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THE ACCURACY OF POINT OF CARE HBA1C IN SCREENING FOR TYPE 2 DIABETES IN ASYMPTOMATIC ADULTS: META-ANALYSIS

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Abstract:

Background: *Diabetes Mellitus represent a major health problem of the 21st century, according to International Diabetic Federation (IDF), three of the Arabian Gulf countries have the highest prevalence of type 2 diabetes worldwide including Saudi Arabia. Screening for diabetes mellitus by using HbA1c point of care devices is a new quick and relatively cheap method.*

Objective: *To collect and combine the available data about the correlation between point of care HbA1c (POC HbA1c) testing and laboratory HbA1c measurement in screening for asymptomatic adult participants for type 2 diabetes.*

Method: *We searched databases for studies addressing the correlation between point of care HbA1c in the screening of type 2 diabetes and laboratory HbA1c measurement (reference method), for asymptomatic adult participants. Risk of bias was assessed using Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2). Screening accuracy measures were pooled using the random-effects model and subgroup, and sensitivity analyses were conducted.*

Results: *Out of 11919 studies identified, only 4 met the eligibility criteria. Three POC HbA1c devices were reviewed in this analysis: A1cNow+, Afinion, and Que-test devices.*

The included studies have a moderate risk of bias, and the pooled results showed a strong positive correlation between POC HbA1c testing and laboratory HbA1c measurement (correlation coefficient, 0.935; 95% confidence interval, 0.893–0.961); however, there is substantial heterogeneity.

Conclusion: *The pooled results showed a strong positive correlation between point of care HbA1c devices and standard laboratory HbA1c method in screening for type 2 diabetes.*

Key words: *Screening, Type 2 Diabetes Mellitus, Glycemic control, HbA1c, Point of Care (POC), A1cNow+, Afinion, and Que-test, Meta-analysis*

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1.INTRODUCTION:

1.1. Background:

Diabetes Mellitus (DM) represents a major health problem of the 21st century, causing severe long-term damage to the multiple systems in the body. In 2014, the WHO estimated the global prevalence of DM to be 9% among adults over 18 years and predicted it to be the 7th most common cause of death by 2030 [1].

According to the International Diabetes Federation (IDF), three of the Arabian Gulf countries (Saudi Arabia, Kuwait, and Qatar) have the highest prevalence of Type 2 diabetes worldwide. In the Saudi population, it increased over time from 12.4% in 1987 to 27.7% in 2011, without significant differences in the prevalence between genders [3,4].

Al-Rubeaan K et al in 2014, reported the prevalence of Saudis with diabetes was 25.4% with 40.3% being unaware of their disease, while impaired fasting glucose affected 25.5% of the total study samples [5]. In a recent study, Menke A etal (2015) reviewed a sample of 2781 for NHANES 2011-2012 data and found that the prevalence for diagnosed subjects with diabetes was 9.1%, 5.2 for undiagnosed diabetes and 38.0% for prediabetes [6].

According to ADA (2016) screening for diabetes should begin at age 45 years; however, it should be started earlier in those who are overweight and have additional risk factors [7].

In 2011 the WHO advocated the use of HbA1c for the screening and diagnosis of type 2 DM which was reflected in most DM guidelines [8,9].

1.2. Hemoglobin HbA1c:

Hemoglobin A1c (HbA1c) is considered as a marker of long-term glycemic control in a patient with diabetes, and it has been widely used for monitoring diabetic control and guiding treatment decision in clinical practices. It is recommended that patients with diabetes have HbA1c tested every 3 to 6 months to assess glycemic control [10].

The concentration of glycated hemoglobin is a surrogate measure for the circulating glucose level over the previous 120 days (typical lifespan of a red blood cell) as well as a strong marker of complications associated with diabetes mellitus [11].

1.3. Point of care (POC) technology:

Point of care (POC) is clinical testing close to the site of patient care, typically with small and portable instruments. There is some evidence supporting the use of POC for HbA1c analysis: studies report on overall improvement of clinical outcomes after usage of POC HbA1c in the management of diabetes mellitus [12].

Most POC devices for HbA1c use a drop of capillary blood, collected via the finger prick procedure. Following application to the test cartridge, the sample is analyzed and quantified within few minutes using methods based on either difference in structure or charge of the glycated and non-glycated hemoglobin. The main 4 methods using in POC HbA1c technology are cation-exchange chromatography, immunoassay, affinity chromatography, and enzymatic assay [14].

POC HbA1c devices must be certified by the United States National Glycohemoglobin Standardization Program (NGSP), and the results must be traceable to the Diabetes Control and Complications Trial Reference Method [15].

1.4. Using of POC HbA1c in clinical practice:

In 2014, Health Quality Ontario reviewed the correlation between POC HbA1c testing and laboratory HbA1c measurement in monitoring patients with diabetes. They reported that the pooled results showed a positive correlation between POC HbA1c testing and laboratory HbA1c measurement (correlation coefficient, 0.967; 95% CI, 0.960–0.973) [17].

Some studies evaluated the cost difference between using POC and laboratory testing of HbA1c. The results showed that the annual costs of POC HbA1c against laboratory HbA1c testing were $ 86.8 million versus $ 91.5 million, meaning that a replacement of all laboratory measurements by POC HbA1c would possibly save $ 4.7 million over the next year, which indicates that the introduction of more POC HbA1c is economical [18,19]. These studies related to the using of POC HbA1c for the monitoring of participants with diabetes, to date no studies have looked at cost impact to screening or diagnosis of type 2 DM, and as such, there is a need for further health economic studies.

The WHO guidance states that HbA1c may be used for diagnosis of type 2 DM provided that, the quality assurance tests are in place and instruments should be standardized to criteria aligned to the international reference results [20].

1.5. The aim of the study:
The systematic review and meta-analysis aimed at summarizing data and appraising the relevant articles of point of care (POC) HbA1c for the screening of asymptomatic adult with type 2 diabetes and provide pooled point estimates.

