second, these townships were divided into clusters, villages in the rural townships and wards (urban unit of township) in the urban townships. Five villages from each of the six rural townships and five wards from each of the six urban townships were randomly selected (60 clusters altogether). Finally, 26–27 households were randomly chosen within each cluster. Eligible household members were listed from selected households, and one was randomly invited to participate in the study. A male participant was selected from half the households and a female participant from the other half, and it was decided in advance which households should include a male and which should include a female. Data were collected during the daytime the first day, and then in the morning of the next day (blood samples). If a participant was not at home, she/he was contacted and an appointment was made for the next day if she/he was willing to participate, most often right after blood samples were taken. As a result, we had 1608 invitees with an equal gender distribution (804 from urban and 804 from rural areas). A total of 755 (94%) from urban areas and of 731 (91%) from rural areas completed STEPs 1 and 2. A total of 692 (86%) participants from urban and 676 (83%) participants from rural areas completed all three STEPs. The reasons given for not participating in STEPs 1 and 2 were 'not willing' and 'not having time'. In STEP 3, non-response was due to worries about blood tests. We excluded 13 pregnant women (3 from urban and 10 from rural areas), as maternal physiological changes in pregnancy might affect some of the risk factors assessed.

Data collection and measurements

Trained medical doctors interviewed the participants on sociodemographics and risk factors, and anthropometric measurements (body height, weight, waist and hip circumference) were taken using the WHO standard technique.[10] For the urban study in 2013, four research assistants were recruited through the Myanmar Medical

Association. A 2-day training and pretest were conducted in the Myanmar Medical Association with technical input from the Department of Medical Research (Lower Myanmar). The trainees were exposed to the methods of sampling and interpersonal communication, obtaining informed consent and a survey questionnaire on the first day. The second day of training was focused on interactive sessions to introduce data collection methods and correct measuring methods for all the STEPs. Anthropometric measures, physiological measurements and laboratory tests were practiced and trained according to the standardised method of the WHO guidelines. The standardisation of the instruments used in the fieldwork was carried out both before and during the training. The trained field researchers conducted a pretest comprising STEPs 1 and 2 of the survey in the Yangon region. Questionnaires were further clarified after the pretest, and the trained field researchers underwent a trial in practical skills after the clarification. The rural study in 2014 had the same principal investigator and person responsible for the training as in the urban study. Four new research assistants were recruited, using the same methods as in the urban study, and we used identical methods of training.

A measuring tape was used to measure individual's height without foot wear and any head gear, (measured to the nearest to 0.1 cm). Body weight was measured with a portable electronic weighing scale to the nearest 0.1 kg, and the participants were requested to wear light clothes without footwear during weighing. Waist and hip circumference measurements were conducted in a private place with the measuring tape. Waist circumference was taken at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest (hip bone), in the standing position directly over the skin, according to the WHO STEP survey guidelines. The hip circumference was horizontally taken at the maximum circumference over buttocks, with both measured to the nearest 0.1 cm.

Fifteen minutes after a face-to-face interview, BP was measured three times with a 3 min pause, using an OMRON M6 automatic BP monitor. Mean BP was calculated from the average of the second and third measurements. Venous blood samples were collected in a lipid tube and glucose tube containing fluoride and transported in cold boxes to the National Health Laboratory, Yangon, a reference laboratory of the Ministry of Health, Myanmar, by boat and/or car or motorcycle. FBG concentration was measured by the enzymatic reference method with hexokinase, using reagents of COBAS from Roche Diagnostics, Indianapolis, Indiana, USA. The serum concentration of TC and TG were determined by using an enzymatic colorimetric test with reagents of COBAS from Roche Diagnostics, all within 3 hours of collection.

Variables

Data on the intake of FV were collected with questions on the number of days a week vegetables or fruit were eaten, in addition to the number of servings on those days. Servings were defined with a pamphlet with pictures of examples of one serving. The number of servings per day of FV combined were calculated and recoded into the following variables: '≥daily intake', '≥2 servings daily' and '≥5 servings daily', as well as 'number of servings/day'. As the numbers of participants reaching the recommended five servings per day was very low, the cut-off '≥2 servings daily' was used in the analyses.

FBG (mmol/L), TG (mmol/L), TC (mmol/L) and BP (mm Hg) values were dichotomised according to established cut-offs for increased risk.[10] For estimating BP, the average of the two last of three measurements were used. BMI was calculated from the measured height and weight (kg/m^2), and the ratio between waist and hip circumference was also calculated. Diabetes was defined as FBG≥7 mmol/L and/or self-reported diabetes, hypercholesterolaemia as TC>5.17 mmol/L, hypertriglyceridaemia as TG≥2 mmol/L, hypertension as systolic BP≥140 mm Hg and/or diastolic BP≥90 and/or self-reported current antihypertensive treatment for hypertension within 2 weeks prior to the interview, overweight and obesity as BMI≥25 kg/m^2 and central obesity as WHR>0.90 in men and >0.85 in women. There were no missing data for BMI, WHR and BP, although 104 participants had missing values on lipid profile and 102 participants on FBG.

Educational level was assessed by asking for the highest level of completed education and recoded into 'primary' (completed primary school or less), 'secondary' (completed secondary school or high school) and 'higher' (completed college or university or a postgraduate). Income details were collected by asking for the average household earning per week, month or year. This was converted into US dollars (US$) per day and recoded according to the World Bank cut-offs for moderate poverty (US$2/day), '<US$2/day' and '≥US$2/day'.[12] Smoking was recorded as currently smoking tobacco products, 'no' or 'yes'. Physical activity was estimated across all domains of work, household tasks, transportation and leisure-time activity. Low physical activity was defined as <3 days of vigorous-intensity activity for at least 20 min/week, or <5 days of moderate-intensity activity (with a minimum of at least 600 metabolic equivalent of task (MET)-min) per week, using standard METs based on the WHO guidelines. All participants gave information on their education, smoking and physical activity, and 91 had missing information (refused to answer) on income. Since income was a covariate in statistical analyses, those with missing information on income were excluded (total n=1395, having completed STEPs 1 and 2).

Statistical methods

We explored associations between risk factors for chronic disease and a daily intake of at least two servings of FV using linear regressions. Risk factors (BMI, WHR, FBG, BP, TC, TG) and intake of FV were included as outcome

and exposure variables, respectively. We also described the relationships between our variables in a causal graph (directed acyclic graph (DAG))[13] (figure 1). Based on the DAG, sex, age, location, education, income, smoking and low physical activity were possible confounders and were therefore adjusted for. BMI was included as a mediator in the analyses in which BMI was not the outcome, and was hence not adjusted for. To explore associations between diabetes, overweight, obesity, hypertension, hypertriglyceridaemia and hypercholesterolaemia and intake of FV, we used logistic regressions, with adjustments for the same potential confounders. We declared the complex sample design using 'svyset' command in STATA based on the different stages of sampling units of the study population using 2014 Myanmar census data.

We tested the assumptions of the linear model (linear effects and constant error variance) and the logistic model (linear effects) by plotting residuals versus predicted values. We looked for observations with a high influence by plotting δ-βs versus the observation numbers and three outliers were removed for FBG. Possible interaction effects between the intake of FV and sex, and between the intake of FV and location, were checked for. Interactions between sex and the intake of FV were found regarding cholesterol and hypercholesterolaemia. Results from these analyses were presented for men and women separately, and Stata V.14 (StataCorp 2015) was used for the analyses.

The paper was written as a part of a course in scientific writing in Myanmar (see online supplementary material).

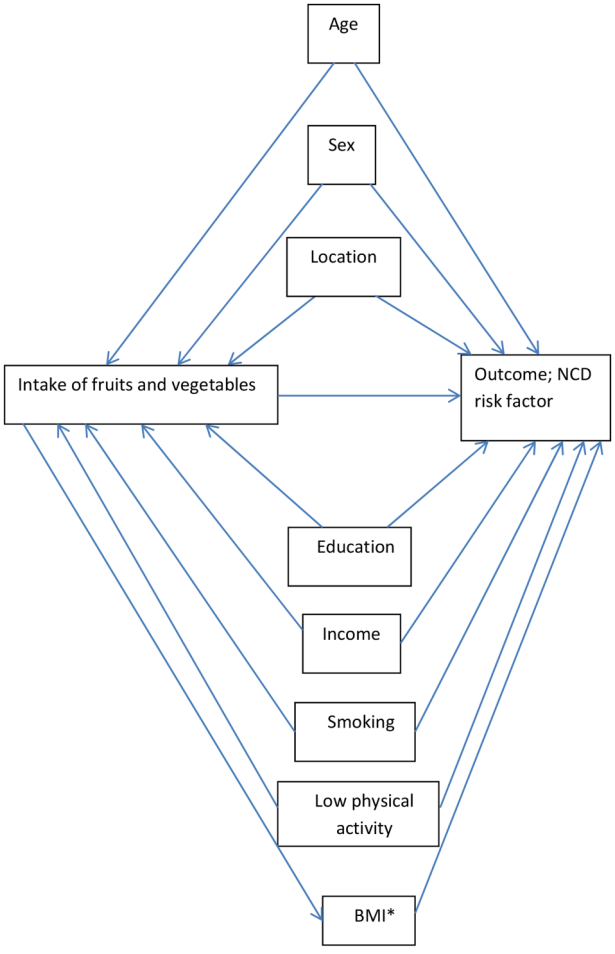

Figure 1 DAG of causal relationships. *BMI was included as a mediator in analyses with all outcomes, except when BMI was the outcome. BMI, body mass index; DAG, directed acyclic graph; NCD, non-communicable disease.

Ethics

Written informed consent was obtained from the study participants; all information was handled with strict confidentially and the results of blood tests were provided to the participants. Participants with abnormal biological risk factors were advised to attend the closest health facility.

RESULTS

The mean age of the participants was 47 years (table 1). Of those living in urban areas, approximately half had an income of ≥US$2/day and one-third had a primary education only, whereas 21% had a college or university degree. In rural areas, almost two-thirds had an income of<US$2/day and three-fourths had a primary education only. Roughly one-fourth of the sample was tobacco smokers, and 11% had low levels of physical activity. The mean intake of fruits was 0.8 (SE 0.1) servings/day in urban areas and 0.6 (0.0) servings/day in rural areas, while the mean intake of vegetables was 2.2 (SE 0.1) servings/day in urban areas and 1.2 (0.1) servings/day in rural areas. Few participants reached the recommended five servings a day. The intake of FV varied with sociodemographic variables (table 2). It increased with education in urban and rural areas, and in rural areas it was highest among women.

On average, women eating at least two servings of FV per day had cholesterol levels 0.28 mmol/L lower than the levels of other women, adjusted for all included confounders (table 3). When adjusted for sex and age only, men eating at least two servings of FV per day had cholesterol levels 0.27 mmol/L higher than the levels of other men. In logistic regressions, adjusted for all included confounders, those eating at least two servings of fruits and vegetables daily had lower odds than others for hypertriglyceridaemia (0.72 (95% CI 0.56 to 0.94); table 4).

DISCUSSION

The intake of FV among adults in the Yangon region of Myanmar was low. A higher intake of FV was associated with lower odds of hypertriglyceridaemia, and among women lower levels of TC. Among men, a higher intake of FV was associated with higher levels of TC before adjustment for confounders other than age and sex.

The present study had a reasonable sample size and a high response rate, thereby strengthening the internal

Table 1 Characteristics of the sample in STEP survey in the Yangon region of Myanmar, 2013–2014

	Urban	Rural	p Value	Total
Sex			NS	
Men (%)	50.0	50.6		50.3
Women (%)	50.0	49.4		49.7
Age, mean (SE)	48.2 (0.8)	46.3 (0.8)	NS	47.4 (0.6)
Education			0.003	
Primary (%)	35.2	74.7		51.5
Secondary or high school (%)	44.2	20.1		34.3
College/university or postgraduate (%)	20.5	5.2		14.2
Income			NS	
≥US$2/day (%)	47.7	34.9		42.4
<US$2/day (%)	52.3	65.1		57.6
Smoking tobacco (%)	26.5	31.9	NS	28.7
Low physical activity (%)	10.9	10.4	NS	10.7
Servings of fruits per day, mean (SE)	0.8 (0.1)	0.6 (0.0)	0.006	0.7 (0.0)
Servings of vegetables per day, mean (SE)	2.2 (0.1)	1.2 (0.1)	<0.001	1.8 (0.1)
Fruits and vegetables			<0.001	
≥Daily (%)	88.7	76.7	0.008	83.8
≥2 servings daily (%)	65.9	30.3	<0.001	51.3
≥5 servings daily (%)	22.8	6.0	<0.001	16.1

N=1395; sampling weights.
NS, not significant.

validity of the study. Non-attendance could have introduced a selection bias, but due to a response rate of >90% in STEPs 1 and 2 and >80% in STEP 3, it is unlikely that it has had a high impact.[14] People in the military, monks and nuns were not invited to participate the study. Owing to different life circumstances or a certain lifestyle, differences in their health compared with the rest of the population may lead to a selection bias. If so, the results are not possible to generalise to the entire Yangon population. Moreover, due to large demographic differences throughout Myanmar, the results may not be generalised to the country as a whole.

Questions about the intake of FV were rather simple, but answers could be subjected to recall bias or difficulties in reporting the correct days of eating these items, especially if consumption took place infrequently. Even though both surveys were carried out between September and November, some seasonal variations in the intake of FV may have occurred. Myanmar is an agricultural country, and fresh FV are available at a low cost throughout the season. Still, based on previous research, a low intake of FV was expected.[5] The proportion of participants eating ≥5 servings of FV daily declined since the last STEP survey in this region 10 years ago, from 30% to 16%.[15] The low intake was also comparable to other countries in the region.[5 16] Average vegetable consumption was at the level found in a larger survey in Thailand, where fruit consumption was lower.[17] The study from Thailand reported higher intakes of FV among women, and with a higher education.[17] In our

Table 2 Mean intake of fruit and vegetables (servings/day, mean (SE)) in various sociodemographic groups among participants in STEP survey in the Yangon region of Myanmar, 2013–2014; N=1395; sampling weights

	Fruit and vegetable intake Urban	p Value differences Urban	Fruit and vegetable intake Rural	p Value differences Rural	Fruit and vegetable intake Total	p Value difference Total
Income		NS		NS		0.014
<US$2/day	2.8 (0.2)		1.6 (0.1)		2.3 (0.1)	
≥US$2/day	3.2 (0.1)		1.9 (0.1)		2.8 (0.1)	
Education		0.03		0.05		0.003
Primary	2.8 (0.1)		1.7 (0.1)		2.1 (0.1)	
Secondary	3.2 (0.2)		2.0 (0.1)		2.8 (0.1)	
Higher	3.1 (0.2)		2.1 (0.2)		3.1 (0.1)	
Sex		NS		0.04		NS
Men	3.1 (0.2)		1.6 (0.0)		2.5 (0.1)	
Women	2.8 (0.1)		2.0 (0.1)		2.5 (0.1)	

NS, not significant.

