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REVIEW ARTICLE

A Meta-Analysis of Essential Trace Elements in Patients with Coronary Heart Disease

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ABSTRAK

Terdapat bukti yang semakin meningkat bahawa kehadiran unsur surih penting yang menimbulkan risiko untuk pesakit penyakit jantung koronari (CHD). Meta-analisis telah dijalankan ke atas tahap unsur surih Kuprum (Cu), Zink (Zn), Besi (Fe), Mangan (Mn), Kobalt (Co) dan Kromium (Cr) dalam pesakit CHD. Artikel yang sesuai daripada pangkalan data Web of Science, Scopus, PubMed, EBSCOHost dan Ovid telah dicari berdasarkan garis panduan PRISMA. Artikel Bahasa Inggeris yang diterbitkan antara 2011 hingga 2021 disertakan dan dianalisis dengan statistik deskriptif dan RevMan 5.4. Penilaian kualiti dinilai dengan skala Newcastle-Ottawa. Terdapat enam kajian telah dipilih dengan 322 data peserta. Unsur surih Cu (SMD=-0.13, 95%CI=[-0.99, 0.73], I2=92%, p=0.77), Zn (SMD=-0.38, 95%CI=[-0.81, 0.06], I2= 71%, p=0.09), Fe (SMD=0.47, 95%CI=[-1.19, 2.13], I2=97%, p=0.58) dan Mn (SMD=0.11, 95%CI=[-0.11, 0.33], I2=0%, p=0.33) menunjukkan tahap tidak signifikan. Analisis sensitiviti mendedahkan tahap Cu yang ketara dalam kalangan pesakit dengan CHD (SMD=-0.54, 95%CI=[-0.85, -0.22], I2=0%, p=0.0008) dan tahap Fe antara kawalan (SMD=1.41, 95% CI=[0.08, 2.73], I2=95%, p=0.04). Dapatan kajian juga menunjukkan paras elemen-elemen surih Co dan Cr berbeza-beza mengikut tingkah laku pemakanan dan tabiat merokok. Penilaian kualiti secara keseluruhan menunjukkan kadar kualiti yang sederhana tinggi. Dari analisis yang telah dijalankan, elemen surih Cu didapati signifikan pada pesakit jantung koronari dan elemen surih Fe didapati signifikan di kalangan kajian kawalan,

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manakala penemuan lain tidak menunjukkan hasil kajian yang muktamad.

Kata kunci: Meta-analisis; penyakit jantung koronari; unsur surih penting

ABSTRACT

There is growing evidence that presence of essential trace elements that pose risk for coronary heart disease (CHD) patients. A meta-analysis was conducted on the levels of trace elements Copper (Cu), Zinc (Zn), Iron (Fe), Manganese (Mn), Cobalt (Co) and Chromium (Cr) in CHD patients. Eligible articles from the databases of Web of Science, Scopus, PubMed, EBSCOHost and Ovid were searched based on PRISMA guidelines. English articles published between 2011 to 2021 were included and analysed by descriptive statistics and RevMan 5.4. Quality assessment was assessed with Newcastle-Ottawa scale. There were six studies selected with 322 participants' data. Trace elements Cu (SMD=-0.13, 95%CI=[-0.99, 0.73], I^2=92%, p=0.77), Zn (SMD=-0.38, 95%CI=[-0.81, 0.06], I^2=71%, p=0.09), Fe (SMD=0.47, 95%CI=[-1.19, 2.13], I^2=97%, p=0.58) and Mn (SMD=0.11, 95%CI=[-0.11, 0.33], I^2=0%, p=0.33) levels were not significant. Sensitivity analysis revealed significant Cu level among patients with CHD (SMD=-0.54, 95%CI=[-0.85, -0.22], I^2=0%, p=0.0008) and Fe level among the controls (SMD=1.41, 95%CI=[0.08, 2.73], I^2=95%, p=0.04). Whereas Co and Cr levels varied according to dietary and smoking behaviours. Overall quality assessment was medium-to-high quality. Elements Cu was found significant in CHD patients and Fe was found significant among the controls, while other findings were inconclusive.