1.6. Study Question in PICO format:
P (population & problem): Asymptomatic, non-diabetic adult participants.
I (Index test): Point of care (POC) HbA1c screening test.
C (Comparison): Standard laboratory HbA1c test.
O (Outcome): Accuracy in terms of correlation coefficient.

2. MATERIALS AND METHODS:

Search and analysis method, eligibility criteria, and the outcomes of interest were specified in advance in a protocol developed by study investigators.

2.1. Inclusion criteria:
Cross-sectional diagnostic studies were included that evaluated the screening accuracy of POC HbA1c in an asymptomatic adult. Articles were included if they reported a correlation coefficient between POC HbA1c testing and reference standard which is HbA1C laboratory assay technology typically is based on either charge differences (high-performance liquid chromatography [HPLC]) or structure (boronate affinity or immunoassay combined with general chemistry) [21].

We excluded studies that enrolled participants under 18 year of age, subjects who presented with hyperglycemia symptoms, known people with diabetes or with complications of diabetes, use any anti-hyperglycemic drugs or those who have hemoglobinopathies. There was no inclusion restriction on the type of POC HbA1c devices as they were NGSP certified. Studies with missing data or correlation coefficient were excluded.

2.2. Search strategy:
A librarian (MNV) searched electronic databases for published and in-press studies from 1995 (the date where POC HbA1c devices became available) through December 2015, and the last update was on July 2016 including PubMed, EMBASE, CINAHL and Co-chrane databases.

The search terms used were "POC", "Point-of-care", "Point of Care", "bedside testing", "Alternate side testing", "bedside Technology", "Near patient testing", "hemoglobin A1c", "HbA1c", "A1c", "Glycosylated Hemoglobin A", "Glycohemoglobin A1c", "Glycated hemoglobin", "screening", "Detection", "Determination", "Type 2 Diabetes", "Type II Diabetes", "T2DM", "Non-Insulin Dependent Diabetes", "NIDDM", "Insulin Resistance Diabetes" with its MeSH terms (Medical Subject Headings) and keywords, as well as for known brand names of POC HbA1c devices.
We used a Boolean operator (OR) to combine synonyms within each PICO element and (AND) to combine the PICO elementstogether. No language restriction was applied. Reference lists were also scanned.

2.3. Study and data selection:
Two authors (MF, AD) screened titles and abstracts for inclusion criteria. Full-text articles were retrieved for relevant articles. An abstraction format developed and tested by authors that includes: study citation, author name and year of publication, participants mean age and other baseline characteristics, POC HbA1c devices variant, reference standard used, time between the index test and reference standard, and screening study data. The disagreement was resolved by consensus.

2.4. Quality assessment:
Two reviewers (MF and AD) independently assessed the quality of the included studies by using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) instrument [22].

This tool is designed to assess the quality of primary diagnostic accuracy studies for inclusion in the systematic review. It consists of four key domains covering patient selection, index test, reference standard, and flow of patients through the study and timing of the index test and reference standard. Each domain is assessed in terms of the risk of bias, and the first three are also assessed in terms of concerns regarding applicability.

Risk of bias is judged as "low", "high", or "unclear". If all signaling questions for a domain are answered "yes" then, the risk of bias can be judged "low". If any signaling question is answered "no" this flags the potential for bias.

Low risk of bias (i.e. high quality) in different domains was considered as follows: participant selection if the asymptomatic adult were enrolled in consecutively. Index test, where it was interpreted independently from the reference standard. The reference standard,

when it correctly classifies patients with diabetes or non-diabetes cases. Flow and time, the appropriate interval between the index test and the reference standard is within seven days, and POC HbA1c samples were collected within one hour.

2.5. Meta-analysis:
MedCalc software free trial was used to pool up the results of the included studies (meta-analysis) using a random effect model (DerSimonian-Laird approach) [23]. The screening measures used in the analysis was the correlation between POC HbA1c and standard laboratory HbA1c results. Heterogeneity was assessed by using the I-squared statistic and Q test and is considered substantial when I^2 is equal or more than 50%.

2.6. Subgroup and sensitivity analyses:
To explore the robustness of our results and evaluate the potential causes of heterogeneity (if any), subgroup analysis was conducted based on the type of POC HbA1c devices among the selected studies.
Sensitivity analysis was done on outlier study with the lowest correlation coefficient, which does not cross most of the other studies visually, to assess its effect on heterogeneity.

3. RESULTS:

3.1. Search result:
The initial search yielded 11919 studies reports that were potentially relevant; of which, 4 studies that fulfilled the study eligibility criteria have enrolled a total of 654 participants were finally included. Figure (1) shows the breakdown of when and for what reason citations were excluded from the analysis.

Most of the quality assessment items articles have a low risk of bias (i.e. high quality) except flow and timing. The agreement between the risk of bias assessment between reviewers was 80%; the disagreement was resolved by discussion and consensus. Figure (2) visually summarizes the risk of bias in the included studies.

3.2. Characteristics of included studies:
Table (1 A and B) shows the characteristics of selected studies that include studies setting, participants, index and reference tests, the time between POC HbA1c and Lab HbA1c tests, cut off level, and limitations of the studies, whereas Table (2) summarizes the characteristics of the excluded studied with causes of exclusion. Of the 4 included studies, 3 compared A1CNow+ device with a reference standard, while 1 study (Zin RMW 2013 study) compared two different devices; Afinion and Que-test devices with the reference standard. Table (3) shows the characteristics of POC HbA1c devices which present in included studies according to the manufacturer's claims [24].

The included studies were conducted in two countries; the United States (3 studies) and Malaysia (1 study), and all were published in English.

The participants were asymptomatic adult above 18 years except (Nam S 2011) study which included 30 years of age and older.

The reference standard tests in the selected studies were NGSP- certified laboratory with different assay principle. One study (Ashley M 2012) used Quantitative turbidimetric inhibition immunoassay method, while other 2 studies (Zin RMW 2013 and Ginde AA 2008) used high-performance liquid chromatography (HPLC) method of test, and (Nam S 2011 study) has not determined the specific method of reference standard test.