Table 3 The effect of having ≥2 servings of fruit and vegetables daily on various risk factors for NCD, compared with those with lower frequency of intake, among 25–74 years old in the Yangon region of Myanmar, taking part in STEP survey 2013–2014

	Crude β (95% CI)	Adjusted for sex, age β (95% CI)	Adjusted for sex, age, location, education, income, smoking and low physical activity β (95% CI)
Body mass index	0.74 (−0.11 to 1.60)	0.68 (−0.02 to 1.38)	0.23 (−0.27 to 0.73)
Waist hip ratio	−0.00 (−0.01 to 0.01)	0.00 (−0.01 to 0.01)	−0.00 (−0.01 to 0.01)
Blood glucose	0.03 (−0.12 to 0.18)	0.04 (−0.11 to 0.19)	−0.11 (−0.29 to 0.05)
Systolic blood pressure	0.02 (−2.43 to 2.48)	0.24 (−1.68 to 2.16)	−0.04 (−2.86 to 2.77)
Diastolic blood pressure	0.55 (−0.31 to 1.41)	0.59 (−0.22 to 2.16)	0.15 (−1.11 to 1.41)
Triglycerides	−0.03 (−0.17 to 0.12)	−0.02 (−0.16 to 0.13)	−0.11 (−0.23 to 0.01)
Total cholesterol	0.01 (−0.21 to 0.24)	0.27 (0.09 to 0.45) men*	0.15 (−0.02 to 0.32) men*
		−0.23 (−0.49 to 0.22) women	−0.28 (−0.53 to −0.02) women

Linear regression analyses with sampling weights; N=1291–1395.
*For total cholesterol there was a significant interaction effect between intake of fruit and vegetables and sex. This interaction term is included in analyses, and separate effects estimated for men and women.
NCD, non-communicable disease.

study, a gender difference was only seen in rural areas, whereas an educational gradient was found in rural and urban areas. Increasing consumption with a higher income was seen in both studies.[17] A higher intake of FV in higher socioeconomic groups has been reported in studies from low-income and high-income countries.[18 19] In contrast to our study, several studies have found lower intakes of FV in urban than in rural areas in low-income countries.[19 20]

In studies from other countries in Asia, a higher intake of FV has been associated with an improved NCD risk profile, such as a lower systolic BP, waist circumference and low-density lipoprotein cholesterol in southern India[6] and lower odds of obesity in Iran,[21] as well as a reduced risk of CVD mortality in Japan.[22] In China, a protective effect of high fruit consumption on coronary heart disease has been found among women, but not among men.[23] In our study, the protective effect of a higher intake of FV is confirmed regarding hypertriglyceridaemia, and among women regarding cholesterol levels, though not regarding cholesterol levels among men. Differences between studies may have several explanations. The types of FV commonly eaten may vary between countries, and some FV have more protective benefits than others.[24 25] How FV are prepared influence their nutritional content, as raw and cooked vegetables may differ in content.[26] Fried vegetables are accompanied by fat, which may counteract any health benefits.[27] Additionally, salt may be added and influence the association with BP. In Myanmar, many dishes are prepared with fish sauce, which contains quite a large amount of salt. Cooked or fried vegetables may also lose heat-sensitive or water-soluble vitamins. We did not ask about types of FV, or how they were prepared. Such

Table 4 The association (OR) between having ≥2 servings of fruit and vegetables daily and various risk factors for NCD, compared with those with a lower frequency of intake among 25–74 years old in the Yangon region of Myanmar, taking part in the STEP survey 2013–2014

	Crude OR (95% CI)	Adjusted for sex, age OR (95% CI)	Adjusted for sex, age, location, education, income, smoking and low physical activity OR (95% CI)
Overweight	1.20 (0.70 to 2.06)	1.18 (0.71 to 1.98)	0.90 (0.62 to 1.56)
Central obesity	1.29 (0.95 to 1.74)	1.31 (0.95 to 1.79)	1.36 (0.98 to 1.89)
Diabetes	1.28 (0.95 to 1.73)	1.30 (0.95 to 1.78)	1.35 (0.98 to 1.86)
Hypertension	0.86 (0.68 to 1.09)	0.85 (0.69 to 1.06)	0.83 (0.63 to 1.11)
Hypertriglyceridaemia	0.78 (0.54 to 1.11)	0.78 (0.59 to 1.11)	0.72 (0.56 to 0.94)
Hypercholesterolaemia	0.98 (0.52 to 1.82)	1.76 (0.86 to 3.59) men*	1.41 (0.72 to 2.76) men*
		0.60 (0.29 to 1.12) women	0.52 (0.26 to 1.01) women

Logistic regressions, with sampling weights; N=1291–1395.
*For hypercholesterolaemia there was a significant interaction effect between intake of fruit and vegetables and sex. This interaction term is included in analyses, and separate effects estimated for men and women.
NCD, non-communicable disease.

questions should be included in future studies to inform the interpretation of the relationship between the intake of FV and NCD and its risk factors in this population.

Some of the associations between the intake of FV and NCD risk factors changed when adjusted for the potential confounders location, income, education, low physical activity and smoking. Previous analyses of our sample showed higher levels of BMI, systolic BP, FBG, TC and TG in urban than in rural areas (ASH, unpublished results). Confounding factors could work through lifestyle factors. Better off people may afford more of healthy and unhealthy foods, thus mitigating the positive effect of FV alone. A systematic review of socioeconomic differences in dietary patterns in low-income and middle-income countries reported that people in higher socioeconomic groups and in urban areas tended to eat more calories, protein, total fat, cholesterol, polyunsaturated and monounsaturated fatty acids, vitamins and fibre, as well as more FV.[20] Consequently, eating more FV may also be an indicator of higher intakes of more unhealthy foods. A higher intake of FV was associated with lower cholesterol levels among women, but higher levels among men. Other Asian studies have found a protective effect of FV among women, but not men.[25 28] Gender differences in associations may be confounded by lifestyle-related variables differing between the sexes, or there could be biological differences. In our study, the intake of FV was slightly higher among women than in men in rural, though not in urban areas. Gender differences in amount and types of FV consumed could possibly influence associations between intake of FV and cholesterol levels. It could also be that men eating more FV have a different eating pattern from women eating more FV, including more unhealthy foods.

Implications

The intake of fruits and vegetables among adults in the Yangon region, Myanmar was far below recommended levels, with socioeconomic differences. According to previous research, a low intake of fruits and vegetables should be an important risk factor for NCD. With the exception of cholesterol level among men, this was confirmed in the present study. People eating more fruits and vegetables had lower odds of hypertriglyceridemia, and among women, more favorable cholesterol levels. Unmeasured aspects of diet may explain the positive association with cholesterol levels among men. Future studies including more detailed information, such as types of fruits and vegetables, more food items and ways of preparation, is warranted to provide a better picture of the association between dietary habits and risk of NCD in the Yangon region, Myanmar.

CONCLUSION

A high intake of FV was associated with a lower prevalence of hypertriglyceridaemia. It was also associated with levels of TC, negatively among women, and positively among men.

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Contributors EB and MK conceived the idea and design for the article. MK drafted the article. All the authors contributed to the identification of the final objectives, conducted the statistical analyses, the interpretation of data, the reporting of results and in the final stage of writing.

Funding This work was supported by the Norwegian Agency for Development Cooperation (Norad), project MY-NORTH 1300650, MMR-13/0049 NORHED Espen.

Competing interests None declared.

Ethics approval Norwegian Regional Committees for Medical and Health Research Ethics (2013/1088) and Department of Health, Myanmar.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Htun et al. BMC Public Health (2021) 21:139
https://doi.org/10.1186/s12889-021-10181-5

BMC Public Health

RESEARCH ARTICLE Open Access

Empowerment and health care access barriers among currently married women in Myanmar

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Abstract

Background: Although Myanmar is moving to attain UHC in 2030, health care utilization indicators are still low, especially among women. Women's health outcomes are determined by the lack of access to health care, and many factors influence this condition. The objective of the present work was to identify the association between women's empowerment and barriers to accessing health care among currently married women in Myanmar.

Method: We performed a secondary analysis using the Myanmar Demographic and Health Survey (2015–16), including 7759 currently married women aged 15–49 years. The outcome variable, barriers to accessing health care, were asked about in terms of whether the respondent faced barriers to getting permission to go, getting money to go, the distance to the health facility, and not wanting to go alone. The variables were recoded into zero, one, and more than one barrier. After performing the exploratory factor analysis for women's empowerment indicators (decision-making power and disagreement to justification to wife-beating), a multinomial logistic regression was carried out.

Results: Among currently married women, 48% experienced no barriers when accessing health care services, 21.9% had one barrier, and 30.1% had more than one barrier. After the exploratory factor analysis, scores were recoded into three levels. Women with low and middle empowerment had 1.5 odds (AOR 1.5, 95% CI: 1.2–1.8) and 1.5 odds (AOR 1.5, 95% CI: 1.3–1.9), respectively, to have barriers to accessing health care when compared to those with high empowerment for one barrier group. For the women who had more than one barrier, women with low empowerment were 1.4 times more likely (AOR 1.4, 95% CI: 1.1–1.7) to experience barriers in comparison to women with high empowerment. The barriers were seen to be reduced in the case of women who had a high level of education, had fewer children, came from rich households, and lived in urban areas.

Conclusion: When women are more empowered, they tend to face fewer barriers when accessing health care services. This finding could contribute to the policy formulation for reducing health inequity issues by increasing women's empowerment.

Keywords: Women's empowerment, Barriers to accessing health care, Myanmar

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Background

All United Nations Member States have agreed to try to achieve universal health coverage (UHC) by 2030 as part of the Sustainable Development Goals. Many countries are already making progress towards UHC, but a lot of people are still left behind, especially vulnerable groups, including women and children from developing countries. Access to all-inclusive and high-quality health care is essential for promoting and maintaining health, preventing and managing diseases, reducing premature deaths, and achieving health equity for all.

Myanmar is one of the countries moving towards Universal Health Coverage in 2030. Though out-of-pocket financing has decreased from 81 to 65% of Myanmar's total health expenditure between 2014 and 2015 after increases in public spending, this kind of financing remains the primary method of payment for health services in the country. Though the government of Myanmar aims to extend access to a Basic Essential Package of Health Services (EPHS) to the entire population by 2020, as of the time of data collection, health facilities charged patients fees for maternal and child health services [1, 2]. In 2018, a study stated that the attainment of universal health coverage in Myanmar in the immediate future would be very challenging as a result of the low health service coverage, high financial risk, and inequalities in access to healthcare. Health care utilization indicators are low, especially for women. The rates of such indicators are low (family planning needs satisfied: 75.9%; at least four antenatal care visits: 55.5%; full immunization: 55.2%; institutional delivery: 37.1%; skill birth attendance: 60.2%) [3].

In recent years, women's empowerment has become an important global issue. The term 'women's empowerment' can be defined as the ability of women to make their own decisions and act accordingly [4, 5]. Women's empowerment is context-specific, and it is determined by various factors. Women's empowerment is influenced by a woman's level of education, employment for cash status, extent of media exposure, and spousal age difference [6]. There is substantial evidence that the lives of women living in low-income countries are characterized by exclusion, and this is reflected in their poor access to basic health care and services [7]. Women's empowerment has a profound influence on the use of health services that could be linked to reproductive health outcomes [8, 9]. Women's empowerment can control the household's decisions regarding health care usage. In many areas—especially rural areas—men often control decisions about the health of their wives and children, including the family's use of health services [4, 10]. A group of studies that were mainly conducted in Asia and Africa showed that women's empowerment is linked with contraception usage [11, 12], lower fertility [13], and longer birth intervals [14].

According to the Global Gender Gap Report 2020, the global gender gap index rank for Myanmar is 114 out of 153 countries. Among four indicators (politics, economic, education, and health), the health indicator gap is the smallest [15]. The main indicators leading to the big gender gap are politics and economic, but there are many inconsistencies in the case of health indicators. In the recent Myanmar census report (2014), the maternal mortality ratio was 282 per 100,000 live births, the second-highest among Southeast Asian countries [16]. The majority (62%) of maternal deaths occurred at home, and 14% occurred on the way to the hospital due to late referrals, primary delays, and long travel distances [17]. A qualitative study was conducted in 2013on an internally displaced person who stayed in the camps in Kachin State by the Gender Equality Network. The findings of the study provided insights into the health problems experienced by women. Furthermore, a lack of access to health care by the women and inability to make their own decisions on contraceptive usage led to increased reproductive health problems and highlighted gender inequality issues in Kachin State, Myanmar [18].

There is a limited understanding in Myanmar regarding the relationship between the empowerment of women and health service utilization by married women, including reproductive, maternal, and child health services.

The present study aimed to provide an insight into the link between women's empowerment and barriers to accessing health care services for women and potentially to inform policy around both, using a standardized index of women's empowerment among currently married women by using Myanmar Demographic and Health Survey (MDHS) (2015–16) data.

Methods

This study used data from the first MDHS, which was conducted between 2015 and 2016. The DHS was a nationally representative cross-sectional survey on demographic and health indicators of women and members of their households and was implemented by the Ministry of Health and Sports, Myanmar, with technical assistance from the ICF (Inner City Fund) (Rockville, Maryland, USA). Detailed methods and data collection procedures have been published elsewhere [19]. Briefly, a two-stage cluster sampling design (441 clusters, 30 households per cluster) was used and stratified by urban and rural status in 15 states and regions. Administratively, Myanmar consists of seven states representing the mountainous areas and eight regions representing the plain area; most of the regions are relatively developed [16]. Rural and urban areas are defined according to the Ministry of Home Affairs, Myanmar. According to the ministry's definition, to be categorized as 'urban,' an area should meet more than 20 criteria (e.g., a large population and the availability

of basic public services such as transportation, electricity, and safe drinking water) [20].

A standardized questionnaire was used to collect the data on demographic, social, and behavioural indicators, including the health status and reproductive health of all men and women aged between 15 and 49 years in the selected households. The focus of the analysis was on 7759 eligible currently married women aged 15–49 years. The sample was restricted to married women because some of the indicators used to calculate women's empowerment are applicable only to currently married women—most notably, decision-making power was not applicable to unmarried women. A conceptual framework was constructed to meet the aim of the study (Fig. 1).

Exposure variables

According to the Guide to DHS statistics DHS-7 version 2, 8 variables were selected as women's empowerment indicators [21]. They can be categorized into two domains—namely, decision-making power and women's disagreement with the justification of wife-beating [6–12]. Decision-making power was assessed through three items household purchases, visits to family members, and husband's earnings. Women's disagreement with the justification of wife-beating was evaluated based on five items: neglecting children, going out without husband's permission, arguing with husband, refusing sex, and burning food. Exploratory factor analysis was performed by analyzing eight variables to extract the main factor components. Sampling adequacy and inter-correlation of variables were checked using Bartlett's test of sphericity and Kaiser-Meyer-Olkin's measure (0.78). The number of components was determined based on the Kaiser criterion (eigenvalues > 1) and scree plots. For ease of interpreting the factors, oblique rotation was performed. The main factor component was obtained, which was mainly contained of women's disagreement with the justification of wife-beating regarding neglecting children and going out without their husband's permission. These disagreements accounted for 89% of the total variance (See Additional file 1). The factor score was categorized into terciles of low, medium, and high levels of the women's empowerment indicator.

Outcome variable

Barriers to accessing health care were the outcome variables of interest. In the MDHS 2015–16, it was defined the percentage of currently married women age 15–49 who reported that they have experienced serious barriers to accessing health care for themselves when they are sick. Responses were categorized by type of barrier: (1) Getting permission to go to the doctor? (2) Getting money needed for advice or treatment? (3) The distance to the health facility? (4) Not wanting to go alone? [21]. All four indicators were pooled together as a single entity and recoded into three groups (0 = no barriers at all, 1 = had faced one barrier, 2 = had faced more than one barrier).

Other relevant socio-demographic factors included in the MDHS data were considered as independent factors in the analysis. The variable of husband's occupation was recorded as either white-collar (professional/

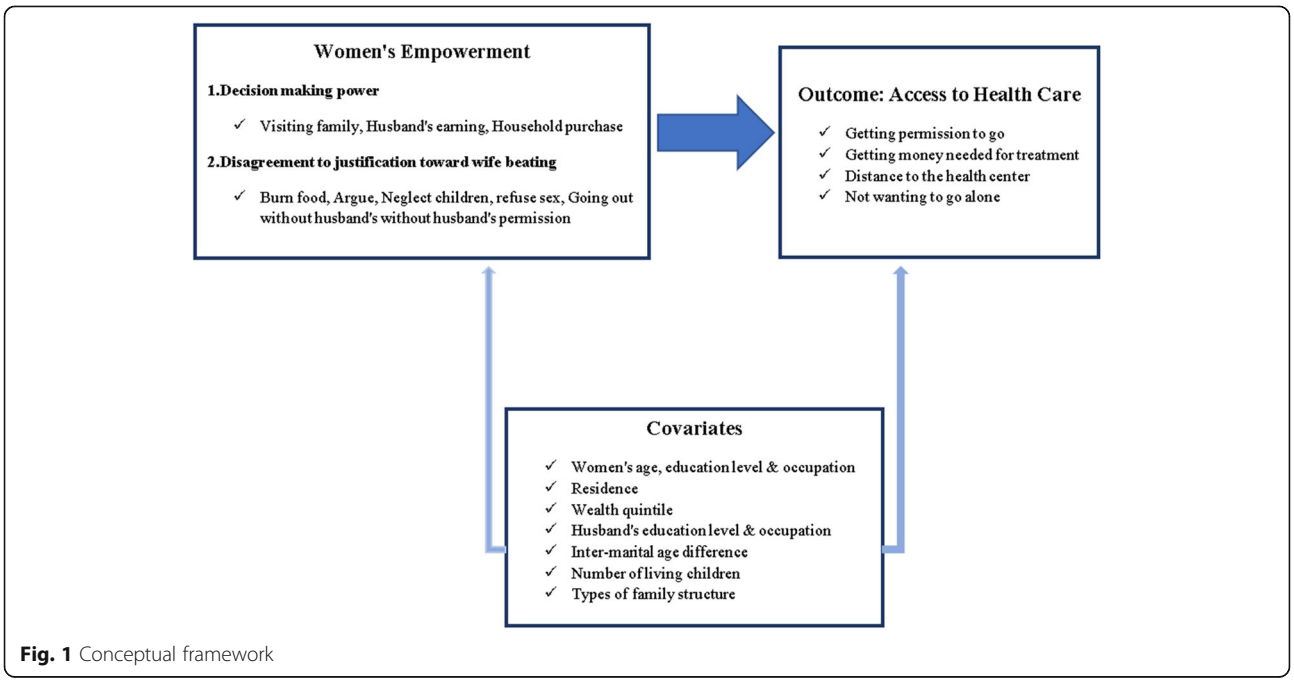

Fig. 1 Conceptual framework

technical/managerial/clerical) or blue-collar (agricultural/manual). DHS sample weights were used in all analyses to make the sample data representative of the entire population [19]. Before doing the multinomial logistic regression analyses with confounders adjusted for the survey sampling design, the multicollinearity between variables was checked, and univariate analysis was done. Only variables with significant associations (p-value < 1) in the univariate analyses were included in the multinomial logistic regression. Reference categories were set according to the MDHS (2015–16) report [13] and a specific coding system [20]. All analyses used the svyset command in STATA 14.