Keywords: Coronary heart disease; essential trace elements; meta-analysis

INTRODUCTION

Coronary heart diseases (CHDs) account for the majority of morbidity and mortality worldwide (Virani et al. 2020). Around 18 million people died of CHD in 2017, equating to 330 million years of life lost and another 35.6 million years lived with disability (Yang et al. 2020) and it is one of the leading mortality rate for both men and women in Malaysia which constituted 17% of all deaths (Department of Statistics Malaysia 2021). With this condition, CHD can be identified as one of the potentially risk factors that deem to be preventable especially for low and middle incomed countries. Many of the trace elements to which people are exposed on a daily basis are necessary for health, others serve no biological purpose. Elements such as Copper (Cu), Zinc (Zn), Iron (Fe), Manganese (Mn), Cobalt (Co), and Chromium (Cr) have been identified as trace elements of interest in terms of nutritional significance in this review (Aliasgharpour & Farzami 2013; Mehri

2020; Mikulewicz et al. 2017). When essential trace elements (ETE) are present in excess of a certain level, they can be toxic. There are developing evidences suggesting that these trace elements which are Cu, Zn, Fe, Mn, Co and Cr may have harmful effects that can present at low levels and these are found to be prevalent in many parts of the world (Mehri 2020).

While current understanding and treatment of CHD are cutting-edge, the precise aetiology is unknown, owing to the disease's multifactorial nature, which includes environmental, dietary, behavioural, lifestyle factors and many others. The emphasis is on identifying risk factors, evaluating their predictive capacity, and determining their implications for disease prevention. Additionally, there is growing evidence that the presence of ETE in the body may be a risk factor for CHD on its own, but this is a less well-characterised risk factor (Mikulewicz et al. 2017). Although the mechanisms by which specific elements or their compounds may influence heart disease risk are unknown, they are likely to involve effects on enzymes, hormones, and messenger molecules. Other mechanisms may be involved in the intricate interplay of interactions with other mineral elements. Furthermore, whether a negative relationship with CHD exists at low or high concentrations is unknown. Inconclusive evidence was found linking ETE to an increased risk of developing certain chronic diseases (Mehri 2020).

Given physiological importance of ETE, it is critical to characterise the relationships between these elements and CHD in order to have better understanding the aetiology of CHD and, more importantly, to inform public health efforts to regulate their concentrations, such as their presence or potential presence in drinking water (Cannas et al. 2020). To aid in the clarification of the evidence, a meta-analysis of the available epidemiological studies was conducted on the circulating levels of Cu, Zn, Fe, Mn, Co, and Cr in patients with CHD.

MATERIALS AND METHODS

Design

This review was conducted by using The Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green 2011). In order to report the findings, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol was used. The PRISMA protocol aims to guide the researchers to source the right information with adequate level of detail by conducting a systemic literature review and the processes involved are identification, screening and inclusion processes. The PRISMA protocol was explained in Table 1 and Table 2 (Page et al. 2021). PROSPERO had been notified of the systematic review process (CRD42021290085).

Search Methods

Five major databases named Web of Sciences, Scopus, PubMed, EBSCOHost and Ovid were utilised

TABLE 1: PRISMA 2020 checklist (Page et al. 2021)

Section and Topic	Item #	Checklist item	Page location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	9
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	13
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	10
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	11
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	14
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	14
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	13
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	13
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	14
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	15
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	15

	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	15
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	15
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	15
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	15
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	15
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	15
Study characteristics	17	Cite each included study and present its characteristics.	15
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	20
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	17-19
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	15&20
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	20
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	20
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	24
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	25
	23b	Discuss any limitations of the evidence included in the review.	27
	23c	Discuss any limitations of the review processes used.	27
	23d	Discuss implications of the results for practice, policy, and future research.	27

OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	1
Competing interests	26	Declare any competing interests of review authors.	33
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	33

TABLE 2: PRISMA 2020 for abstracts checklist

Section and Topic	**Item #**	**Checklist item**	**Reported (Yes/No)**
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	-
Registration	12	Provide the register name and registration number.	Yes

for this research. Articles published between year 2011 and year 2021 were included for this review. Population/ Intervention/Comparison/Outcome (PICO) framework was used to identify keywords that can aid the authors in developing suitable questions for this review. The information would supplement the existing knowledge of essential trace elements detection methods and CHD diagnostic criteria. The Boolean search was conducted based on three main concept which were Population (identified as "adult"), Intervention (identified as "essential trace elements"), Comparison (identified as "no exposure") and Outcome (identified as electrocardiography" and ischaemic heart disease") and listed in Table 3.