There were variations in the participants who received the reference standard test in different studies. All participants in 2 studies (Zin RMW 2013 and Ginde AA 2008) had received both index (POC HbA1c devices) and reference tests. However, the participants in the other two studies screened by POC first and only used the reference standard test if the POC HbA1c result was above the cut off reading of HbA1c. Accordingly, not all study participants performed the reference standard, and those studies considered to have verification bias, which was reflected by a high risk of bias at the flow and timing domain. There were also differences between the cut off level of abnormal result among these 2 studies, it was $\geq$ 7.5 % HbA1c at Nam S 2011 study, and it was $\geq$ 5.7 % HbA1c at Ashley M 2012 study.

The interval between the index and reference standard tests was also varied among the included studies, ranging from conducted at the same visit to a mean of 28 days.

3.3. The pooled estimate for POC HbA1c devices:
The correlation coefficient (R) of these 4 studies comparing POC HbA1c with reference standard HbA1c measurement were pooled in (Figure 3). Which shows a high correlation between the two tests (0.935, 95% CI 0.893 to 0.961). However, correlation coefficient (R) varies in different studies from 0.83 in Nam S 2011 study, and 0.96 in Ginde AA 2008 study.

3.4. Test of heterogeneity

There was a high degree of statistical heterogeneity associated with this analysis; I^2 is 89.72%. Inconsistency between results among studies was statistically significant ($P < 0.0001$).

3.5. Subgroup analysis

In an attempt to explore the source of the heterogeneity, the analysis was stratified by type of POC HbA1c devices. Three out of four included studies were conducted using A1CNow+ device, while the fourth one (Zin RMW 2013 study) used two different devices, Afinion and Que-test (Non-A1cNow+) devices (Table 1).

The first subgroup (Figure 4A), which pooled up the point estimates for the Non-A1cNow (Afinion and Que-test) devices, showed no heterogeneity (I^2 = 0.00%), while the second subgroup (Figure 4B), which pooled up the results of A1CNow+ devices, showed a serious statistical heterogeneity (I^2 = 94.76%).

3.6. **Sensitivity analysis**:

Nam S. 2011 study was an outlier with the lowest correlation coefficient (R = 0.830), and visually it does not cross most of the other studies (Figure 3). Figure (5) shows the pooled result without Nam S. 2011 study, with high correlation coefficient 0.952 (CI 95% 0.941 to 0.961), non-substantial heterogeneity (I^2 = 26.72%).

4. DISCUSSION:

POC HbA1c is a bedside test used in this study for screening of HbA1c among asymptomatic adult participants, where four studies were included in this meta-analysis.

The correlation coefficient was chosen as the outcome of interest for this systemic review because it was the most commonly reported measure of POC HbA1c screening performance in the literature. There were studies reported the sensitivity and specificity but in monitoring of HbA1c among patient with the diabetic.

The result of the meta-analysis showed that the POC HbA1c performance was high and the test has significant discrimination power between those who have the abnormal HbA1c result and those who have not.

However, the quality of this evidence is considered moderate due to the high risk of bias at the flow & timing item in the quality assessment, which also due to verification bias in (Nam 2011 and Ashley 2012), and selection bias, in addition to heterogeneity.

Sensitivity analysis (Figure 4 B) revealed that the main source for heterogeneity was Nam S 2011 study, which has certain characteristics that may share the light on the sources of heterogeneity. The study was conducted on an ethnic group, with high HbA1c cut off level and with verification bias.

Other potential sources of heterogeneity could be due to the differences in POC HbA1c devices used, differences in laboratory HBA1c reference methods, differences in the interval between index and reference tests, differences in ethnicity group of participants, differences in cut off level of HbA1c, and differences in the study setting. e.g., Ginde AA 2008 recruits participants from the emergency department while other recruits the participants from primary care centers or national diabetic institutes.

The main shortcoming of reference laboratory HbA1c tests as a screening test is the non-availability in poor and rural areas and their dependency on the good health care system. POC HbA1c provides a real-time screening of patient with diabetes at the same visit as it took only 3 to 5 minutes to be completed, which assists the health care providers to make a proper clinical decision at the same visit which in turn cuts off the frequent visits. As well as it speeds-up the management of those patients, which affects the immediate & remote outcomes positively.

4.1. Strengths and limitations:

The primary strength of this systemic review relates to the search of electronic databases for relevant studies and the careful appraisal of quality assessment. The limitations mainly relate to collecting the data from selected studies that limit our ability to extract enough information about participant's characteristics and pre-test risk level. Another significant limitation relates to heterogeneity that was not fully explained, although it was mainly due to one study (Nam S 2011).

The verification bias was present is two studies (Nam S 2011 and Ashley 2012), because not all recruited participants included in the final analysis, those with normal HbA1c results were excluded and did not do reference standard test. The included studies had variability in the cut off values of POC HbA1c and another variability in the time interval between the index and reference tests performance. All these factors in this meta-analysis could have contributed to

the persistence of heterogeneity even after subgroup analysis.

CONCLUSION:

POC HbA1c devices have high screening accuracy for HbA1c in the asymptomatic adult. More widespread adoption of POC HbA1c testing may be indicated to simultaneously improve public health and reduce the preventable complication of type 2 DM. The reliability of the meta-analysis screening estimates is limited by significant heterogeneity among included studies, and the findings from this research should be interpreted with appropriate caution.

Conflict of Interest

The authors declare no conflict of interest.