Results

Background characteristics

Table 1 shows the background characteristics of currently married women aged 15–49 years. Among them, most of the women were aged between 20 and 39. About 74% were living in rural areas. Nearly half of the women were from the poorer and poorest households. Most of the women were working and had primary education. In terms of familial and marital composition, half of the women were in a nuclear family type, while 49.2% were in an extended family type. Among married couples, the majority of the wives were younger than their husbands. The education level of respondents' husbands showed that 15.1% had no education. Only 6.7% had received higher education. Regarding the occupations of respondents' husbands, most were blue-collar workers.

Barriers to health care access

In Table 1, the distribution of barriers to accessing health care among currently married women across background characteristics is shown. Among currently married women, 48.0% had no barrier while accessing health care, whereas 21.9% had one barrier, and about 30.1% had more than one barrier. Experience of barriers to accessing health care varied by respondent's age, residence, education, occupation, wealth index, husband's education and occupation, number of living children, inter-marital age differences, and family structure.

Associations between women's empowerment and barriers to health care access

Table 2 presents the multinomial regression results from the examination of the relationship between women's empowerment and barriers to accessing health care among currently married women. We adjusted residence, education, occupation, wealth index, husband's education and occupation, number of children, and family structure, which were significant at univariate analysis (p-value < 1). Women with low and middle levels of empowerment had 1.5 odds (AOR 1.5, 95% CI: 1.2–1.8) and 1.5 odds (AOR 1.5, 95% CI: 1.3–1.9), respectively, of facing barriers to accessing health care in comparison to those with high empowerment for one barrier group. Women with low empowerment were 1.4 times more likely (AOR 1.4, 95% CI: 1.1–1.7) to face more than one barrier in comparison to women with high empowerment.

For the one-barrier group, rural residence was associated with a 1.3-times higher chance of experiencing barriers when compared to urban residence (95% CI: 1.0–1.8). Rural residence made it 1.8 times more likely that a woman would face more than one barrier when compared to urban residence (95% CI: 1.6–2.1). Women who had no education were more likely than educated women to have one barrier (AOR 1.8, 95% CI: 1.0–1.8). The lower a woman's education level, the more likely she would be to face more barriers to accessing health care. As the wealth index increased, the risk of facing barriers decreased in both groups. Women from the poorest households were 10.3 more likely to face more than one barrier than the women from the richest households (95% CI: 7.0–15.2) and 3.6 times more likely to have one barrier (95% CI: 2.6–5.1). The odds of having one barrier was higher for women whose husbands had primary education (AOR 1.5, 95% CI: 1.0–2.3). Women with more children were 2.0 times more likely to face more than one barrier when compared to women with fewer children (95% CI:1.6–2.5).

Discussion

This study was conducted to identify the association between empowerment among currently married women and the barriers to accessing health care based on MDHS (2015–16) data. About half of the women who participated faced barriers while attempting to access health care. In this study, barriers were evaluated by asking whether the respondent faced barriers when accessing health care in terms of getting permission to go, getting money to go, the distance to the health facility, and not wanting to go alone. These factors negatively influenced accessing health care in different settings [22–25]. A qualitative study done in a country in West Africa stated that poor health decision making and the unaffordability of health care were major barriers to accessing health care for women [26]. A study done in the ethnic minority regions of Northeastern Myanmar showed there was a gender-based inequality in health care access in those regions. Women were 45% less likely to seek inpatient treatment and 14% less likely to seek outpatient services than men [27]. Rural and ethnic minority women in Myanmar, in particular, could barely achieve equal rights with men.

Table 1 Distribution of background characteristics and status of barriers in health care access among currently married women age 15–49 year

Background characteristics	Total = 7759	Barriers in health care access			Chi-square	*p*-value
		No barrier 3780 (48.0%)	1 barrier 1725 (21.9%)	> 1 barrier 2364 (30.1%)		
Women's empowerment						
Low	2278(33.4)	1054 (46.3)	494(21.7)	729(32.0)	70.9	< 0.001
Medium	2928(42.9)	1532(51.6)	704(23.7)	734(24.7)		
High	1620(23.7)	848(57.3)	250(16.9)	383(25.8)		
Age						
15–19	227(2.9)	104(46.0)	46(20.0)	77(34.0)	12.9	0.17
20–29	2092(26.7)	1016(48.5)	491(23.5)	585(28.0)		
30–39	2988(38.8)	1526(51.1)	629(21.0)	832(27.9)		
40–49	2452(31.6)	1274(51.9)	495(20.2)	685(27.9)		
Residence						
Urban	2022(26.1)	1256 (62.1)	461 (22.8)	305 (15.1)	242.8	< 0.001
Rural	5737(73.9)	2665 (46.5)	1200(20.9)	1872 (32.6)		
Education						
None	1193(15.4)	433(36.3)	231(19.4)	529(44.3)	485.9	< 0.001
Primary	3656(47.1)	1681(46.0)	811(22.3)	518(22.7)		
Secondary	2285(29.4)	1329(58.2)	518(22.7)	438(19.1)		
Higher	625(8.1)	477(76.7)	101(16.1)	45(7.2)		
Occupation						
Not working	2280(29.4)	1178(51.7)	514(22.5)	58(25.8)	8.9	0.09
Working	5479(70.6)	2745(50.1)	1144(20.9)	1590(29.0)		
Wealth Index						
Poorest	1622(20.9)	463(28.5)	342(21.1)	817(50.4)	974.2	< 0.001
Poorer	1586(20.4)	644(40.6)	376(23.7)	566(35.7)		
Middle	1555(20.1)	811(52.1)	342(21.9)	402(26.0)		
Richer	1509(19.5)	917(60.8)	331(21.9)	261(17.3)		
Richest	1487(19.1)	1086(73.0)	270(18.2)	131(8.8)		
Husband's occupation						
White collar	715(9.2)	486(68.0)	130 (18.3)	99 (13.7)	101.0	< 0.001
Blue collar	7044 (90.8)	3459 (49.1)	1507(21.4)	2078 (29.5)		
Husband's education						
None	1173(15.1)	467(39.8)	202 (17.2)	504 (43.0)	403.9	< 0.001
Primary	3128(40.3)	1395 (44.6)	723 (23.1)	1010 (32.3)		
Secondary	2941(37.9)	1662(56.5)	662 (22.5)	617(21.0)		
Higher	517(6.7)	402 (77.6)	77 (14.9)	38 (7.5)		
No. of living children						
No child	916(11.8)	496(54.2)	204 (22.2)	217 (23.6)	82.5	< 0.001
1–3	5437(70.1)	2825(52.0)	1178 (21.6)	1433 (26.4)		
4 and more	1406(18.2)	699 (42.6)	279 (19.8)	528 (37.6)		

Table 1 Distribution of background characteristics and status of barriers in health care access among currently married women age 15–49 year *(Continued)*

Background characteristics	Total = 7759	Barriers in health care access			Chi-square	*p*-value
		No barrier 3780 (48.0%)	1 barrier 1725 (21.9%)	> 1 barrier 2364 (30.1%)		
Inter marital age difference						
Same age	818 (10.5)	430(52.6)	177 (21.7)	211(25.8)	7.3	0.27
Husband>wife	5274(68.0)	2616 (49.6)	1139 (21.6)	1519 (28.8)		
Wife>husband	1667(21.5)	877 (52.6)	343 (20.6)	447 (26.8)		
Family structure						
Nuclear	3942(50.8)	1812(46.0)	868 (22.0)	1263 (32.0)	79.9	< 0.001
Extended	3817 (49.2)	2186 (55.2)	791(20.8)	911 (24.0)		

After adjusting for some variables, it was found that women with a high empowerment score experienced fewer barriers. Women's empowerment had a significant impact on accessing health care, confirming the results of previous studies [9, 23–25]. A study done by DHS data in Myanmar stated more than 80% of married women were participated in the decision-making process [28]. In Myanmar, due to cultural and social norms, women traditionally participate in domestic decisions. But women's empowerment is context-specific, and many other aspects have to be considered. Myanmar was used to claim as high empowerment for women within the region due to cultural and religious beliefs, and most of the evidence was based on the economic aspect only. According to the economic forum 2020, Myanmar ranked 57 and scored 0.977 in the Global Gender Gap Index rankings by subindex [15]. In the report, the main measured health indicators were sex ratio at birth and healthy life expectancy. Therefore, the report could not cover the whole picture of the health care access of women in Myanmar. On the other hand, this study showed women in Myanmar still had problems accessing health care, and it was influenced by women's empowerment, which was still neglected in Myanmar.

However, women's empowerment was not the only variable with a significant association with barriers to accessing health care. Women from rural areas still faced more barriers compared to those from urban areas. It might be that geographical and transportation difficulties were one of the main causes of barriers to accessing health care in different states and regions of Myanmar. Moreover, unequal resource allocation caused disparities in health and health care in Myanmar. Conventional budget allocation, which is based on population and infrastructure, gave disproportionately more resources to more developed regions, urban areas, and places with better health and fewer resources to remote states with high health needs [29]. Together with geographical and transportation difficulties, other factors, including women's empowerment, might influence the health-seeking behavior of women [21, 30]. In the study done in Bangladesh [11], access to health care for married women was better if they had higher education and married to educated men. These findings were consistent with those from a study done in Myanmar, where women who had a higher education participated more in decisions, including decisions about one's own health care. Moreover, women married to educated men were more likely to participate in the decision-making process [28]. Therefore, respondents' education and husbands' education influenced the wife's access to health care [5, 25]. In our study, we found that women who had more than four children were more likely to face barriers to accessing health care. A study done in Zambia stated the same, as the lack of family planning in certain families resulted in a woman having 2–3 children under the age of five at one time, therefore making it difficult for her to go with all of them to the health facility [31].

Since this study was a secondary data analysis, the variables were limited to women's empowerment and barriers to accessing health care, along with influencing factors such as diversities in religion and ethnicity, relationships among household members, perceptions of health care access, and readiness of health care providers, which were not included in MDHS 2015–16. Women's empowerment is a complex concept, and we could not include other factors, cultural contents, or social contents. Moreover, the findings of this study cannot be generalized to all women in Myanmar since only currently married women were included. Further qualitative studies should be considered to obtain more information to link women's empowerment with health care, as well as other development sectors.

Table 2 Association between women's empowerment and barriers in health care access adjusted for covariates

	No barrier (n = 3780) vs 1 barrier (n = 1725)		No barrier (n = 3780) vs > 1 barrier (n = 2364)	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
Women empowerment				
Low	1.6 (1.3–2) **	1.5 (1.2–1.8) **	1.5 (1.3–1.8) **	1.4 (1.1–1.7) **
Middle	1.6 (1.3–1.9) **	1.5 (1.3–1.9) **	1.0 (0.9–1.3)	1.1 (0.9–1.3)
High	**1**	**1**	**1**	**1**
Residence				
Urban	**1**	**1**	**1**	**1**
Rural	1.2 (1.0–1.5) *	1.3 (1.0–1.8) *	2.9 (2.2–3.7) **	1.8 (1.6–2.1) *
Education				
None	2.6 (1.7–3.8) **	1.8 (1.0–2.4) *	12.9 (7.8–21.5) **	2.4 (1.4–3.9) **
Primary	2.3 (1.7–3.1) **	1.3 (0.9–1.9)	7.3(4.8–11.3) **	1.8 (1.1–2.8) *
Secondary	1.9 (1.4–2.5) **	1.3 (0.9–1.8)	3.5 (2.3–5.4) **	1.5 (1.0–2.4) *
Higher	**1**	**1**	**1**	**1**
Occupation				
Not working	1.0 (0.9–1.2)	1.0 (0.9–1.2)	0.9 (0.7–1.0)	0.9 (0.8–1.1)
Working	**1**	**1**	**1**	**1**
Wealth Index				
Poorest	2.9 (2.3–3.8) **	3.6 (2.6–5.1) **	14.6(10.7–20.1) **	10.3 (7.0–15.2) **
Poorer	2.3 (1.9–2.9) **	2.6 (1.9–3.5) **	7.3 (5.3–9.9) **	5.4 (3.7–7.8) **
Middle	1.7 (1.3–2.1) **	2.0 (1.5–2.8) **	4.1 (3.1–5.5) **	3.3 (2.3–4.8) **
Richer	1.5 (1.2–1.8) **	1.5 (1.2–1.9) *	2.4 (1.8–3.1) **	2.0 (1.4–2.8) **
Richest	**1**	**1**	**1**	**1**
Husband's occupation				
White collar	0.7 (0.5–0.8) *	0.9 (0.7–1.3)	0.3 (0.2–0.5) **	0.9 (0.6 t- 1.3)
Blue collar	**1**	**1**	**1**	**1**
Husband's education				
None	2.2 (1.5–3.5) **	1.1 (0.7–1.9)	11.1(6.6–18.6) **	1.6 (0.9–2.8)
Primary	2.7 (1.9–3.9) **	1.5 (1.0–2.3) *	7.5 (4.7–11.8) **	1.4 (0.8–2.3)
Secondary	2.1 (1.4–2.9) **	1.4 (0.9–2.1)	3.8 (2.4–6.1) **	1.2 (0.8–2.1)
Higher	**1**	**1**	**1**	**1**
No of living children				
No	**1**	**1**	**1**	**1**
1–3	1.0 (0.8–1.3)	0.9 (0.7–1.1)	1.2 (0.9–1.4)	1.0 (0.8–1.3)
> = 4	1.1 (0.9–1.4)	0.8 (0.6–1.1)	2.0 (1.6–2.5) **	1.1 (0.8–1.5)
Family structure				
Nuclear	**1**	**1**	**1**	**1**
Extended	0.8 (0.7 t- 0.9) *	1.0 (0.8–1.1)	0.6 (0.5–0.7) **	0.9 (0.8 t- 1.1)

OR Odds ratio, *AOR* Adjusted Odds ratio, *95%CI* 95% Confidence Interval
** $p < 0.001$, *$p < 0.05$

Conclusion

The study investigated the association between women's empowerment and barriers to accessing health care. Women's empowerment was an important determinant of one's ability to access health care, especially in rural areas. Women from rural areas experienced more barriers to accessing health care. Barriers to access to health care were reduced for women from rich households, who had attained higher education, who had educated husbands, and

who had few children. We believe that the present findings would contribute to the policy formulation in reducing health inequity issues in terms of increasing women's empowerment by enabling women getting equal rights to education and jobs.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-021-10181-5.

Additional file 1. Women's empowerment indicator factor component after factor analysis.

Abbreviations

DHS: Demographic and Health Surveys; MDHS: Myanmar Demographic and Health Survey; USAID: United States Agency for International Development

Acknowledgements

We would like to acknowledge USAID and ICF for their funding support and holding this 2018 DHS Fellows Program. Furthermore, we would like to express our sincere thanks to the facilitators Ms. Kerry LD Mac Quarrie, Ms. Elma Laguna, Ms. Jennifer Yourkavitch and Mr. Khin Kyu for their guidance and valuable advice throughout the program. Our sincere gratitude to Susy K. Sebayang, Ferryy Efendi and Erni Astuik for referred conceptual framework for women's empowerment and Ms. Kerry LD Mac Quarrie for English editing. Finally, our special thanks go to Dr. Thet Thet Mu, Deputy-Director General, Ministry of Health and Sports, Myanmar.

Authors' contributions

All authors contributed to protocol development. Wk completed methods, and statistical analysis and provided close supervision on each component, such as the conceptualization, methods, statistical analysis and presentation of data, and preparation of the manuscript. Nmmh completed the abstract, the statistical analysis, background, result and discussion. Zlh contributed to statistical analysis, results, and conclusions. All authors read and approved the final manuscript.

Funding

This research received no external funding.

Availability of data and materials

The datasets analyzed during the current study are available in the https://dhsprogram.com/data/dataset/Myanmar_Standard-DHS_2016.cfm?flag=0. This article is present on a university repository website and can be accessed on https://www.researchsquare.com/article/a28a9ef9-39d2-4785-b5c9-e631e2046e41/v1 . This article is not published nor is under publication elsewhere.