Search Outcome

A total of 936 articles written in English were retrieved and 40 articles were removed as these were duplicated articles. The 896 articles were furthered screened according to the preset criteria to determine inclusion which were: (a) studies with

TABLE 3: Search string used for all databases

Database	Search String
Web of Science	((((ALL=("Adult" OR "Young Adult" OR "Middle Aged" OR "Man" OR "Woman" OR "Men" OR "Women" OR "Patient" OR "Person")) AND ALL=("Essential trace elements" OR "Micronutrient" OR "Biometal" OR "Trace minerals" OR "Transition elements" OR "Selenium" OR "Calcium" OR "Nickel" OR "Chromium" OR "Zinc" OR "Manganese" OR "Iron" OR "Cobalt" OR "Vanadium" OR "Molybdenum")) AND ALL=("No exposure" OR "Healthy controls" OR "Control" OR "Placebo" OR "Placebo effect" OR "Placebo response" OR "Nocebo effect")) AND ALL=("Electrocardiography" OR "Echocardiography" OR "Serum cardiac biomarkers" OR "Cardiac magnetic resonance imaging" OR "Radionuclide ventriculography" OR "Chest x-ray" OR "ECG abnormalities" OR "ST-T changes" OR "P waves" OR "Sinus tachycardia" OR "Echocardiographic changes" OR "Left ventricular dysfunction" OR "Left ventricular end diastolic diameter" OR "Deaths" OR "Arrythmia" OR "Heart failure" OR "Cardiotoxicity")) AND ALL=("Ischaemic Heart Disease" OR "Ischemic Heart Disease" OR "Coronary artery disease" OR "Coronary atherosclerosis" OR "Coronary arteriosclerosis" OR "Left main disease" OR "Left main coronary disease" OR "Left main coronary artery disease")
Scopus	(TITLE-ABS-KEY ("Adult" OR "Young Adult" OR "Middle Aged" OR "Man" OR "Woman" OR "Men" OR "Women" OR "Patient" OR "Person")) AND (TITLE-ABS-KEY ("Essential trace elements" OR "Micronutrient" OR "Biometal" OR "Trace minerals" OR "Transition elements" OR "Selenium" OR "Calcium" OR "Nickel" OR "Chromium" OR "Zinc" OR "Manganese" OR "Iron" OR "Cobalt" OR "Vanadium" OR "Molybdenum")) AND (TITLE-ABS-KEY ("No exposure" OR "Healthy controls" OR "Control" OR "Placebo" OR "Placebo effect" OR "Placebo response" OR "Nocebo effect")) AND (TITLE-ABS-KEY ("Electrocardiography" OR "Echocardiography" OR "Serum cardiac biomarkers" OR "Cardiac magnetic resonance imaging" OR "Radionuclide ventriculography" OR "Chest x-ray" OR "ECG abnormalities" OR "ST-T changes" OR "P waves" OR "Sinus tachycardia" OR "Echocardiographic changes" OR "Left ventricular dysfunction" OR "Left ventricular end diastolic diameter" OR "Deaths" OR "Arrythmia" OR "Heart failure" OR "Cardiotoxicity")) AND (TITLE-ABS-KEY ("Ischaemic Heart Disease" OR "Ischemic Heart Disease" OR "Coronary artery disease" OR "Coronary atherosclerosis" OR "Coronary arteriosclerosis" OR "Left main disease" OR "Left main coronary disease" OR "Left main coronary artery disease"))