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List of Abbreviations

DM: Diabetes Mellitus
T2DM: Type two Diabetes Mellitus
IDF: the International Diabetes Federation
POC: point of care
HbA1c: Hemoglobin A1c (glycated hemoglobin)
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies tool- version 2
HPLC: high-performance liquid chromatography
NHANES: The National Health and Nutrition Examination Survey
WHO: World Health Organization

REFERENCES:

1. Organization WH. Diabetes Fact sheet Number 312 Geneva [updated January 2015; cited 2015 15/07/15]. Available from: http://www.who.int/mediacentre/factsheets/fs312/en/.
2. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes research and clinical practice. 2014;103(2):137-49.
3. Fatani HH, Mira SA, el-Zubier AG. Prevalence of diabetes mellitus in rural Saudi Arabia. A reply. Diabetes care. 1988;11(3):297.
4. Al-Daghri NM, Al-Attas OS, Alokail MS, Alkharfy KM, Yousef M, Sabico SL, et al. Diabetes mellitus type 2 and other chronic non-communicable diseases in the central region, Saudi Arabia (Riyadh cohort 2): a decade of an epidemic. BMC medicine. 2011;9:76.
5. Al-Rubeaan K, Al-Manaa HA, Khoja TA, Ahmad NA, Al-Sharqawi AH, Siddiqui K, et al. Epidemiology of abnormal glucose metabolism in a country facing its epidemic: SAUDI-DM study. Journal of diabetes. 2014.
6. Menke, Andy, et al. "Prevalence of and trends in diabetes among adults in the United States, 1988-2012." Jama 314.10 (2015): 1021-1029 Beagley J, Guariguata L, Weil C, Motala AA. Global estimates of undiagnosed diabetes in adults. Diabetes Res Clin Pract. 2014;103(2):150-60.
7. http://care.diabetesjournals.org/content/suppl/2015/12/21/39.Supplement_1.DC2/2016-Standards-of-Care.pdf
8. Organization WH. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus (abbreviated Report of a WHO Consultation). 2011.
9. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada [Internet]. Ottawa, ON: Canadian Diabetes Association; 2013 [cited 2013 Sep 19]. 212 p. Available from: http://guidelines.diabetes.ca/App_Themes/CDACPG/resources/cpg_2013_full_en.pdf
10. English E, Milosovich ET, John WG. In vitro determination of hemoglobin A1c for diabetes diagnosis and management: technology update. Pathology and Laboratory Medicine International.
11. 2014;6:21-31.
12. Al-Ansary L, Farmer A, Hirst J, Roberts N, Glasziou P, Perera R, et al. Point-of-Care Testing for Hb A(1c) in the Management of Diabetes: A Systematic Review and Meta-analysis. Clinical Chemistry. 2011;57(4):568-76.
13. Larissa-Nele Schaffert, Emma English, Carl Heneghan, Christopher P. Price, Ann Van den Bruel, Annette Plüddemann. Point-of-care HbA1c tests - diagnosis of diabetes. Horizon scan report 0044 March 2016.
14. English E, Milosovich ET, John WG. In vitro determination of hemoglobin A1c for diabetes diagnosis and management: technology update. Pathology and Laboratory Medicine International. 2014;6:21-31.
15. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, et al. Guidelines and recommendations for laboratory analysis in the

diagnosis and management of diabetes mellitus. Clin Chem. 2011 Jun;57(6):e1-e47.
16. National Glycohemoglobin Standardization Program. Obtaining certification [Internet]. Missouri: National Glycohemoglobin Standardization Program; 2013 [cited 2013 Sep 19]. 7 p. Available from: http://www.ngsp.org/cert/Manufinfo1113.pdf.
17. Health Quality Ontario. Point-of-care hemoglobin A1c testing: an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2014 July;14(8):1–30. Available from: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series/eba-point-of-care-a1c
18. Chadee A, Blackhouse G, Goeree R. Point-of-Care Hemoglobin A1c Testing: A Budget Impact Analysis. Health Technology Assessment (HTA) Database. 2014.
19. Wiwanitkit V. Comparison of costs of hemoglobin a1c determination by point-of-care testing (POCT) and standard hemoglobin a1c analyzer. Archives of Hellenic Medicine. 2010;27:953-5.
20. Organization WH. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus (abbreviated Report of a WHO Consultation). 2011.
21. Bode BW, Irvin BR, Pierce JA, et al. Advances in hemoglobin A1c point of care technology. J Diabetes Sci Technol. 2007;1(3):405–11.
22. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155: 529-536 [PMID: 22007046 DOI: 10.7326/0003-4819-155-8-201110180-00009].
23. MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016.
24. Larissa-Nele Schaffert, Emma English, Carl Heneghan, Christopher P. Price, Ann Van den Bruel, Annette Plüddemann. Point-of-care HbA1c tests - diagnosis of diabetes. Horizon scan report 0044 March 2016.
25. MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016.
26. Larissa-Nele Schaffert, Emma English, Carl Heneghan, Christopher P. Price, Ann Van den Bruel, Annette Plüddemann. Point-of-care HbA1c tests - diagnosis of diabetes. Horizon scan report 0044 March 2016.