Ethics approval and consent to participate

The datasets of the MDHS (2015–16) were accessed with the permission of ICF International. The primary demographic and health surveys data were collected in accordance with international and national ethical guidelines. The protocol for the 2015–2016 MDHS was reviewed and approved by the Ethics Review Committee of Department of Medical Research, Ministry of Health and Sports. For this secondary analysis, we got permission from Department of Public Health, Ministry of Health and Sports.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interest.

Received: 18 February 2020 Accepted: 6 January 2021
Published online: 15 January 2021

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Publisher's Note

Original Article

Seroprevalence of Hepatitis B and C Virus Infections and Related Risk Factors of Hepatitis B Virus Infection among Newly Diagnosed Tuberculosis Patients at National Tuberculosis Program (Central), Mandalay Office, Myanmar

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Objective: To study the seroprevalence of hepatitis B and C virus infections and related risk factors of hepatitis B virus infection among newly diagnosed tuberculosis patients.

Materials and Methods: This cross-sectional descriptive study was done at Outpatient Department (OPD), National Tuberculosis Program (Central), Mandalay Office from 1st May 2019 to 31st August 2019. A total of 200 newly diagnosed patients were tested for HBsAg and anti-HCV and knowledge, attitude, and preventive practice against hepatitis B were interviewed using pre-tested, structured questionnaires.

Results: In this study, hepatitis B or C prevalence was 9.5% (95%CI:5.43 to 13.57) and prevalence of HBsAg was 4.5% (95%CI:1.6 to 7.4), and anti-HCV was 5% (95%CI:1.95 to 8.05) among newly diagnosed tuberculosis patients. Prevalence is higher in the age above 40 years, and male patients, and low education levels, resided in other cities. Generally, 93% of patients had a good attitude, but 55.5% had poor knowledge of hepatitis B infection. Knowledge level was statistically significantly associated with the education level of patients ($\chi 2=20.418$, p value= <0.001). Histories of taking injections without necessary and dental procedures un-screening were risk factors for the occurrence of HBsAg.

Conclusion: The prevalence of hepatitis was high among newly diagnosed tuberculosis patients. All TB patients should be screened for hepatitis before starting anti-TB treatment. Nationwide health education programs for hepatitis should be promoted according to the education status of patients.

Keywords: Hepatitis B, Hepatitis C, Risk factors, Seroprevalence, Tuberculosis

Received: 1 Feb 2022 | **Revised:** 21 Feb 2022 | **Accepted:** 30 Mar 2022

J Med Glob 2022 May;1(1)

Website: https://he01.tci-thaijo.org/index.php/JMedGlob/ss

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How to cite this article: Aung T; Khaing W. Seroprevalence of hepatitis B and C virus infections and related risk factors of hepatitis B virus infection among newly diagnosed tuberculosis patients at National Tuber-culosis Program (Central), Mandalay Office. J Med Glob 2022; 1(1): 36-46.

INTRODUCTION

More than 1 million people die each year from diseases caused by hepatitis B & C. Most of those infected persons do not know they have such an infection, increasing the risk of developing severe liver disease and transmitting the infection to others [1]. In 2017, World Health Organization (WHO) released a report that the global burden of hepatitis B (HBV) and C (HCV) were the leading causes of all hepatitis-related deaths. A large number of these were due to chronic liver disease and hepatocellular carcinoma [2]. Among them, only 1 in 10 had received a diagnosis and was aware of their infection. Hepatitis B causes 60 to 80 percent of primary liver cancer cases. Although hepatitis B is a vaccine-preventable disease, many people became infected before the hepatitis B vaccine was widely available [3]. Globally, an estimated 130–170 million persons (2%–3% of the world's population) are living with hepatitis C virus (HCV) infection. Each year, >350 000 die of HCV-related conditions, including cirrhosis and liver cancer [4].

In South-East Asia Region, WHO estimated that 39 million people live with chronic hepatitis B and 10 million people live with chronic hepatitis C. Mortality due to viral hepatitis is increasing with time, while that due to TB, HIV, and malaria is declining [5]. Early detection, prevention, and treatment of hepatitis B and C infection and associated diseases are necessary for low-income countries with an intermediate or high endemicity level [6]. In Myanmar, a national survey for hepatitis B and C screening in eighteen townships was conducted in 2015. The prevalence of hepatitis B and C in the general population is 6.5%, and 2.7%. But in Yangon Region, it is 12.3% and 2%. In Mandalay Region is 7.5% and 7.2% [7]. The country faces some major challenges in providing adequate screening and treatment for hepatitis [8]. The preventive measures, effective screening of those infections, and early treatment are important to consider and perform to reduce transmission [9].

Tuberculosis is one of the deadliest infectious diseases in the world. And TB is a major public health problem in Myanmar and is included in 30 highest TB burden countries in the world, 11th position global, 4th position in WHO SEAR. According to a global TB report [10], the current incidence of TB in Myanmar is 358(263-466) per 100,000 populations. Most of the drugs used in tuberculosis are hepatotoxic. Group of patients at increased risk of infection with hepatitis B or C viral infections are also at risk of infection with TB, largely because they live in regions of the world that are endemic to both infections. This makes a particular challenge for clinical management and warrants extra clinical vigilance. Drug-induced liver injury with elevation of aminotransferases is three- to six-fold higher in persons coinfected with HBV, HCV or HIV who are receiving anti-tuberculosis drugs, due to hepatotoxicity with isoniazid, rifampicin and pyrazinamide [11]. So, special caution should be exercised when administering these anti- TB drugs to patients with co-existing hepatitis B or hepatitis C viral infection [12].

The incidence of chronic hepatitis B among young adults is declining in Asia. But in older adults born before the vaccination era, vulnerable groups of people may unknowingly be chronically infected with or be susceptible to acquiring hepatitis B or hepatitis C and remain at risk for developing cirrhosis or liver cancer. To reduce mortality related to chronic viral hepatitis, all countries will be needed an enabling political environment with sufficient resources to facilitate reaching the hepatitis elimination goals set for 2030. Increased efforts to improve public awareness and listen to the voices of those affected by viral hepatitis will also be important to reduce stigma and discrimination [13]. The World Health Organization (WHO) has global goals for eliminating viral hepatitis infections. These goals include reducing 90% of new infections and 65% of deaths from viral hepatitis infections worldwide by 2030 [14]. To achieve these reductions, accessing early diagnosis, treatment, and prevention of transmission are important. To save lives, improve clinical outcomes of persons living with chronic hepatitis; reduce hepatitis B or hepatitis C incidence and transmission, and stigma due to disease, policymakers and implementers in LMICs face the practical challenges due to resource limitations [15]; infection, increasing the risk of developing severe liver disease and transmitting the infection to others [16]. There is no study on the seroprevalence, knowledge, attitude, and preventive practice of hepatitis B and C infection among tuberculosis patients in Myanmar. By knowing the HBsAg and anti- HCV status early and giving effective treatment, the risk of liver dysfunction can be reduced. The information from this study will provide the National Tuberculosis Program for better management in tuberculosis treatment. So, the main objective of this study is to find the seroprevalence of hepatitis B and C virus infections and related risk factors of hepatitis B virus infection among newly diagnosed tuberculosis patients.

MATERIALS AND METHODS

Study Design, study population and study period

A newly diagnosed 200 cases of tuberculosis from the Outpatient Department (OPD), National Tuberculosis Program (Central), Mandalay Office, during the period of 1st May 2019 to 31st August 2019 were included in the study. This study used a cross-sectional descriptive design. The University of Medicine, Mandalay's Institutional review panels, was approached to take the approval for the study. Patients the age of fifty years old and above and of any race were included in the study. The study was conducted by designing the questionnaire comprising of queries based on seroprevalence of hepatitis B and C virus infections and related risk factors of hepatitis B virus infection among newly diagnosed tuberculosis patients.

Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Intervention studies involving animals or humans, and other studies that require ethical approval, must list the authority that provided approval and the corresponding ethical approval code.

Research Instrument

Participants were interviewed face to face by using pre-tested, structured questionnaires by the researcher. Survey Questionnaires consist of 4 sections; A – Socio-demographic characteristics of tuberculosis patients, which has eight questions regarding age, sex, marital status, residence, education, occupation, family members, and family income of tuberculosis patients; B – Questions regarding knowledge about hepatitis B virus infection which was also having eight questions regarding on hepatitis B infection. Multiple response questions and True/False questions were asked. The questions regarding knowledge of hepatitis B infection will consist of the cause of hepatitis B, mode of transmission, signs, and symptoms, consequences of the infection, prevention, and treatment of hepatitis B. The total scores are categorized into the poor and good levels as follows; ≤ 70% of the total score as "poor knowledge", >70% of the total score as "good knowledge"; C – Questions regarding the attitude towards hepatitis B virus infection which were having 9 questions regarding attitude towards hepatitis B infection among tuberculosis patients. The questions were with negative statements and positive statements and rated as 5-point Likert scale. The questions consisted of attitude on hepatitis B and HB/TB co-existing infections regarding screening, prevention, and treatment. The total scores are categorized into negative and positive attitudes as follows; ≤ 60% of the total score as "negative attitude", > 60% of the total score as "positive attitude"; and D – Questions regarding the preventive practice against hepatitis B virus infection which 3 questions on preventive practice against hepatitis B infection about screening, vaccination, avoiding injection without necessary and history of risk factors for transmission. The answers were stated in "Yes" or "No" on preventive practice.

Data collection procedure

Data were collected by using this questionnaire. Outpatient department, NTP (Central), Mandalay Office is open on weekdays, office hours. From newly diagnosed tuberculosis patients, the first fifteen patients were selected consecutively every week according to inclusion criteria. Therefore, a maximum of 60 patients were studied within one month of the study period. First, the permission was taken from NTP (Central), Mandalay Office. Before conducting the research, structured questionnaires were pre-tested with a sample of 20 tuberculosis patients at Tuberculosis Hospital, Patheingyi. Cronbach's alpha was 0.77. Then all eligible patients were explained the study, objectives, and procedures. Then written informed consent was taken. After getting consent, firstly, the patients were interviewed face to face by using pre-tested, structured questionnaires by the researcher. For HBsAg and anti-HCV testing, code number, name, age, and date of specimen collection will be recorded first. Under the aseptic condition, 3 ml of blood were collected by venipuncture using sterile needles and syringes and transferred into sterile plain tubes. Then the tubes will be labeled with person's name, age, sex, and date & time of collection and sent to National Health Laboratory. If the test results were positive, post-test counseling was done and informed to TB MO and referred to Mandalay General Hospital, Liver unit for further management. HBsAg negative patients were advised to take vaccination against HBV infection. Post-test counseling was done in the private room.

Data processing and analysis

Data was collected by using pre-tested, structured questionnaires and results of the blood tests. After that, proper scoring and coding were made manually. After checking the data, data entry was done by using Microsoft Excel 2010. Data summarization for description was done by showing frequency distribution tables.

Table 1. Socio-Demographic Characteristics with Prevalance of HBsAg and Anti-HCV among newly diagnosed tuberculosis patients.

Socio-Demographic Characteristics		HBsAg			Anti-HCV		
		Positive n (%)	Negative n (%)	χ2, p-value	Positive n (%)	Negative n (%)	χ2, p-value
Age (years)	<40	4 (3.9)	99 (96.1)	0.188, 0.742*	4 (3.9)	99 (96.1)	0.557, 0.528*
	≥ 40	5 (5.2)	92 (94.8)		6 (6.2)	91 (93.8)	
Sex	Male	5 (2.5)	108 (54.0)	0.003, 1.00*	7 (3.5)	106 (53.0)	0.781, 0.518*
	Female	4 (2.0)	83 (41.5)		3 (1.5)	84 (42.0)	
Residents	Mandalay city	2 (1.0)	80 (40.0)	1.374, 0.313*	6 (3.0)	76 (38.0)	1.571, 0.323*
	Other cities	7 (3.5)	111 (55.5)		4 (2.0)	114 (57.0)	
Marital Status	Single	3 (1.5)	46 (23)	0.398, 0.691*	1 (0.5)	48 (24.0)	1.196, 0.456*
	Married	6 (3.0)	144 (72)		9 (4.5)	141(70.5)	
	Divorced	1 (0.5)	0 (0.0)		0 (0.0)	1 (0.5)	
Education	Illiterate	0 (0.0)	5 (2.5)	1.285, 0.603*	0 (0.0)	5 (2.5)	0.04, 1.00*
	Read and write	1 (0.5)	7 (3.5)		0 (0.0)	8 (4.0)	
	Primary School	2 (1.0)	53 (26.5)		2 (1.0)	53 (26.5)	
	Middle School	4 (2.0)	75 (37.5)		4 (2.0)	75 (37.5)	
	High School	2 (1.0)	27 (13.5)		2 (1.0)	27 (13.5)	
	University	0 (0.0)	6 (3.0)		0 (0.0)	6 (3.0)	
	Graduate	0 (0.0)	18 (9.0)		2 (1.0)	16 (8.0)	
Occupation	Unemployed/Dependent	0 (0.0)	16 (8.0)	0.819, 1.00*	1 (0.5)	15 (7.5)	0.057, 0.574*
	Employed	8 (4.0)	171 (85.5)		9 (4.5)	170 (85.0)	
	Retired	1 (0.5)	4 (2.0)		0 (0.0)	5 (2.5)	
Household Income per capita in Kyats	≤ 90000	5 (2.5)	67 (33.5)	1.561, 0.288*	2 (1.0)	70 (35.0)	1.170, 0.335*
	>90000	4 (2.0)	124 (62)		8 (4.0)	120 (60)	

* Fisher's Exact p-value

Statistical analysis was performed by using statistical software Stata version 14. To describe the age, mean and standard deviation are used. Sex, address, marital status, occupation, income, education, knowledge level, attitude level, preventive practice, and seroprevalence of HBsAg and anti-HCV were shown by frequency and percentage. The association between socio-demographic characteristics and knowledge, attitude, preventive practice, the occurrence of HBsAg and anti-HCV, and the association of preventive practice with HBsAg status were determined by Chi- square test. If the Chi-square test assumption does not meet, Fisher's exact test was used. The statistical significance level was denoted as 0.05.

RESULTS

Socio-demographic characteristics with Prevalence of HBsAg and Anti-HCV among newly diagnosed tuberculosis patients

Most of the patients were belonged to age >40 with 47% and least patients were belonged to age ≤ 20 with 9%. The ages of the patients ranged from 15 to 84 years with a mean of 41 years and SD of 15.803. Above 40 years were 47% and only 9% were ≤20 years. Among the study patients, 56.5% were male and 58% of patients were living in other cities. Middle school education was 39.5% and primary school education 27.5%. Nearly 90% have

Table 2. Socio-Demographic Characteristics with knowledge and attitude towards HBsAg and Anti-HCV among newly diagnosed tuberculosis patients.

Socio-Demographic Characteristics		Knowledge			Attitude		
		Good n (%)	Poor n (%)	χ2, p-value	Positive n (%)	Negative n (%)	χ2, p-value
Age (years)	<40	47(45.6)	56(54.4)	0.110,	92(89.3)	11(10.7)	4.417,
	≥ 40	42(43.3)	55(56.7)	0.74	94(96.9)	3(3.1)	**0.036**
Sex	Male	55(48.7)	58(51.3)	4.903,	104(92.0)	9(8.0)	0.371,
	Female	31(35.6)	56(64.4)	**0.027**	31(94.3)	5(5.7)	0.542
Residents	Mandalay city	42(51.2)	40(48.8)	1.031,	75(91.5)	7(8.5)	0.504,
	Other cities	69(58.5)	49(41.5)	0.310	111(94.1)	7(5.9)	0.478
Marital Status	Single	18(36.7)	31(63.3)	1.585,	43(87.8)	6(12.2)	2.742,
	Married/Divorced	71(47.0)	80(53.0)	0.208	143(94.7)	8(5.3)	0.112*
Education	≤High school	68(38.6)	108(61.4)	20.418,	162(92.0)	14(8.0)	2.053,
	>High school	21(87.5)	3(12.5)	**<0.001**	24(100.0)	0(0.0)	0.227
Occupation	Employed/ Retired	82(44.6)	102(55.4)	0.004,	172(93.5)	12(6.5)	0.808,
	Unemployed	7(43.8)	9(56.3)	0.95	14(87.5)	2(12.5)	0.310*
Household Income per capita in Kyats	≤ 90000	21(29.2)	51(70.8)	10.710,	66(91.7)	6(8.3)	0.307,
	>90000	68(53.1)	60(46.9)	**0.001**	120(93.8)	8(6.3)	0.579

* Fisher's Exact p-value

been employed. And more than half had a household income per capita >90000 kyats.