PubMed	((((("Adult"[Title/Abstract] OR "Young Adult"[Title/Abstract] OR "Middle Aged"[Title/Abstract] OR "Man"[Title/Abstract] OR "Woman"[Title/Abstract] OR "Men"[Title/Abstract] OR "Women"[Title/Abstract] OR "Patient"[Title/Abstract] OR "Person"[Title/Abstract]) AND ("Essential trace elements"[Title/Abstract] OR "Micronutrient"[Title/Abstract] OR "Biometal"[Title/Abstract] OR "Trace minerals"[Title/Abstract] OR "Transition elements"[Title/Abstract] OR "Selenium"[Title/Abstract] OR "Calcium"[Title/Abstract] OR "Nickel"[Title/Abstract] OR "Chromium"[Title/Abstract] OR "Zinc"[Title/Abstract] OR "Manganese"[Title/Abstract] OR "Iron"[Title/Abstract] OR "Cobalt"[Title/Abstract] OR "Vanadium"[Title/Abstract] OR "Molybdenum"[Title/Abstract])) AND ("No exposure"[Title/Abstract] OR "Healthy controls"[Title/Abstract] OR "Control"[Title/Abstract] OR "Placebo"[Title/Abstract] OR "Placebo effect"[Title/Abstract] OR "Placebo response"[Title/Abstract] OR "Nocebo effect"[Title/Abstract])) AND ("Electrocardiography"[Title/Abstract] OR "Echocardiography"[Title/Abstract] OR "Serum cardiac biomarkers"[Title/Abstract] OR "Cardiac magnetic resonance imaging"[Title/Abstract] OR "Radionuclide ventriculography"[Title/Abstract] OR "Chest x-ray"[Title/Abstract] OR "ECG abnormalities"[Title/Abstract] OR "ST-T changes"[Title/Abstract] OR "P waves"[Title/Abstract] OR "Sinus tachycardia"[Title/Abstract] OR "Echocardiographic changes"[Title/Abstract] OR "Left ventricular dysfunction"[Title/Abstract] OR "Left ventricular end diastolic diameter"[Title/Abstract] OR "Deaths"[Title/Abstract] OR "Arrythmia"[Title/Abstract] OR "Heart failure"[Title/Abstract] OR "Cardiotoxicity"[Title/Abstract])) AND ("Ischaemic Heart Disease"[Title/Abstract] OR "Ischemic Heart Disease"[Title/Abstract] OR "Coronary artery disease"[Title/Abstract] OR "Coronary atherosclerosis"[Title/Abstract] OR "Coronary arteriosclerosis"[Title/Abstract] OR "Left main disease"[Title/Abstract] OR "Left main coronary disease"[Title/Abstract] OR "Left main coronary artery disease"[Title/Abstract])
EBSCOHost	AB ("Adult" OR "Young Adult" OR "Middle Aged" OR "Man" OR "Woman" OR "Men" OR "Women" OR "Patient" OR "Person") AND AB ("Essential trace elements" OR "Micronutrient" OR "Biometal" OR "Trace minerals" OR "Transition elements" OR "Selenium" OR "Calcium" OR "Nickel" OR "Chromium" OR "Zinc" OR "Manganese" OR "Iron" OR "Cobalt" OR "Vanadium" OR "Molybdenum") AND AB ("No exposure" OR "Healthy controls" OR "Control" OR "Placebo" OR "Placebo effect" OR "Placebo response" OR "Nocebo effect") AND AB ("Electrocardiography" OR "Echocardiography" OR "Serum cardiac biomarkers" OR "Cardiac magnetic resonance imaging" OR "Radionuclide ventriculography" OR "Chest x-ray" OR "ECG abnormalities" OR "ST-T changes" OR "P waves" OR "Sinus tachycardia" OR "Echocardiographic changes" OR "Left ventricular dysfunction" OR "Left ventricular end diastolic diameter" OR "Deaths" OR "Arrythmia" OR "Heart failure" OR "Cardiotoxicity") AND AB ("Ischaemic Heart Disease" OR "Ischemic Heart Disease" OR "Coronary artery disease" OR "Coronary atherosclerosis" OR "Coronary arteriosclerosis" OR "Left main disease" OR "Left main coronary disease" OR "Left main coronary artery disease")
Ovid	(("Adult" or "Young Adult" or "Middle Aged" or "Man" or "Woman" or "Men" or "Women" or "Patient" or "Person") and ("Essential trace elements" or "Micronutrient" or "Biometal" or "Trace minerals" or "Transition elements" or "Selenium" or "Calcium" or "Nickel" or "Chromium" or "Zinc" or "Manganese" or "Iron" or "Cobalt" or "Vanadium" or "Molybdenum") and ("No exposure" or "Healthy controls" or "Control" or "Placebo" or "Placebo effect" or "Placebo response" or "Nocebo effect") and ("Electrocardiography" or "Echocardiography" or "Serum cardiac biomarkers" or "Cardiac magnetic resonance imaging" or "Radionuclide ventriculography" or "Chest x-ray" or "ECG abnormalities" or "ST-T changes" or "P waves" or "Sinus tachycardia" or "Echocardiographic changes" or "Lect ventricular dysfunction" or "Left ventricular end diastolic diameter" or "Deaths" or "Arrythmia" or "Heart failure" or "Cardiotoxicity") and ("Ischaemic Heart Disease" or "Ischemic Heart Disease" or "Coronary artery disease" or "Coronary atherosclerosis" or "Coronary arteriosclerosis" or "Left main disease" or "Left main coronary disease" or "Left main coronary artery disease")).ab.

quantitative data on the levels of Cu, Zn, Fe, Mn, Co, and Cr trace elements; and (b) patients with CHD aged 18 or older. Restrictions were imposed on commentary, editorials, proceedings, and review articles.