Figure 1: Citation Flow Chart

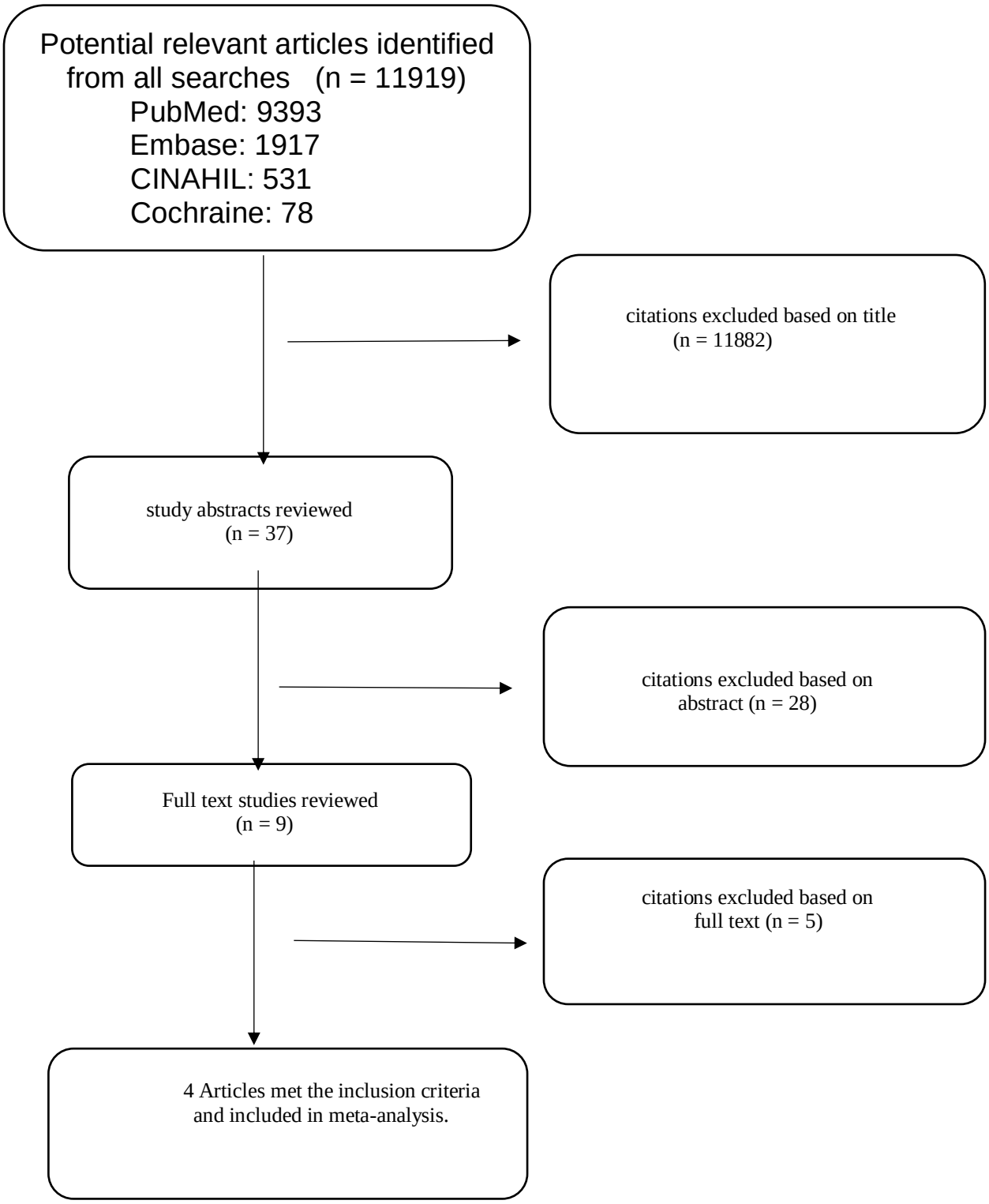
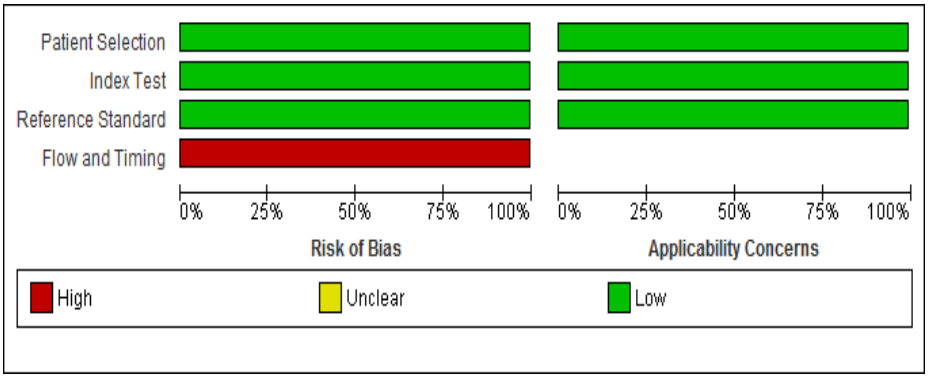