The prevalence of HBsAg and Anti-HCV among newly diagnosed tuberculosis patients is shown in Table 1. Only 4.5% (95%CI: 1.6% to7.4%) patients were positive in HBsAg and 5% (95%CI: 1.9% to 8%) positive patients with Anti-HCV while maximum patients were negative in both HBsAg and Anti-HCV in this study. The occurrence of Hepatitis B or C among newly diagnosed tuberculosis patients was 9.5% (95%CI: 5.4% to 13.5%).

The occurrence of HBsAg and anti-HCV by socio-demographic characteristics among newly diagnosed tuberculosis patients are shown in Table 1. Hepatitis B prevalence was 2.5%, and C was 3% among the age group above 40 years, and in the male gender, it was 2.5% for B and 3% for C. Hepatitis C prevalence was high in Mandalay city (3%), but Hepatitis B prevalence was high in other cities (3.5%). Both Hepatitis B and C prevalence was high in the employed group, 4% for B and 4.5% for C.

Knowledge, Attitude and Preventive Practice on Hepatitis infection among newly diagnosed tuberculosis patients

Among 200 patients, 78% were unaware that hepatitis B was caused by a virus. However, 87% were aware that the condition was contagious. Except for the loss of appetite and yellowish skin and sclera, most patients did not accurately answer questions about hepatitis B symptoms. In terms of complications, most patients could appropriately answer. Most patients answered wrong when asked about the route of transmission, which is that hugging and sharing meals, bowls, or utensils can transmit the sickness. Sixty percent of the patients were unaware that hepatitis B was curable. Ninety-eight percent of patients were aware that a blood test might be performed to detect hepatitis B. More than three-quarters of the patients (81.5%) were already aware that hepatitis B might be avoided by getting vaccinated. After that, the level of knowledge was put into two groups: those with less than 70% of the total score and those with more than 70% of the total score. The knowledge level of 200 patients was 44.5% good and 55.5% bad.

Regarding the attitude on hepatitis B, 96% believed that having hepatitis B made tuberculosis worse. Negative attitudes toward knowing one's hepatitis B status and attitudes toward a vaccination to prevent the

Table 3a. Socio-Demographic Characteristics with knowledge, attitude and preventive practice towards HBsAg and Anti-HCV among Newly Diagnosed Tuberculosis Patients.

Socio-Demographic Characteristics	Screening of hepatitis B			Vaccination against hepatitis B			Avoid injection without necessary		
	Yes n (%)	No n (%)	χ2, p-value	Yes n (%)	No n (%)	χ2, p-value	Yes n (%)	No n (%)	χ2, p-value
Age (years)									
<40	14(13.6)	89(86.4)	1.303,	9(8.7)	94(91.3)	0.469,	68(66.0)	35(34.0)	7.049,
≥ 40	19(19.6)	78(80.4)	0.254	6(6.2)	91(93.8)	0.493	46(47.4)	51(52.6)	**0.008**
Sex									
Male	22(19.5)	91(80.5)	1.662,	10(8.8)	103(91.2)	0.682,	57(50.4)	56(49.6)	4.557,
Female	11(12.6)	76(87.4)	0.197	5(5.7)	82(94.3)	0.409	57(65.5)	30(34.5)	**0.033**
Residents									
Mandalay city	18(22.0)	64(78.0)	2.998,	9(11.0)	73(89.0)	2.420,	48(58.5)	34(41.5)	1.34,
Other cities	15(12.7)	103(87.3)	0.083	6(5.1)	112(94.9)	0.120	66(55.9)	52(44.1)	0.714
Marital Status									
Single	6(12.2)	43(87.8)	0.853,	4(8.2)	45(91.8)	0.041,	29(59.2)	20(40.8)	0.126,
Married/ Divorced	27(17.9)	124(82.1)	0.356	11(7.3)	140(92.7)	0.764*	85(56.3)	66(43.7)	0.722
Education									
≤High school	26(14.8)	150(85.2)	3.176,	9(5.1)	167(94.9)	12.039,	92(52.3)	84(47.7)	13.372,
>High school	7(29.2)	17(70.8)	0.084*	6(25.0)	18(75.0)	**0.004***	22(91.7)	2(8.3)	**<0.001**
Occupation									
Employed/ Retired	31(16.8)	153(83.2)	0.202, 1.00*	15(8.2)	169(91.8)	1.410, 0.615*	103(56.0)	81(44.0)	0.98, 0.322
Unemployed	2(12.5)	14(87.5)		0(0.0)	16(100.0)		11(68.8)	5(31.3)	
Household Income per capita in Kyats									
≤ 90000	10(13.9)	62(86.1)	0.557,	1(1.4)	71(98.6)	6.056,	36(50.0)	36(50.0)	2.249,
>90000	23(18.0)	105(82.0)	0.456	14(10.9)	114(89.1)	**0.014**	78(60.9)	50(39.1)	0.134

* Fisher's Exact p-value

disease were 72.5 % and 73.5 %, respectively. Patients were enthusiastic about not sharing razors, needles, or blades, as well as having their screenings, vaccinations, and future treatment completed. If HBsAg was found to be positive, most patients (93.5%) showed a positive attitude toward self-care. Then, attitude status was classified as negative attitude if less than 60% of the total score and positive attitude if more than 60% of the entire score. Most patients (93%) had a good attitude about hepatitis B virus infection, with only a few individuals (7%) having a negative attitude.

In terms of preventative practice, 83.5% of 200 patients had not been checked for HBsAg, and 92.5% had not received the vaccination. Almost all the patients (99%) had no history of blood transfusion, 84.5% of tattooing, and 53.5% of dental procedures. None of the patients shared a toothbrush, and 57% of the patients took injections when they were not necessary.

Socio-demographic characteristics and knowledge, attitude towards Hepatitis B Infection

Table 2 shows the relationship between socio-demographic characteristics and knowledge as well as an attitude about hepatitis B infection. There was a statistically significant relationship between hepatitis B knowledge level and gender (p value=0.027), an education level (p value=0.001), and income (p value=0.001). There was also a statistically significant relationship between age groups of 40 years and

Table 3b. Socio-Demographic Characteristics with knowledge, attitude and preventive practice towards HBsAg and Anti-HCV among Newly Diagnosed Tuberculosis Patients.

Socio-Demographic Characteristics	History of Blood Transfusion			History of Dental Procedures			History of getting tattooing		
	Yes n (%)	No n (%)	χ2, p-value	Yes n (%)	No n (%)	χ2, p-value	Yes n (%)	No n (%)	χ2, p-value
Age (years)									
<40	2(1.9)	101(98.1)	1.903,	33(32.0)	70(68.0)	17.852,	16(15.5)	87(84.5)	0.00,
≥ 40	0(0.0)	97(100.0)	0.498*	60(61.9)	37(38.1)	**<0.001**	15(15.5)	82(84.5)	0.989
Sex									
Male	1(0.9)	112(99.1)	0.035,	58(51.3)	55(48.7)	2.433,	31(27.4)	82(72.6)	28.245,
Female	1(1.1)	86(98.9)	1.0*	35(40.2)	52(59.8)	0.119	0(0.0)	87(100.0)	**<0.001**
Residents									
Mandalay city	1(1.2)	81(98.8)	0.053,	31(37.8)	51(62.2)	4.224,	11(13.4)	71(86.6)	0.461,
Other cities	1(0.8)	117(99.2)	1.0*	62(52.5)	56(47.5)	**0.04**	20(16.9)	98(83.1)	0.497
Marital Status									
Single	0(0.0)	49(100.0)	0.656,	16(32.7)	33(67.3)	5.002,	8(16.3)	41(83.7)	0.034,
Married/ Divorced	2(1.3)	149(98.7)	1.0*	77(51.0)	74(49.0)	**0.025**	23(15.2)	128(84.8)	0.854
Education									
≤High school	2(1.1)	174(98.9)	0.275,	90(51.1)	86(48.9)	12.673,	30(17.0)	146(83.0)	2.675,
>High school	0(0.0)	24(100.0)	1.0*	3(12.5)	21(87.5)	**<0.001**	1(4.2)	23(95.8)	0.135*
Occupation									
Employed/ Retired	1(0.5)	183(99.5)	4.842,	91(49.5)	93(50.5)	8.081,	31(16.8)	153(83.2)	3.190,
Unemployed	1(6.3)	15(93.8)	0.154*	2(12.5)	14(87.5)	**0.004**	0(0.0)	16(100.0)	0.140*
Household Income per capita in Kyats									
≤ 90000	0(0.0)	72(100.0)	1.136,	40(55.6)	32(44.4)	3.708,	12(16.7)	60(83.3)	0.117,
>90000	2(1.6)	126(98.4)	0.537*	53(41.4)	75(58.6)	0.054	19(14.8)	109(85.2)	0.732

* Fisher's Exact p-value

attitude toward hepatitis B infection (p-value =.036). Other socio-demographic factors of patients were found to have no statistically significant association.

Socio-demographic characteristics and preventive practices towards Hepatitis B Infection

The association between socio-demographic variables and preventative practice against Hepatitis B infection among newly diagnosed tuberculosis patients was examined (see Tables 3a and 3b). There was a statistically significant link between getting a Hepatitis B vaccine and a person's level of education (p = 0.004) and household income (p = 0.014). There was also a statistically significant association between patients receiving unnecessary injections and their age group (p value=0.008), gender (p value=0.033), and education level (p value=0.001). There was no statistically significant relationship found between blood transfusion history and socio-demographic variables. There were statistically significant associations between dental procedure history and age group (p-value = 0.001), residents (p value = 0.04), marital status (p-value = 0.025), education level (p-value = 0.001), and occupation (p-value = 0.004). There was also a statistically significant relationship between gender and tattooing history (p value =.001). The result showed that female taking tattooing was uncommon in Myanmar society.

Table 4. Association between preventive practice and occurrence of HBsAg among newly diagnosed tuberculosis patients.

Preventive Practices	HBsAg		$\chi 2$	p-value
	Positive n (%)	Negative n (%)		
Screening of hepatitis B				
Yes	4(44.4)	29(15.2)	5.341	**0.043***
No	5(55.6)	162(84.8)		
Vaccination against hepatitis B				
Yes	0(0.0)	15(7.9)	0.764	1.00*
No	9(100.0)	176(92.1)		
Avoid injection without necessary				
Yes	1(11.1)	113(59.2)	8.097	**0.006***
No	8(88.9)	78(40.8)		
History of Blood Transfusion				
Yes	0(0.0)	2(1.0)	0.095	1.00*
No	9(100.0)	189(99.0)		
History of Dental Procedures				
Yes	8(88.9)	85(44.5)	6.807	**0.013***
No	1(11.1)	106(55.5)		
History of getting tattooing				
Yes	2(22.2)	29(15.2)	0.325	0.632*
No	7(77.8)	162(84.8)		

* Fisher's Exact p-value

Association between preventive practices and occurrence of HBsAg among newly diagnosed tuberculosis patients

Regarding preventive practice against hepatitis B infection, there was also a statistically significant association between the occurrence of HBsAg and screening (p-value = 0.043), taking unnecessary injections (p value= 0.006), and history of dental procedure (p value=0.013). There was no association with vaccination, blood transfusion, tattooing, and occurrence of HBsAg (see Table 4).

DISCUSSION

A cross-sectional study of 200 newly diagnosed tuberculosis patients was tested for HBsAg and anti-HCV, and their knowledge, attitude, and preventive practice against hepatitis B were assessed. In this study group, ages ranging from 15 to 84 years were assessed. The mean age was 41 years (SD=15.803). More than half of the patients were male, not from Mandalay, and under high school education.

In Myanmar, according to the National and Regional Survey for hepatitis B and C [9], hepatitis B prevalence was 6.5%, and hepatitis C prevalence was 2.7% and 2 persons had both. In this study, hepatitis B prevalence among newly diagnosed tuberculosis patients was lower than the average prevalence in Myanmar. But hepatitis C prevalence was higher than the average prevalence. Hepatitis B has occurred high percentage among the age group above 40 years, male gender, patients living outside the Mandalay, and low education level. This occurrence was the same for hepatitis C except for residents in which more common in Mandalay.

Our study's findings emphasized the need for hepatitis testing and prompt action. Because more than half of the patients lacked knowledge, although most patients had a positive attitude toward hepatitis B infection. The findings were similar to those of a community-based cross-sectional survey of hepatitis B knowledge and awareness among Malaysian households [17], which found that 36.9% of participants had strong understanding of hepatitis B. In the current study, whereas more than four fifths of the patients (87%) were aware that hepatitis B is a contagious disease, more than three quarters of the patients (78%) were unaware that hepatitis B is caused by a virus. Most patients accurately identified how hepatitis B was transmitted. Our findings

were comparable to those of research conducted in Asian communities in British Columbia [18]. In the current study, most patients were aware that hepatitis B could induce liver malfunction, cirrhosis of the liver, liver cancer, and chronic hepatitis. However, three-fifths (60%) of patients were unaware that lung cancer is not a complication of hepatitis B. Knowledge level was a statistically significant association with gender, education level, and income in this study.

Regarding the attitude towards hepatitis B, almost all (96%) of patients believed that having hepatitis B made tuberculosis worse, three quarters (72.5%) were afraid of knowing their hepatitis B status, and 73.5% of patients did not believe that vaccination could prevent hepatitis B. Except for the age group, there was no statistically significant link between socio-demographic factors and the way people with hepatitis B felt. Generally, almost all the patients had a positive attitude towards hepatitis B infection. Having a good attitude and improving their education status and health knowledge would affect good preventive practice against hepatitis B infection.

According to Vicky et al., hepatitis B knowledge and practices among Chinese immigrants to the United States [19], 48% of study participants had received hepatitis B screening, and 31% had received hepatitis B immunization. More than half of the patients in our study received unnecessary injections. These findings could be related to the patients' educational level and level of health knowledge. The findings revealed that, despite being aware of the risk of infection from needles and surgical procedures, the participants were unable to adhere to the principles. No patients in this study shared a toothbrush. There were statistically significant associations between socio-demographic characteristics and risk factors such as vaccination, avoiding unnecessary injections, dental procedures, and tattooing. Previous research [19] found lower results than ours. There was no statistically significant relationship discovered. It could be because patients in Mandalay were more easily accessible than patients who did not live in Mandalay. A statistically significant link was found between education level and household income and getting vaccinated against hepatitis B.

In a survey of internet users in Taif, Saudi Arabia [20], 42.4% had received hepatitis vaccination as part of premarital screening. Age, gender, and education level were statistically associated with unnecessary injections in this study. Injections were commonly used by people under the age of forty and by women. By education level, 57% of patients used to take injections, with 46% having completed high school and 11% have completed college. These findings could be attributed to patient age, gender, and health education. A dental operation was performed on 61.9% of study patients over the age of 40. It could be the cause of the high prevalence of HBsAg in people over the age of 40. In terms of education, 93 out of 200 patients (46.5%) had a history of dental procedures, and 45% were in high school or below. It was discovered that the lower the education level, the more patients engaged in risky procedures to spread the diseases. In this study, no female patients were tattooed. It could be related to Myanmar culture, where female tattooing is uncommon, and HBsAg is more prevalent in men. This study found a statistically significant link between HBsAg and screening, injections, and dental procedures.

According to a 2015 Myanmar National and Regional Hepatitis B and C survey [9], anti-HCV positivity was associated with male gender, age >50 years, blood transfusion, dental treatment, and surgery. However, no risk variables were linked to HBsAg. Only four of the nine HBsAg-positive patients in the current study had previously undergone screening. Only 29 of 191 HBsAg negative patients had previously been screened for HBsAg, and four-fifths of the patients had never been screened. It could be related to disease awareness, disease prevention, and disease treatment. In terms of injections, 8 out of 9 HBsAg-positive patients used to take them without need. In this study, the prevalence of hepatitis B was high among patients who received unnecessary injections, and a statistically significant association was discovered. It could be due to the patients' educational status and a lack of health knowledge. A study of knowledge, attitudes and the prevalence of Hepatitis B and C seromarkers among Tehran barbers [21] discovered that a history of finger-cuts with needles, blades, and scissors was more likely to be positive for HBsAg. Eight out of nine HBsAg-positive patients had a history of dental procedures. Although the occurrence may vary depending on the type of dental procedure used, a statistically significant association was discovered.

This study has some strengths. To begin, the prevalence of hepatitis B and C in that specific population of newly diagnosed tuberculosis patients could be determined. Second, tuberculosis patients with hepatitis B or C were identified before beginning anti-TB treatment. As a result, these co-infected patients would be referred to the liver unit for additional treatment. Third, this study included hepatitis B patients' knowledge, attitudes, and preventive practices. As a result, basic knowledge of patients' risk factors for hepatitis B could be assessed and preventive measures implemented in public health management. However,

this study had some limitations. Only newly diagnosed tuberculosis patients had blood tests. This study did not include all tuberculosis patients, including those who had relapsed, those who had been treated, and those who were currently taking anti-TB drugs. Furthermore, occult HBV infection could not be determined. As a result, the prevalence may be underestimated.

CONCLUSION

Only newly diagnosed tuberculosis patients had high hepatitis B or C prevalence, not all TB patients. All TB patients should get hepatitis B and C tests. All tuberculosis patients should get health education regarding tuberculosis and hepatitis B. Thus, patients' health knowledge would improve. Health education should inform patients about the availability and efficacy of vaccinations and urge hepatitis B vaccination. Health education should include avoiding unnecessary injections and getting the hepatitis B vaccine before dental work. Public health campaigns should target less educated people and provide health education at different levels. TB patients with hepatitis B or C are more prone to develop liver failure and have poor outcomes.

Author Contributions: Both authors contributed equally to conceptualization, methodology, data validation, formal analysis, data curation, writing—original draft preparation, review and editing.

Conflicts of Interest: The authors declare no conflict of interest.

Funding: This research was funded by External Grant Committee, Department of Medical Research, Myanmar, grant number 477/UMM/2019.

Acknowledgments: We would like to acknowledge Dr. Thandar Thwin, Regional TB Officer, National TB Control Programme (Central-Mandalay Office Branch) for her detailed assessment for questionaries construction and valuable comments and advices on this thesis paper. We are also very much grateful to all staffs at the UMTBC for their effective help in data collection.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of University of Medicine, Mandalay, Myanmar.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study as well as to publish this paper

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Original Article

The Impact of Motivation on Productivity: A Study of Healthcare Professionals at City Hospital, Mandalay, Myanmar

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Objective: Motivation is one of the major drives that integrate the internal and external stimuli that motivate a person's continued interest and dedication to a professional role or subject. This study aimed to determine how extrinsic and intrinsic motivational factors influence the productivity of healthcare personnel at City Hospital in Mandalay, Myanmar.

Materials and Methods: Two hundred healthcare professionals (46 medical officers, 95 nurses, 22 pharmacists, and 37 medical technologists) from City Hospital were selected at random using a quantitative methodology. To collect the data, questionnaires and face-to-face interviews are administered to healthcare professionals. The collected data was examined using descriptive analysis.

Results: The study revealed that external factors such as financial reward, accommodation, and transportation also affect work performance. Healthcare personnel was not extrinsically driven, particularly because they were dissatisfied with their current workload, salary, and hospital benefits. The healthcare professionals, on the other hand, were intrinsically motivated due to the nature of their work and their joyful and pleasant working environment. According to the study, there is a substantial correlation between extrinsic and intrinsic motivations and the productivity of health personnel at City Hospital.

Conclusion: City Hospital should use motivational policies that are based on both external and internal motivational blocks.

Keywords: Extrinsic motivation; Intrinsic motivation; Productivity

Received: 1 Apr 2022 | **Revised:** 21 Apr 2022 | **Accepted:** 1 May 2022

J Med Glob 2022 May;1(1)

Website: https://he01.tci-thaijo.org/index.php/JMedGlob/

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How to cite this article: Aye YN, Win MKK, Khaing W. The impact of motivation on productivity: A study of healthcare professionals at City Hospital, Mandalay, Myanmar. J Med Glob 2022; 1(1): 21-27.

INTRODUCTION

Healthcare is one of the basic needs of every country. Hospitals are critical organizations in the healthcare systems of every country, providing healthcare services to patients. Healthcare is a highly labor-intensive industry, with its workforce representing the major and most important component of its service. The demand for healthcare is continually growing because of population growth, a rise in the aging population, advancements in drug provision, and technological growth [1]. The impact of new diseases and infections such as COVID 19, chronic diseases, and long-term conditions is shifting the way public expectations of the healthcare workforce are being considered.

A well-motivated healthcare workforce is a key to meeting the continuous and changing demand for healthcare services and threatening diseases [2]. Recently, the issue of low productivity among healthcare professionals has risen to a great deal of importance in both the private and public healthcare sectors in Myanmar. Due to the falling standards in both private and public healthcare service organizations, motivation has now become a very vital factor to be taken into consideration to enhance organizational productivity.

Motivation is the psychological process that gives behavior purpose and direction; it is a tendency to behave purposefully to achieve specific, unsatisfied desires; it is an inner force to gratify an unsatisfied need, and it is the will to accomplish [3]. There are two main forms of motivation, which are: extrinsic motivation and intrinsic motivation. Extrinsic motivation is when a task is done for external reasons such as money, recognition, avoiding punishment, earning a grade, or possibly competition. It usually originated without someone offering it as a reward. Individuals are said to be intrinsically motivated when they seek interest, the satisfaction of curiosity, self-expression, or personal challenge in their work. Intrinsic motivation, on the other hand, involves doing something primarily for its own sake, for the enjoyment it provides, the learning it permits, and the satisfaction it brings. This type of motivation originated entirely from within itself. Hence, there is a natural connection apparent between one and the reason why one is doing something. Intrinsic motivation tends to be more powerful and is more likely to lead to personal success. Intrinsic forms of motivation are also far more beneficial to a business.

According to Wentzel & Miele (2009) [4], the relationship between employee motivation and productivity has not been established. The consensus, however, is that in the long run, motivation leads to increased productivity. Motivation and productivity may be largely separate casual paths: one set of factors (e.g., investment in technology) determines productivity, and another set (e.g., perceived equity of rewards) produces job satisfaction [5]. There are some conditions under which high productivity more clearly leads to motivation. The first condition is that the employees' perceived extrinsic and intrinsic rewards are contingent upon their productivity, and the second condition is that the extrinsic rewards (for example, pay) are distributed equitably. Inequitable distribution does not persuade employees to maintain close relationships between hard work and rewards [6].

Motivation is a poignant state, triggering people to want or need something strong enough to put forth the required effort to attain it. The link between motivation and productivity seems to be an obvious one. If individuals are highly motivated, they will perform better. If they perform better, their productivity will rise. In turn, better productivity because of higher performance may well lead to a sense of achievement and result in greater motivation. Most people have an intuitive sense that motivation is linked to performance and productivity. The purpose of this study was to investigate the relationships between motivation and productivity of healthcare professionals. Therefore, this study was done at City Hospital in Mandalay, Myanmar to determine the effect of motivation factors (both extrinsic and intrinsic) on the productivity of healthcare professionals.

MATERIALS AND METHODS

Study Design, study population and study period

This study uses a quantitative approach descriptive-analytical design, collecting data through a structured questionnaire. Participants were chosen using simple random sampling from August 15th to August 30th, 2020, and included 46 medical officers, 95 nurses, 22 pharmacists, and 37 medical technologists working at City Hospital in Mandalay, Myanmar.

Data collection

The questionnaire was created in Google Form and is divided into three sections: section A is for socio-demographic characteristics, section B is for extrinsic motivation, intrinsic motivation assessment, and section C is for productivity assessment, with answers on a five-Likert scale for each statement. The statement of agreement scale is 1-5, ranging from strongly disagree to strongly agree. Questionnaires were distributed to 200

healthcare professionals and were filled out voluntarily, with the researcher requesting permission before filling out the questionnaire.

Conceptual Model and Variables

Extrinsic and intrinsic motivation domains were independent variables. Both domains have five items each, while the dependent variable in this study is health care professionals' productivity, which has eight items. Extrinsic motivation is operationally defined as motivation driven by external benefits such as money, fame, grades, and admiration. The operational definition of intrinsic motivation is the act of performing something without visible external incentives. Someone does things because they find it fun and intriguing, rather than because of an external incentive or pressure, such as a prize or a deadline. Productivity is operationally defined as a ratio of output to input. It is a measure of a person's efficiency in completing a task.

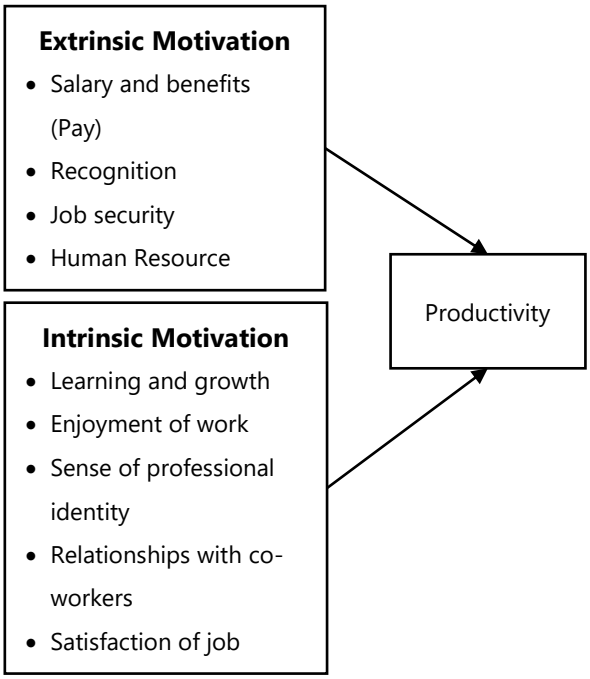

Figure 1. Conceptual framework of the study

Data analysis

Using the frequencies and percentages of the categorical variables, a descriptive analysis was performed to illustrate the general characteristics of the study participants. We used correlation analysis, as well as single and multiple linear regression analyses, to identify the extrinsic and intrinsic factors influencing respondents' productivity. IBM SPSS software version 25 was used to analyze the data. All tests were two-sided, with a p-value of (0.05) considered significant.

RESULTS

Socio-demographic characteristics of respondents

There were 46 medical officers, 95 nurses, 22 pharmacists, and 37 medical technologists who participated in this study. Out of the 200 healthcare professional participants, 14.3% were male, and 83.7% were female.

Table 1. Socio-demographic characteristics of participants (n=200)

Characteristics	Frequency	Percentage
Gender		
Male	24	12
Female	176	88
Age group		
21 – 30 years	154	77
31 – 40 years	41	20.5
Over 40 years	5	2.5
Occupation		
Medical officer	46	23
Nurse	95	47.5
Pharmacist	22	11
Medical Technologist	37	18.5
Education		
Diploma	31	15.5
Bachelor's degree	161	80.5
Master's degree	8	4
Working experience		
1 – 4 years	120	60
4 – 7 years	52	26
More than 7 years	28	14
Current salary (Kyats)		
200,001 – 500,000	102	51
500,001 – 800,000	91	45.5
More than 800,000	7	3.5

Most of the respondents belonged to the young age group which was 21 to 30 years which represented (77%)

Table 2. Descriptive statistics for the likert-scale questionnaire of extrinsic, intrinsic motivation and productivity

Items	SD	D	N	A	SA	Mean	SD
Extrinsic motivation							
The salary I get from the hospital is enough	33 (16.5)	68 (34.0)	48 (24.0)	45 (22.5)	6 (3.0)	2.80	1.10
I get praise and recognition for doing a good job	30 (15.0)	64 (32.0)	57 (28.5)	48 (24)	1 (0.5)	2.81	1.03
My job provides steady and secure employment	9 (4.5)	34 (17.0)	63 (31.5)	73 (36.5)	21 (10.5)	3.35	0.99
My hospital has good employment policies	18 (9.0)	47 (23.5)	70 (35.0)	54 (27.0)	11 (5.5)	3.05	1.03
I never feel my work is overloaded and working too long	50 (25.0)	56 (28)	35 (17.5)	51 (25.5)	8 (4.0)	2.70	1.25
Intrinsic motivation							
My job provides chances for advancement in my future career	10 (5.0)	32 (16.0)	48 (24.0)	93 (46.5)	17 (8.5)	3.57	0.98
I am happy and enjoy working in this hospital	3 (1.5)	27 (13.5)	57 (28.5)	102 (51.0)	11 (5.5)	3.50	0.85
I feel proud to work as a healthcare professional in this hospital	2 (1.0)	10 (5.0)	20 (10.0)	133 (66.5)	35 (17.5)	3.96	0.74
I have a good relationship with my supervisor and co-workers	1 (0.5)	1 (0.5)	21 (10.5)	143 (71.5)	34 (17.0)	4.04	0.58
I am satisfied to work as a healthcare professional in this hospital	1 (0.5)	7 (3.5)	35 (17.5)	121 (60.5)	36 (18.0)	3.92	0.73
Productivity							
I execute defined duties as work plan and standards	2 (1.0)	1 (0.5)	1 (0.5)	92 (46.0)	104 (52.0)	4.48	0.64
I submit a report on performed duties on time	1 (0.5)	0 (0)	14 (7.0)	106 (53)	79 (39.5)	4.31	0.65
All the assigned duties meet deadlines	1 (0.5)	3 (1.5)	6 (3.0)	93 (46.5)	97 (48.5)	4.41	0.67
This organization motivates me to go above and beyond in my role	15 (7.5)	30 (15.0)	60 (30.0)	66 (33.0)	29 (14.5)	3.32	1.12
I put discretionary effort into my work	2 (1.0)	2 (1.0)	18 (9.0)	117 (58.5)	61 (30.5)	4.17	0.71
I collaborate with my colleagues to carry out departmental assigned tasks	1 (0.5)	1 (0.5)	4 (2.0)	84 (42.0)	110 (55.0)	4.51	0.62
I support my team members	2 (1.0)	0 (0)	9 (4.5)	83 (41.5)	106 (53.0)	4.46	0.68
We can perform to achieve departmental goals in the set budget period	1 (0.5)	0 (0)	20 (10.0)	98 (49.0)	81 (40.5)	4.29	0.68

** Correlation is significant at the 0.01 level (2-tailed).

SD, Strongly Disagree; D, Disagree; N, Neutral; A, Agree; SA, Strongly Agreed; SD, Standard Deviation

of the participants. Most participants were bachelor's degree holders (80.5%), followed by diploma holders (15.5%) and master's degree holders (4%). Among them, 60% of respondents have 1 to 4 years of experience in healthcare, 26% have 4-7 years, and 14% have more than 7 years. Regarding monthly income salary, 51% of respondents earn between 200,000 and 500,000 kyats each month, and 45.5 % earn between 500,000 and 800,000 kyats. Only 3.5 percent gets above 800,000 kyats (see Table 1).

Assessment of extrinsic motivation

The extrinsic motivational factors of healthcare professionals at City Hospital were not strong enough with a mean value of 2.94 (see Table 2). Most of the healthcare professionals indicated that they were not motivated by existing extrinsic motivating factors, and only a small percentage found current extrinsic

motivating factors to be satisfactory. Everyone prefers extrinsic motivation. Not all extrinsic factors were made available to healthcare professionals in City Hospital. Most healthcare professionals, particularly nurses, believe that their salary and bonus are unmotivating and that their workload exceeds their capabilities.

Assessment of intrinsic motivation

The intrinsic motivation of healthcare professionals at City Hospital was good, with a mean value of 3.80 (see Table 2). The healthcare professionals, working as nurses or doctors or pharmacists, or medical technologists at City Hospital, enjoy or prefer their profession and the challenging nature of healthcare. They thrive on having responsibilities that give them a sense of control and get a call from the recognition and respect they get from patients and their guardians. Moreover, intrinsically motivated healthcare professionals are satisfied with the view that being a doctor or nurse is a noble profession, and there are prospects for career development in both the short and long term, which indicates that a healthcare profession.

Assessment of Productivity

Regarding productivity, the overall performance is 4.24, which reaches a good productivity level. The maximum mean value of 4.51 represents healthcare professionals collaborating with their colleagues to carry out the departmental assigned tasks. The second highest mean value of 4.48 shows they execute defined duties such as work plans and standards. The two lowest mean values are 4.17 and 4.29, which means they put discretionary effort into their work, and they can perform to achieve departmental goals in the set budget period (see Table 2).

Table 3. Correlations between extrinsic and intrinsic motivation factors and productivity

Variables	(1)	(2)	(3)
1. Productivity	1		
2. Intrinsic Motivation	0.464**	1	
3. Extrinsic Motivation	0.224**	0.358**	1

** Correlation is significant at the 0.01 level (2-tailed).

Correlations between extrinsic, intrinsic motivation and productivity

Table (3) indicates extrinsic motivation is significantly correlated with productivity ($r = 0.224$, $p < 0.001$) and intrinsic motivation is also significantly correlated with productivity ($r = 0.464$, $p < 0.001$). Therefore, there was a strong positive correlation between extrinsic motivation, intrinsic motivation factors, and productivity. The results of the study found a strong positive relationship between intrinsic motivation and healthcare professionals' productivity. Therefore, if the intrinsic motivation of the employees is increased, that will also increase the productivity level.