Figure 2: Risk of Bias Assessment



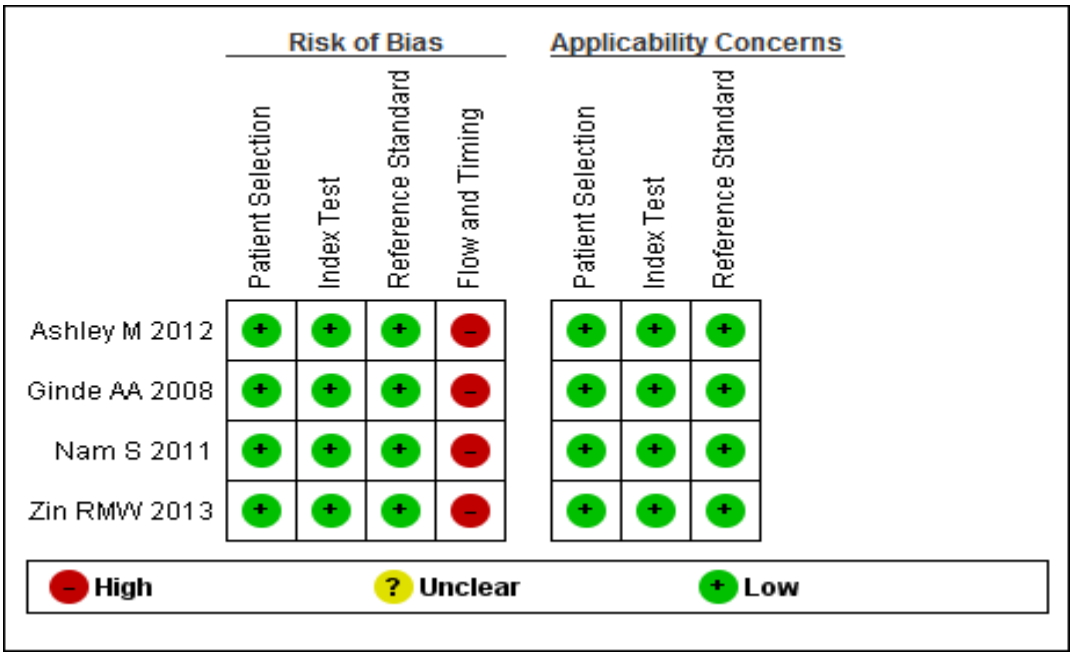


Table 1 A: Characteristic of included studies

NO#	Author Year	Setting	Participants	NO# of particip-ants	Purpose of test	Index test	Reference test	Time Between POC and Lab Tests
1	Zin RMW 2013	National Diabetes Institute, Klang Valley, Malaysia	Normal healthy adults during the community screening Programs.	135	Screening	Afinion	Cationic exchange HPLC.	48 hours.
				139	Screening	Que-test		
2	Nam S 2011	Korean Resource Center, Baltimore-Washington Metropolitan Area, USA.	participants had to be Korean Americans, healthy, 30 years of age or older, with A1c ≥7.5%.	Out of 237 screened participants with POC, only 92 had done the reference standard.	Screening	A1CNOW+	NGSP-certified laboratory	1-2 weeks.
3	Ashley M 2012	Primary care centers in eastern North Carolina, USA.	Participants were at least 18 years of age; resident in a migrant camp in Wilson, Nash, or Edgecombe counties of North Carolina.	Out of 206 screened participants with POC, only 23 had done the reference standard	Screening	A1CNOW+	Roche Tina Quant Hemoglobin A1C immunoassay on the Cobas Integra 800.	28 ± 18 days.
4	Ginde AA 2008	Emergency Department (ED), Massa-chusetts General Hospital, USA	Consecutive patients without known Diabetes, 18 years and older, who visited (ED).	265	Screening	A1CNoW+	HPLC in the hospital's laboratory	Same visit.

Table 1 B: Characteristic of included studies

NO#	Author Year	Cut off level	Limitations
1	Zin RMW 2013	All the participants received both; POC HbA1c and laboratory tests.	The interference from hemoglobin variants was not evaluated, the study did not include the higher HbA1c levels since samples were from community screening programmes, and diabetes status was determined from a single measurement when ideally diagnosis should be confirmed by repeat testing on a different day.
2	Nam S 2011	Only the participants with POC HbA1c ≥ 7.5%, were scheduled to receive laboratory HbA1c test.	There was Verification bias because individuals with POC A1c < 7.5% did not receive the confirmatory laboratory test, so, the findings may either overestimate or underestimate without having a sample whose A1c is between 6.5% and 7.5%. Included only Korean Americans immigrants in this community-based diabetes intervention, made the issue of generalizability beyond other participants is carefully considered based on the characteristics of targeted population.
3	Ashley M 2012	Only the participants with POC HbA1c ≥ 5.7%, were scheduled to receive laboratory HbA1c test.	There was verification bias, because not all participants performed the reference laboratory test. The major limitation of this study was that participants were screened using a POC device and then diagnosed based on one laboratory encounter (ADA diagnostic criteria require two abnormal laboratory values on separate Occasions). Another limitation was that a POC A1C value greater than 5.7% (i.e., 5.8%) was used to define a positive POC A1C screening. Also, financial constraints is negatively affected the follow-up rates. In addition, the findings are specific to a Hispanic Population.
4	Ginde AA 2008	All the participants received both; POC HbA1c and laboratory tests.	The study was performed at a single academic center, which may limit generalizability. Sampling design, exclusion criteria, and nonenrolled eligible patients create potential for selection bias. Additionally, the ED had a relatively small proportion of minority and low socioeconomic status patients compared to many urban EDs.

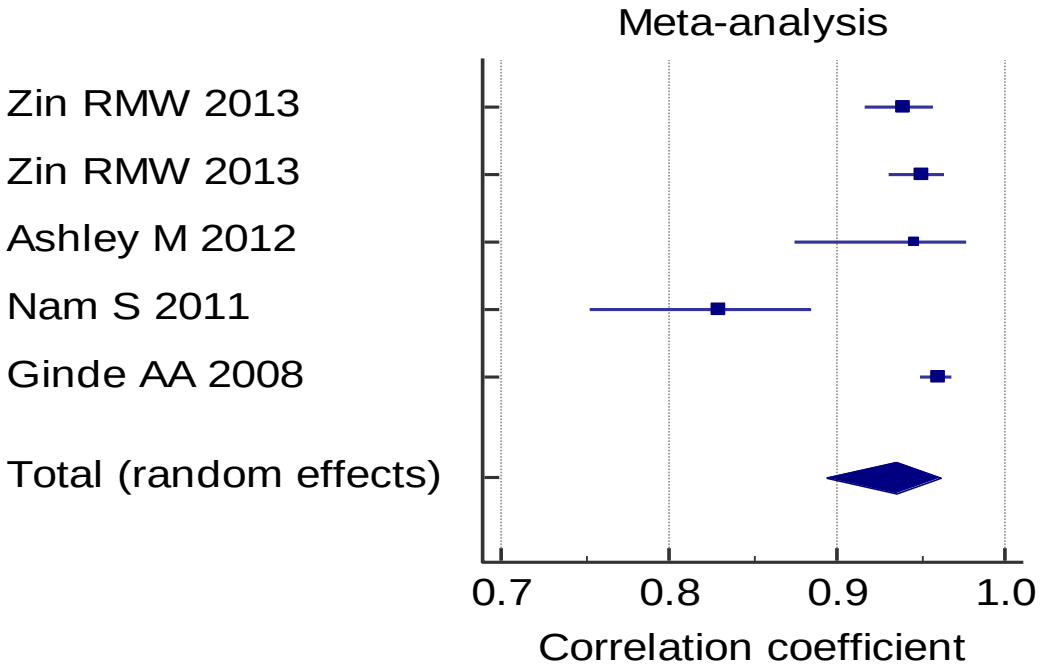
Table 2: Characteristic of Excluded studies.

NO #	Author Year	Setting	Participants	Number of participants	Time Between POC HbA1c and Lab Tests	Index test	Reference test	causes of exclusion
1	Marley JV 2014	6 primary healthcare sites in the remote Kimberley region of Western Australia	All Aboriginal and Torres Strait Islander people ≥15 years old in Kimberley for screening of DM annually.	241	7 days	DCA 2000+ Analyzer	Cobas Integra 800 (Roche Diagnostics, Switzerland).	- The purpose was for diagnosis, not for screening. - No coefficient correlation for screening of DM between 2 tests.
2	Magee MF 2011	Emergency Department, Project for the District of Columbia, USA	participants presenting to an urban tertiary care hospital Emergency Department with blood glucose (BG) ≥ 200 mg/dl.	86	2 - 4 weeks	A1C-NOW+	No data	- There is no comparison between index and reference tests. - The patients presented to ER with hyperglycemia. - The purpose: to assess potential role of index test in hyperglycemia.
3	Chang A 2010	This clinical trial was conducted at two clinical sites in the United States.	Participants ≥18 years of age with known DM (type 1 or 2)or prediabetes as well as those with no known diagnosis of DM.	110	No data	A1C Now SELFCHECK test kit	HPLC on a TOSOH 2.2 laboratory analyzer	- Participants were known diabetics and 20% of them were Type 1. - Purpose of study: for evaluation of index test when used by lay users and health care professionals.
4	Schwartz KL 2009	Recruited from 5 family medicine centers, metropolitan Detroit primary care practices, USA.	consecutive diabetic patients 18 years of age or older, with ordered of HbA1c analysis for routine care.	99	Same visit	A1c Now	4 different laboratories all of which were aligned to Diabetes Control and Complications Trial and NGCP standards.	- Participants were diabetic patients - Purpose of study: for evaluating new technology in clinical practice. - Type of DM not determined.
5	Martin DD 2005	community-based capacity-building program, Kimberley region. Australian.	Participants ≥12 years. 88 residents aged 11–76 years; 36 are diabetic, the other Undiabetic.	88	No data	DCA 2000+ Analyzer.	HPLC on the Bio-Rad Variant II.	- Participants were known diabetics, 41% are on self-reported DM - Included children with age ≥ 12 years.

Table 3: characteristics of POC HbA1c devices available in included studies - manufacturer's claims.			
Product	**Afinion**	**Que-Test**	**A1cNow+**
Manufacturer	Alere Technologies AS, Norway	Quotient Diagnostics, UK	PTS/Chek Diagnostics, USA
Blood type analysed	C / V	C / V	C / V
sample volume (µL)	1.5	4	5
Analysis time (mins)	3	4	5
Weight (kg)	5.0	1.3	0.18
Dimensions	320 mm x 170 mm x 170 mm	205 mm x 135 mm x 205 mm	51 mm x 63.5 mm x 10 mm
Detection Range/ Limit	20.2-140.4mmol/mol (4.0-15.0%)	20.2-140.4mmol/mol (4.0-15.0%)	20.2-119.0mmol/mol (4.0-13.0%)
Method Principle	Boronate affinity	Boronate affinity	Immuno-assay
Im-precision (%CV)	<3%	<3%	3.0-4.02%
NGSP certified	Yes	Yes	Yes
FDA approved	Yes	No	Yes

Abbreviation: C: capillary blood, V: venous blood.

Figure 3: Included Studies Comparing POC HbA1c with Lab HbA1c



Meta-analysis: correlation

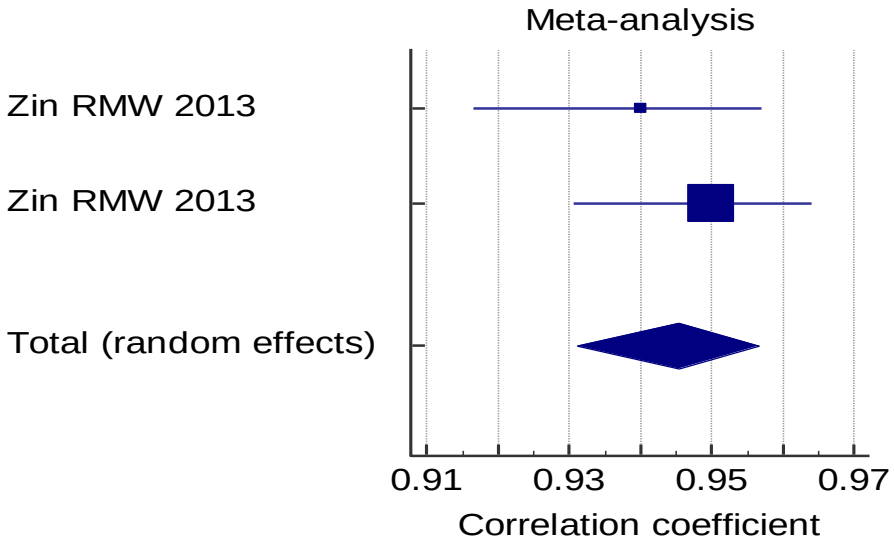
Variable for studies	Study
Variable for number of cases	Sample_Size Sample Size
Variable for correlation coefficients	Coeffecient_Correlation

Study	Sample size	Correlation coefficient	95% CI	z	P	Weight (%)	
						Fixed	Random
Zin RMW 2013	135	0.940	0.917 to 0.957			20.66	21.41
Zin RMW 2013	139	0.950	0.931 to 0.964			21.28	21.47
Ashley M 2012	23	0.946	0.875 to 0.977			3.13	14.17
Nam S 2011	92	0.830	0.753 to 0.884			13.93	20.51
Ginde AA 2008	265	0.960	0.949 to 0.968			41.00	22.43
Total (fixed effects)	654	0.943	0.934 to 0.951	44.701	<0.001	100.00	100.00
Total (random effects)	654	0.935	0.893 to 0.961	12.744	<0.001	100.00	100.00

Test for heterogeneity

Q	38.9017
DF	4
Significance level	P < 0.0001
I^2 (inconsistency)	89.72%
95% CI for I^2	78.83 to 95.01

Figure 4 A: Subgroup Analysis of Afinion and Que-test Devices (Non-A1CNOW+ devices) .