Regression analysis of motivation predicting productivity

A multiple linear regression was calculated to predict productivity based on extrinsic and intrinsic motivation (see Table 4). A significant regression equation was found ($F(2, 197) = 38.884$, $p < 0.001$), with an adjusted R^2 of 0.276. Participants' predicted productivity is equal to 1.372 + 0.194 Extrinsic Motivation + 0.437 Intrinsic Motivation. The adjusted R-squared is 0.276, indicating that extrinsic and intrinsic motivation could explain 27.6 percent of the variation in healthcare professional productivity. That means productivity is influenced by two variables of motivation, such as extrinsic and intrinsic motivation. Between the two motivational factors, intrinsic motivation had a stronger influence on the productivity of healthcare professionals at a 1% level, with a coefficient of 0.437. Besides, extrinsic motivation has a positive significant influence on the productivity of healthcare professionals at a 1% level as well, with a coefficient of 0.194. According to the results, the extrinsic and intrinsic motivation factors can improve the productivity of healthcare professionals at 0.01 significant levels. According to the findings, extrinsic and intrinsic motivation are strongly influenced in determining healthcare professionals' productivity.

Table 4. Regression analysis summary for motivation predicting productivity

Predictors	b	SE	t	p
(constant)	1.372	0.287	4.779	<0.001*
Extrinsic motivation	0.194	0.045	4.320	<0.001*
Intrinsic motivation	0.437	0.067	6.525	<0.001*

** Significant at the 0.01 level (2-tailed).

DISCUSSION

A descriptive-analytical study was conducted at City Hospital to investigate the effect of motivation on the productivity of healthcare personnel. This survey included 200 healthcare experts in total. Correlation

analysis was performed to investigate the relationship between extrinsic and intrinsic motivational factors and productivity. The influence of extrinsic and intrinsic motivating factors on productivity was investigated using regression analysis.

In the study, most of the healthcare professionals indicated that they were not motivated by existing extrinsic motivational factors because not all extrinsic factors were made available to healthcare professionals in the hospital. Studies have confirmed that motivation factors are essential and natural. However, they differ based on the profession and the work environment of the employees. Most people who work in health care feel that the salary and bonus don't motivate them and that the amount of work is more than they can handle, especially nurses. This study is in line with Herzberg's two-factor theory because the theory suggests that salary is a motivator but that after some time, it tends to become a (hygiene factor) for employees.

Moreover, healthcare professionals enjoy or prefer their profession and the challenging nature of healthcare; they thrive on having responsibilities that give them a sense of control and get a call from the recognition and respect they get from patients and their guardians. They are satisfied with the view that being a doctor or nurse is a noble profession, and there is a prospect for career development in both the short and long term and indicated that a healthcare profession. As noted by Kosteas (2011) [7], intrinsic motivational factors are important for achieving productivity and satisfaction. Based on the research, extrinsic and intrinsic motivation factors can improve the productivity of healthcare professionals, and it is proved that there is a strong positive direct relationship between work motivation (extrinsic and intrinsic) and employee productivity. The findings from the research are aligned with the studies of Christian et al., (2011) [8] and Chalofsky & Krishna (2009) [9], which suggest that there is a link between productivity and motivational factors (contextual as well as individual factors). May et al. (2004) [10] also relate employee productivity to motivation. Fairlie (2011) [11] and Macey & Schneider (2008) [12] both said that more research is needed to find the link between what motivates people at work and how well they do their jobs.

This is a cross-sectional study on the productivity of healthcare professionals at Mandalay City Hospital. More research on healthcare personnel's motivation is required at other public and private hospitals to reflect the results to the broader population. Because motivation is a dynamic condition, longitudinal research is required to track changes in the impact of extrinsic and intrinsic motivational factors on employee productivity over time.

Based on the key findings, it is suggested that the following may have implications for this study. To begin, hospital management should implement tailored motivational tactics for each healthcare professional's group by talking with representatives of healthcare professionals to set up appropriate motivating materials for each group. As a result, a motivating policy and strategy should address each group's personal professional-based desire. Second, it is proposed that study be conducted to determine which extrinsic variables can inspire healthcare providers. Furthermore, motivation policy guidelines targeted at enhancing the job productivity of City Hospital's healthcare personnel should be implemented by establishing appropriate salary scales and allowances that are in keeping with the present economic environment. Workload and financial incentives are important factors in increasing the work performance of healthcare personnel at City Hospital.

However, it is critical to emphasize teamwork among healthcare professionals, as well as between healthcare professionals and the management team, and its impact on productivity, responsiveness, job satisfaction, absence, and staff turnover, all of which require additional research to address some of the identified limitations.

CONCLUSION

In conclusion, healthcare professionals were not motivated by extrinsic factors, especially since they were not satisfied with their current workload and the salary and benefits that they got from the hospital. On the other hand, healthcare professionals were intrinsically motivated because of the nature of their work and a happy and pleasant working environment. The study shows that there is a strong link between extrinsic and intrinsic motivation and the amount of work done by healthcare workers at City Hospital.

Author Contributions: Both authors contributed equally to conceptualization, methodology, data validation, formal analysis, data curation, writing—original draft preparation, review, and editing.

Conflicts of Interest: The authors declare no conflict of interest

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and

approved by the Ethics Committee of YEC Learning Center, Mandalay, Myanmar, in MBA Course, which is affiliated with Lincoln University College, Malaysia.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study as well as to publish this paper.

Acknowledgments: I would like to express my gratitude to Dr. Khin Sandar Lwin for her excellent supervision and guidance. Additionally, I would like to extend my gratitude to the management team and to all the clinical staff of City Hospital, Mandalay, Myanmar, who participated in this study.

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Acta Tropica 111 (2009) 275–278

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Efficacy of oral single dose therapy with artemisinin–naphthoquine phosphate in uncomplicated falciparum malaria

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ARTICLE INFO

Article history:
Received 24 August 2008
Received in revised form 10 May 2009
Accepted 14 May 2009
Available online 21 May 2009

Keywords:
Naphthoquine phosphate
Artemisinin
Combination
Antimalarial
Falciparum malaria
Myanmar

ABSTRACT

All artemisinin-based combination therapies (ACTs), recommended by the World Health Organization, are 3-day regimens. A considerable level of non-compliance on ACTs has been reported from some countries. The study aimed to assess the therapeutic efficacy of single dose treatment with new generation ACT containing artemisinin plus naphthoquine. An oral single dose of eight tablets (400 mg of naphthoquine + 1000 mg artemisinin) of the combination drug was administered to adult uncomplicated falciparum malaria patients. Observations of fever, parasite clearance and reappearance, and other clinical manifestations were made on Days 0, 1, 2, 3, 7, 14, 21 and 28. Fifty-three adult falciparum positive cases, with fever or history of fever within the previous 24 h, were included in the final evaluation of the study. Mean fever clearance time, parasite clearance time were 18.2 ± 8.6 h and 34.6 ± 14.3 h, respectively. Adequate clinical and parasitological response was achieved in 52 cases, the rate being 98.1% (95% CI, 91.1–99.9). One patient was classified as late parasitological failure because of the reappearance of falciparum parasite on Day 14. The drug was well tolerated and no adverse reactions were detected in the patients. Since it is a single dose therapy, health workers can administer the drug as directly observed treatment.

1. Introduction

The treatment policy on falciparum malaria in all countries experiencing resistance to monotherapies should be artemisinin-based combination therapies (ACTs). The four ACTs recommended by the World Health Organization are artemether–lumefantrine, artesunate–mefloquine, artesunate–amodiaquine and artesunate plus sulfadoxine–pyrimethamine. The treatment courses of all currently recommended ACTs are 3-day regimens. Patients have to take a large number of tablets per course with a minimum of 15 tablets to a maximum of 24 tablets for adults (WHO, 2006). The number of tablets taken per day and the dosing schedule may influence the adherence. Artemether–lumefantrine is found to be 10% definitely or probably non-adherent in Uganda (Fogg et al., 2004) and 40.9% certainly or probably non-adherent in Southern Sudan (Depoortere et al., 2004a). With regard to artesunate plus sulfadoxine–pyrimethamine, it is 60.6% certainly or probably non-adherent in Zambia (Depoortere et al., 2004b) and 10.4% and 25% non-adherent at 24 h and 48 h respectively in Tanzania (Kachur et al., 2004). Taking drugs in incomplete dosages, including non-adherence, is a likely factor for the development of drug resistance leading to a reduction in drug efficacy.

ACTs are shown to be very effective in the treatment of uncomplicated *Plasmodium falciparum* malaria in the region of sub-Saharan Africa (Ogbonna and Uneke, 2008). However, efficacy of ACTs, particularly artesunate–mefloquine, is declining in the South-east Asia Region. The efficacy of artesunate–mefloquine against falciparum malaria showed 85.7% at 28-day follow-up in 2002 and 79.3% at 42-day follow-up in 2004 at Palin on the Cambodian side (Denis et al., 2006a) and 78.6% at 28-day follow-up with a 2-day regimen in 2003 at Trat on the Thailand side of the Cambodia–Thailand border (Vijaykadga et al., 2006). Development of new ACT regimens which have the properties of good efficacy as well as good compliance is essential.

The single dose therapy is usually better than the 3-day regimen for ideal compliance. The Academy of Military Medical Science of China developed an oral single dose therapy of artemisinin and naphthoquine phosphate [4-(7-chloro-4-aminoquinoline)-2-*tert*-butylaminomethyl-5,6,7,8-4hydro-1-naphthol diphosphate] combination. Naphthoquine is absorbed rapidly and completely following oral administration, and reaches peak plasma concentration 2–4 h after administration. The elimination half-life is 41–57 h. It is excreted mainly from urine. It is widely distributed, being highest in the liver, kidneys and lungs. The blood cells' concentration

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doi:10.1016/j.actatropica.2009.05.007

is higher than the blood plasma. The synergistic index of naphthoquine phosphate and artemisinin is more than 4 in the test against chloroquine-sensitive strain of *P. berghei* in mice and more than 8 in chloroquine-resistant strain (Wang et al., 2004).

A study conducted in China on 320 patients with falciparum malaria showed that the artemisinin–naphthoquine combination gave rapid parasite and fever clearance with high efficacy (Wang et al., 2004). This finding in China needs to be supported by another study in different epidemiological settings. Therefore, we conducted this study to assess the therapeutic efficacy of artemisinin–naphthoquine combination in one of the malaria endemic townships in Upper Myanmar.

2. Material and methods

2.1. Participants

The study was conducted from June to September 2007 in an area with moderate malaria transmission. Screening of patients was done at Wet-Won Village of Pyin-Oo-Lwin Township in Mandalay Division. Clinically suspected malaria cases were initially tested for *P. falciparum* with Rapid Diagnostic Test kit (RDT) (Paracheck P.f.; Orchid Biomedical Systems, Verna, Goa, India). Microscopic examination of blood smears from the RDT positive patients was done for determination of parasite density and confirmation of mono-infection. Patients aged between 15 and 55 years, *P. falciparum* mono-infection, parasite density in the range of 1000–100,000 per μl, axillary temperature ≥37.5 °C or history of fever during the previous 24 h, being able to return for the follow-up visits were eligible to participate in the study.

Patients with presence of one or more of the general danger signs or any sign of severe or complicated malaria, presence of mixed species infection, severe malnutrition, febrile conditions caused by diseases other than malaria, any type of severe disease, contraindications related to the antimalarial drugs used, especially history of allergy and pregnancy in females, were excluded from the study. Patients who fulfilled the inclusion criteria were then asked to join in the study. Written informed consent was obtained from each and every participant. All participants were admitted to temporary in-patient unit of Department of Medical Research (Upper Myanmar) for 3 days and were requested to come back for follow-up on respective days.

2.2. Ethical approval

Pharmacodynamics studies, toxicity tests and clinical efficacy trials of this combination were conducted in China (Wang et al., 2004). Since the above studies confirmed that the combination was effective, safe and well tolerated, this study was approved by the Institutional Ethical Committee of the Department of Medical Research (Upper Myanmar).

2.3. Sample size

Sample size was determined according to WHO protocol based on the population proportions of clinical failures of 5% in a previous study, with a confidence interval of 95% and a precision of 10%. Although the calculated sample size was only 18, WHO has recommended a minimum sample size of 50 patients in antimalarial drug efficacy trials (WHO, 2003). A total of 55 patients participated in this study.

2.4. Intervention

The test drug was manufactured and supplied by Kunming Pharmaceutical Corporation (KPC), China. Each tablet contained artemisinin 125 mg and naphthoquine 50 mg (equal to naphthoquine phosphate 78.3 mg). A single dose of eight tablets (400 mg of naphthoquine + 1000 mg of artemisinin) was given orally with water under supervision on Day 0. Baseline data such as age, sex and occupation, were collected on Day 0. Liver function tests were done on Days 0 and 14. Blood smear collection, microscopic examination of blood slides and recording of vital signs, temperature, signs and symptoms of adverse drug reactions were carried out on Days 0–3, 7, 14, 21 and 28. In this study, we followed the protocol of "Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria" developed by WHO (WHO, 2003).

2.5. Laboratory methods

Thick and thin blood smears were taken, stained with Giemsa's stain and examined under 100 × oil immersions for detection of parasite, species identification and parasite count, 12 hourly in the first 3 days and once a day on subsequent scheduled days. Parasite density was calculated by counting the number of asexual parasites against 200 white blood cells (WBC) in the thick blood film using a hand counter, up to a maximum of 500 parasites. Parasite density, expressed as the number of asexual parasites per micro-litre, was calculated by dividing the number of asexual parasites by the number of WBCs counted and then multiplying by an average count of 8000 leukocytes per micro-litre. The blood slides were recorded as negative when the examination of 200 thick-film fields did not show the presence of asexual parasites. Three consecutive negative findings were defined as a negative result and clearance of parasite. All the blood slides were examined blindly by two separate technicians; a trained technician from DMR (Upper Myanmar) and an experienced technician from the Malaria Control Programme of Department of Health.

2.6. Classification of therapeutic outcome

The therapeutic outcomes were classified according to the WHO classification for low to moderate transmission areas, which included three categories for treatment failure (early treatment failure, late clinical failure, and late parasitological failure) and one for treatment success (adequate clinical and parasitological response) (WHO, 2003).

2.7. Statistical analysis

Data entry and analysis were done using Microsoft Excel based Efficacy Calculation Software, developed jointly by the Centres for Disease Control and Prevention (CDC) and WHO and Epi-info 6 software. Frequencies, means and proportions of baseline data were calculated by using Epi-info 6 software. Proportions of treatment success and treatment failure were calculated by using Microsoft Excel based Efficacy Calculation Software.

3. Results

3.1. Characteristics of the patients

Of the 55 enrolled patients, two patients showed appearance of *P. vivax* on Day 28 and were excluded leaving only 53 patients for final analysis. The mean age of the patients was 26.7 years (range 15–54). Males accounted for 67.9% (36/53) of the participants and females 32.1% (17/53). The average body weight was 47.8 ± 4.3 kg. More than half (56.6%) of the participants were forest related workers. About 80% (42/53) of the patients gave a previous history of malaria. The average body temperature at the time of admission was 38.8 ± 0.6 °C. The average duration of illness at the time of

admission was 3.2 ± 1.0 days. The mean parasite count on Day 0 was 17,556 (95% CI, 13,427–21,685) per micro-litre with the range from minimum 2400 to maximum 56,000.

3.2. Safety and tolerability

Slight dizziness was reported by two female patients on Day 1, relieved by oral glucose. No other adverse reactions were observed in the remaining 51 patients. Liver function tests showed no significant abnormal changes between Days 0 and 14.

3.3. Efficacy

None of the patients vomited within the first hour after drug intake. The mean fever clearance time was 18.2 ± 8.6 h and that for parasite clearance was 34.6 ± 14.3 h. The 28-day adequate clinical and parasitological response (ACPR) rate was 98.1% (52/53) (95% CI, 91.1–99.9). One patient was classified as late parasitological failure because of reappearance of falciparum parasites on Day 14.

4. Discussion

Artemisinin has rapid onset of schizontocidal action. It is quickly absorbed through the intestine after oral administration, the peak plasma concentration occurring around 3 h. The half-life of artemisinin is very short (1 h approximately) (WHO, 2006). Taken alone, a long therapy course is essential (Li et al., 1994) otherwise the recrudescence rate is high (Alin et al., 1996). Naphthoquine phosphate has a long half-life and the dosage is small. The treatment success rate is high and the recrudescence rate is relatively low. It has properties that, when used in combination with artemisinin, make it more efficient. Tests on *P. knowlesi* in monkey conducted in China revealed that the appropriate proportion of naphthoquine and artemisinin was 1:2.5, and the appropriate regimen was only one dose (Wang et al., 2004).

Only one dose of artemisinin derivatives may provide less protection from the resistance of its long acting partner drug. On the other hand, one possible disadvantage of 3-day regimens of ACTs is poor compliance which can lead to early development of drug resistance. Therefore, both regimens have their own potential limitations.

The length of the follow-up in the therapeutic efficacy test is based on the time for complete clearance of drug from the body. Naphthoquine clearance will take 10.2–14.4 days, which is six times its elimination half-life (WHO, 2003). In order to cover the actual treatment failure rate of napthoquine, it is assumed that 28 days is enough for post-treatment follow-up.