Meta-analysis: correlation

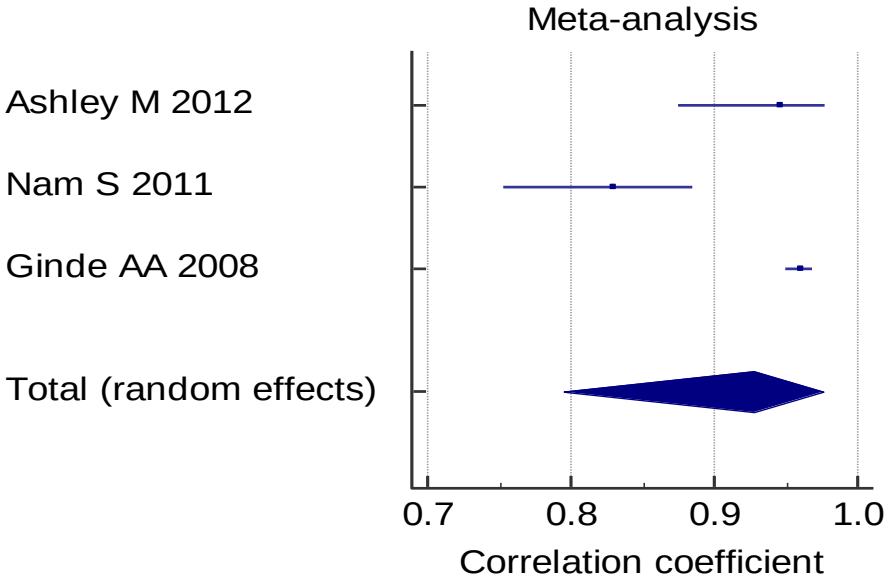
Variable for studies	Study
Variable for number of cases	Sample_Size Sample Size
Variable for correlation coefficients	Coeffecient_Correlation

Study	Sample size	Correlation coefficient	95% CI	z	P	Weight (%)	
						Fixed	Random
Zin RMW 2013	135	0.940	0.917 to 0.957			49.25	49.25
Zin RMW 2013	139	0.950	0.931 to 0.964			50.75	50.75
Total (fixed effects)	274	0.945	0.931 to 0.957	29.232	<0.001	100.00	100.00
Total (random effects)	274	0.945	0.931 to 0.957	29.232	<0.001	100.00	100.00

Test for heterogeneity

Q	0.5885
DF	1
Significance level	P = 0.4430
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 0.00

Figure 4 B: Subgroup Analysis of A1cNOW+ Device.



Meta-analysis: correlation

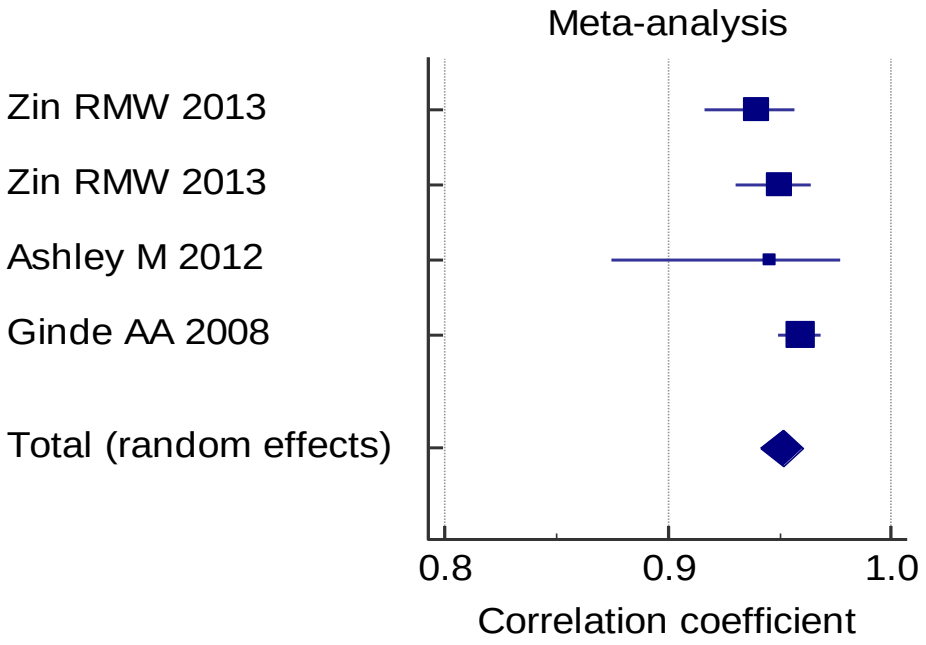
Variable for studies	Study
Variable for number of cases	Sample_Size Sample Size
Variable for correlation coefficients	Coeffecient_Correlation

Study	Sample size	Correlation coefficient	95% CI	z	P	Weight (%)	
						Fixed	Random
Ashley M 2012	23	0.946	0.875 to 0.977			5.39	29.66
Nam S 2011	92	0.830	0.753 to 0.884			23.99	34.60
Ginde AA 2008	265	0.960	0.949 to 0.968			70.62	35.74
Total (fixed effects)	380	0.942	0.929 to 0.952	33.820	<0.001	100.00	100.00
Total (random effects)	380	0.927	0.794 to 0.975	5.776	<0.001	100.00	100.00

Test for heterogeneity

Q	38.1753
DF	2
Significance level	P < 0.0001
I^2 (inconsistency)	94.76%
95% CI for I^2	88.04 to 97.70

Figure 5: Sensitivity Analysis (Nam S 2011 was removed).



Meta-analysis: correlation

Variable for studies	Study
Variable for number of cases	Sample_Size Sample Size
Variable for correlation coefficients	Coeffecient_Correlation

Study	Sample size	Correlation coefficient	95% CI	z	P	Weight (%)	
						Fixed	Random
Zin RMW 2013	135	0.940	0.917 to 0.957			24.00	26.53
Zin RMW 2013	139	0.950	0.931 to 0.964			24.73	27.10
Ashley M 2012	23	0.946	0.875 to 0.977			3.64	5.31
Ginde AA 2008	265	0.960	0.949 to 0.968			47.64	41.06
Total (fixed effects)	562	0.953	0.945 to 0.960	43.673	<0.001	100.00	100.00
Total (random effects)	562	0.952	0.941 to 0.961	34.881	<0.001	100.00	100.00

Test for heterogeneity

Q	4.0941
DF	3
Significance level	P = 0.2515
I^2 (inconsistency)	26.72%
95% CI for I^2	0.00 to 72.35