Poor compliance and low efficacy of some recommended ACTs have been encountered in some areas of the world. In one study in Kenya, a few health workers suggested that a shorter duration of Artemether–lumefantrine with fewer tablets were likely to improve patients' compliance to the treatment regimen (Wasunna et al., 2008). According to data from the national malaria control programme of Myanmar, the 28-day cure rate of a 3-day regimen of artesunate–mefloquine combination at Kawthaung, Thai–Myanmar border, was only 88% in 2003. Artemether–lumefantrine is the currently recommended ACT in Myanmar. It is best taken with fatty food (Hutagalung et al., 2005). One study conducted in Cambodia showed a poor result of 71.1% cure rate at 28-day follow-up in patients taking Artemether–lumefantrine without fatty food (Denis et al., 2006b).

Trials have been conducted to discover new ACTs with regimen of shorter duration. Single day regimens of artesunate plus sulfamethoxypyrazine–pyrimethamine demonstrated high efficacy, with a cure rate of 92.3% in eastern Sudan (Adam et al., 2006) and 99% in Ivory Coast (Penali and Jansen, 2008). In both studies, participants were followed up for 28 days. Our study with an oral single dose artemisinin–naphthoquine combination showed 98.1% efficacy at 28-day follow-up. This rate was consistent with a finding from China which demonstrated a 28-day cure rate of 97.5% with the same drug and same dose (Wang et al., 2004).

Studies indicate that efficacy of antimalarial drugs is enhanced in partially immune individuals (Cravo et al., 2001; Dorsey et al., 2000). The majority of the participants in our study were forest related workers who frequently went with or without their families into the forests where they contracted malaria. Since 80% of them gave previous history of malaria attacks, our finding would represent mostly the partially immune population. The single dose treatment with artemisinin–naphthoquine combination may not yield a similarly high cure rate in non-immune subjects. However, all the remaining 20% (11/53) with no history of malaria attack before, who were assumed as non-immunes, showed no recrudescence up to Day 28. But the number was too small to give a conclusive remark about efficacy of the drug in non-immune patients.

The present findings in Myanmar, as well as previous results from China, have confirmed the high efficacy and safety of the artemisinin–naphthoquine combination. With the single dose therapy, all *P. falciparum* positive cases can be treated as directly observed treatment, immediately after confirmation of diagnosis. In favour of operational aspect including compliance, this combination may become the preferable regimen in the treatment of uncomplicated falciparum malaria in future.

Acknowledgements

We would like to thank Kunming Pharmaceutical Corporation (KPC), China for supplying ACT containing artemisinin and naphthoquine used in this study.

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Late initiation of antenatal care and its determinants: a hospital based cross-sectional study

Article *in* International Journal of Community Medicine and Public Health · April 2016

DOI: 10.18203/2394-6040.ijcmph20160926

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International Journal of Community Medicine and Public Health
Aung TZ et al. Int J Community Med Public Health. 2016 Apr;3(4):900-905
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: http://dx.doi.org/10.18203/2394-6040.ijcmph20160926

Research Article

Late initiation of antenatal care and its determinants: a hospital based cross-sectional study

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Received: 03 February 2016
Accepted: 05 March 2016

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ABSTRACT

Background: Antenatal care (ANC) is important for both maternal and fetal health. Pregnant women with late initiation of ANC are more likely to attain poor outcomes of pregnancy. Little is known about the magnitude of receiving late ANC among pregnant women in Myanmar. Therefore, the present study was conducted to determine the prevalence of late initiation of ANC and its determinants among pregnant women attending antenatal clinic at Pyin-Oo-Lwin General Hospital, Mandalay region during 2014.
Methods: A hospital-based cross-sectional study was conducted. Altogether 333 pregnant women were included in the study. Data were collected through face-to-face interview after getting informed consent from the respondents.
Results: The prevalence of late initiation of ANC was 56.2% (95% CI: 50.6%, 61.6%). Univariate analysis revealed that residence; education and occupation of pregnant woman, husband's occupation, gravidity, parity and being planned pregnancy were significantly related to late initiation of ANC. Based on the results of multivariate logistic regression analysis, residence, education of pregnant woman, occupation of husband, parity and being planned pregnancy were identified as significant determinants of receiving late ANC.
Conclusions: Late ANC attendance is high in the study area. Hence, it is important to provide health education on the timing of ANC among women with reproductive age. Community's awareness on importance of receiving early ANC also needs to be promoted. Family planning program (i.e., birth-spacing in Myanmar) should be enhanced to prevent unplanned pregnancies.

Key words: Antenatal care, Late antenatal care, Late initiation, Mandalay, Myanmar

INTRODUCTION

In the life of a woman, a family and a society, pregnancy is one of the important periods. Antenatal care (ANC) is special care for pregnant women with the aim of preventing health problems or getting early detection if any in both fetus and mother.[1-3] Moreover, pregnancy is a crucial time to promote healthy lifestyles and parenting skills. Therefore, ANC is important for health of both mother and fetus. Although there has been little meticulous evaluation of optimal timing of the initiation of ANC, pregnant women who receive late or no ANC are more likely to have poor or unfavorable outcomes of pregnancy.[4-6] Late initiation of ANC was reported as a significant risk factor for maternal mortality in some studies.[7-9] Therefore, ANC should begin as early as possible either at hospital/health center or during domiciliary visit of health workers in order to have sufficient time to manage risk factors, if present or to perform appropriate screening for early and timely referral.[10,11]

Although maternal mortality worldwide drops by about 44% between 1990 and 2015, more than 800 women

(99% of them are from developing countries) die daily due to preventable causes related to pregnancy and childbirth.[12] In Myanmar, maternal mortality ratio is reduced from 520 to 130 maternal deaths per 100,000 live births between 1990 and 2015, and coverage of ANC is more than 80%.[13,14] However, maternal death remains high among South-East Asian countries.[15] Besides, little is known about the magnitude of receiving late ANC among pregnant women in Myanmar. Therefore, this study aimed to determine the prevalence of late initiation of ANC and its determinants among pregnant women attending antenatal clinic at Pyin-Oo-Lwin General Hospital, Mandalay Region, Myanmar during 2014.

METHODS

A hospital-based cross-sectional study was carried out between September and November, 2014. Sample size was calculated using Epi-info version 7.0 statistical software. The prevalence of receiving late ANC was estimated to be 30% with 95% confidence level and 5% absolute precision.[16] Therefore, the sample size requirement was 323. All pregnant women who received ANC at Pyin-Oo-Lwin General Hospital during study period were recruited after getting informed consent. Data were collected by face-to-face interview. Information on last menstrual period, date of receiving first ANC and gestational age at first ANC were confirmed by observing prenatal record/register. Late initiation of ANC was defined as getting first ANC after 16 completed weeks of gestation.[17,18] Socio-demographic characteristics of both pregnant woman and her husband such as education, occupation and residence, and obstetric characteristics such as gravidity, parity and whether or not the present pregnancy was planned were considered as potential determinants. Age of pregnant woman, perception of pregnant woman on ANC, size and type of family, and per capita household's income were regarded as confounders. Perception towards ANC was assessed by means of questionnaires. If a pregnant mother reported that ANC was important for both mother and baby, she was considered to have good perception. Otherwise her perception towards ANC was regarded as unfavorable.

Statistical analysis

Data entry and analysis was done using Stata 11.0 statistical package. Proportion with 95% confidence interval was used to estimate the prevalence of late initiation of ANC among study population. Multivariate logistic regression analysis with manual backward deletion procedure was applied in assessing the determinants of late initiation of ANC. A variable with p-value ≤0.25 in univariate logistic regression was selected as a candidate for inclusion in multivariate analysis.

RESULTS

Altogether 333 pregnant women voluntarily participated in this study. Socio-demographic and obstetric characteristics of the respondents are shown in Table 1. Most of the respondents were ages of 25 years and older (61.0%), and rural dwellers (70.6%).

Table 1: Socio-demographic, economic and familial characteristics.

Variables	Frequency (n = 333)	Percentage
Age in completed years		
<25	130	39.0
≥25	203	61.0
Residence		
Urban	98	29.4
Rural	235	70.6
Education of pregnant women		
Primary (up to grade 5)	146	43.9
Secondary (grade 6 to 11)	132	39.6
Tertiary (University and graduates)	55	16.5
Occupation of pregnant women		
Absent (Housewife)	145	43.5
Present	188	56.5
Education of husbands		
Primary (up to grade 5)	139	41.7
Secondary (grade 6 to 11)	159	47.8
Tertiary (University and graduates)	35	10.5
Occupation of husbands		
Farmers	115	34.5
Laborers	130	39.1
Others	88	26.4
Monthly per-capita household's income		
< Median	207	62.2
≥ Median	126	37.8
Type of family		
Nuclear family	194	58.3
Three generation family	105	31.5
Joint (or) extended family	34	10.2
Size of family		
≤5	265	79.6
>5	68	20.4

Mean (sd) ages were 26.9 (6.1) years and median (range) monthly per-capita household's income were 50,000 (10,000 – 750,000) kyats. Mean (sd) size of family was 4.1 (2.1).

Table 2: Obstetric characteristics and perception of respondents on ANC.

Variables	Frequency (n = 333)	Percentage
Gravidity		
One	172	51.7
Two	89	26.7
Three and above	72	21.6
Parity		
Zero	187	56.2
One	91	27.3
Two and above	55	16.5
Planned-pregnancy		
Yes	215	64.6
No	118	35.4
Perceptions on ANC		
Good	200	60.1
Unfavorable	133	39.9

Obstetric characteristics and perception of pregnant mothers on ANC were described in Table 2. More than half of the participants were first gravida (51.7%) and did not have any experience on live birth (56.2%). Almost two thirds (64.6%) and three fifths (60.1%) had planned-pregnancy and good (or) favourable perception towards ANC, respectively.

Table 3: The prevalence of late ANC among respondents.

Late initiation of ANC	Frequency (n = 333)	Percentage (95% CI)
Present	187	56.2% (50.6%, 61.6%)
Absent	146	43.8% (38.4%, 49.4%)

Table 4: Results of logistic regression analyses.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age of respondents	1.02 (0.98, 1.05)	0.375		
Residence				
Urban	Reference		Reference	
Rural	0.48 (0.29, 0.79)	0.004	0.47 (0.27, 0.83)	0.009
Education of respondents				
Primary	Reference		Reference	
Secondary	0.84 (0.52, 1.36)	0.490	0.80 (0.47, 1.37)	0.416
Tertiary	0.38 (0.20, 0.73)	0.003	0.34 (0.16, 0.75)	0.007
Occupation of respondents				
Absent	Reference			
Present	0.56 (0.36, 0.87)	0.010		
Education of husbands				
Primary	Reference			
Secondary	1.10 (0.70, 1.75)	0.679		
Tertiary	0.66 (0.31, 1.39)	0.272		
Occupation of husbands				
Farmers	Reference		Reference	
Laborers	2.54 (1.51, 4.27)	0.000	2.19 (1.24, 3.86)	0.007
Others	1.22 (0.70, 2.13)	0.476	1.50 (0.76, 2.96)	0.242
Per-capita household's income	1.00 (0.99, 1.00)	0.915		
Type of family				
Nuclear family	Reference			
Three generation family	0.81 (0.50, 1.30)	0.382		
Joint (or) extended family	1.60 (0.74, 3.46)	0.235		
Size of family				
≤ 5	Reference			
>5	1.45 (0.83, 2.50)	0.189		
Gravidity				
One	Reference			
Two	1.37 (0.82, 2.30)	0.227		
Three and above	2.49 (1.38, 4.48)	0.002		
Parity				
Zero	Reference		Reference	
One	1.98 (1.18, 3.31)	0.009	1.85 (1.07, 3.22)	0.029
Two and above	3.29 (1.68, 6.45)	0.000	2.17 (1.02, 4.61)	0.045
Planned-pregnancy				
Yes	Reference		Reference	
No	2.39 (1.48, 3.83)	0.000	1.86 (1.09, 3.18)	0.024
Perceptions on ANC				
Unfavorable	Reference			
Good	0.98 (0.63, 1.53)	0.944		

Table 3 shows the prevalence of late initiation of ANC among respondents. More than half of pregnant women (56.2%) took first ANC for their present pregnancies after 16 weeks of gestation. Gestational age at the time of first ANC visit ranged between 7 and 34 weeks. Mean (standard deviation) and median gestational ages at the time of initiation of ANC were 18.23 (4.98) and 18 weeks, respectively.

Main reasons of receiving late ANC reported by the respondents were 'being busy' (29.0%), 'misbelieve that it is appropriate time' (26.3%) and 'due to someone's advice' (18.3%). 'Economic reason' (i.e., financial constraint) was the least (1.5%).

Results of logistic regression analyses were described in Table 4. Although both gravidity and parity were significantly related to late ANC in univariate analysis, only parity was selected for multivariate analysis to avoid collinearity. Based on multivariate logistic regression analysis, residence, education of pregnant mothers, occupation of their husbands, having planned-pregnancy and parity were identified as significant determinants of late initiation of ANC.

DISCUSSION

The prevalence of late initiation of ANC among study population was 56.2%. Almost similar estimates were reported by previous studies done in Myanmar (more than 50%) and Laos (about 60%).[14,19] However, studies conducted in developed countries revealed lower proportions (4.4% to 27.3% % in USA, about 15% in UK and 41% in Australia) whereas some African studies reported comparable or higher values (53% in Ethiopia, 61.1% in Rwanda, 70.3% in Zambia, 81% in Nigeria, more than 70% in Tanzania and Malawi).[5,16-18,20-25]

Utilization of different cut-off points in defining late initiation of ANC could explain these discrepancies (first trimester or 12 completed weeks was used in USA and UK studies, 16 weeks in Ethiopian, Zambian, Tanzanian and Malawi studies, and second/third trimester in some studies).[5,16-20,22,24,25] The proportions of pregnant women who initiate ANC before 4 months of gestation among neighboring and ASEAN countries were 40.4% in Bangladesh, 32.2% in Cambodia, 56.9% in India, 78.6% in Indonesia, 37.5% in Nepal, 46.9% in Pakistan, 56.1% in the Philippines and 65% in Vietnam.[26] Differences in culture or socioeconomic status or health knowledge including awareness on the importance of early booking for ANC or education level among study populations, or differences in time of study or study area whether urban or rural may also be responsible.

In this study mean gestational age at the time of first ANC was 18.23±4.98 weeks. A study done in Ethiopia also reported almost similar result (17.7 weeks).[27] However, a previous study conducted in Myanmar reported much lower gestational age at first ANC (15 weeks) while those detected in Ethiopian and Tanzanian studies were more than 20 weeks.[14,18,24] These discrepancies may be due to differences in time or site of study or differences in education and/or socioeconomic status among study population. Difference in culture or level of awareness on the significance of early initiation of ANC could explain these variations.

Education status of pregnant women, parity, being planned pregnancy, residence whether urban or rural and husband's occupation were identified as significant determinants of late ANC in the present study. This is consistent with findings of previous studies carried out in different countries. Independent studies conducted in USA and some African countries reported that there is significant relationship between late ANC and being planned pregnancy.[16-18,22,28] Parity is also reported as a significant predictor of late initiation of ANC in studies done in UK,[20] Zambia,[17] Rwanda[22] and Ethiopia.[28] Besides, similar studies conducted in USA and Malawi revealed that maternal education has significant effect on receiving late ANC.[16,25] These findings highlight that obstetric characteristics such as parity and being planned pregnancy, and maternal education are important in preventing late initiation of ANC among pregnant mothers.

The present study is not free from limitations that should be considered while interpreting the results. This study was carried out in a government hospital. Pregnant women who received ANC at health centers and private clinics or hospitals were not included in the study. Besides, gestational age at first ANC was determined, based on self-report of LMP. Assessment of gestational age using ultrasound scan was not performed. The study could have been strengthened further by increasing sample size and expanding study sites.

CONCLUSION

Late ANC attendance is high in the study area. Hence, it is important to provide health education on the timing of ANC among women within reproductive ages. Priority should be given to women with low level of education, multiparous women, women with unplanned pregnancies and urban dwellers. Community awareness on the significance of early initiation of ANC should also be raised. Family planning or birth spacing program should be enhanced to prevent unplanned or unwanted pregnancies. Future research should focus on effective interventions to encourage and enable pregnant mothers to engage with the ANC services early, especially during first trimester. Similar study that is community-based with larger sample size should also be conducted.

ACKNOWLEDGEMENTS

The investigators are grateful to the participants in this study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: This study was undertaken after obtaining approval from 'Research and Ethical Committee' of the University of Public Health, Yangon and informed written consent from the participants

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Cite this article as: Aung TZ, Oo WM, Khaing W, Lwin N, Dar HT. Late initiation of antenatal care and its determinants: a hospital based cross-sectional study. Int J Community Med Public Health 2016;3:900-5.