On further screening, the authors identified 30 articles from the pool of 896 articles that shown basic relevant information. Comparators included studies with healthy participants or volunteers or those without CHD as controls. Further 24 articles were filtered as these were based on non-essential trace elements, irrelevant outcome and intervention, for example, medication trial and review articles. In the final eligibility process, six articles (Anonna et al. 2020; Cappelletti et al. 2016; Cebi et al. 2011; Ilyas & Shah 2015; Morfeld et al. 2017; Zengin et al. 2015) were included, however only three (Anonna et al. 2020; Cebi et al. 2011; Ilyas & Shah 2015) were identified for further analysis in view of their data compatibility. The PRISMA flow diagram was shown in Figure 1.

Three independent reviewers

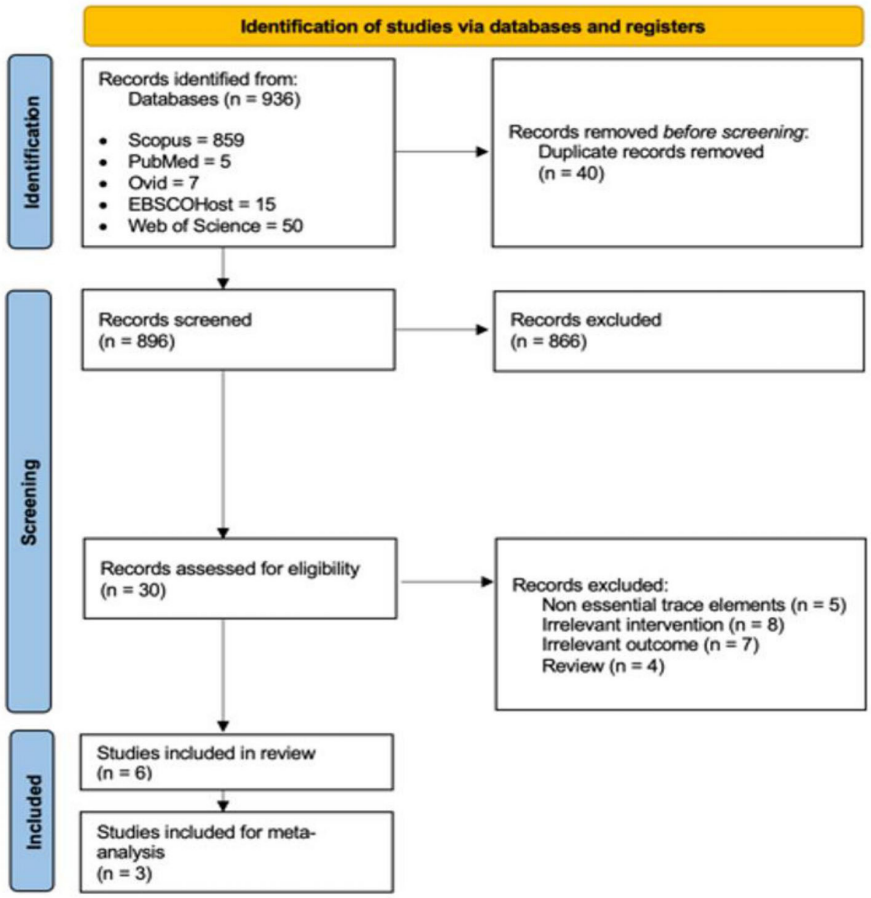

FIGURE 1: PRISMA diagram of identifying studies of essential trace elements (Page et al. 2021)

(PSNMK, AMN, and MHJ) reviewed and selected studies sequentially, eliminating duplicates from the initial title and abstract screen to the full text for eligibility. Any discrepancies regarding the study's inclusion were resolved through consultation with a fourth investigator (MNY). A review author (AMAM) transferred the data to the Review Manager 5.4 software (The Cochrane Collaboration 2014), and the second review author (MNY) verified the data entry accuracy.

Quality Assessment

Two independent reviewers (MNY and AMAM) evaluated the quality of the included studies using the Newcastle-Ottawa scale (Wells et al. 2011). Any disagreement was resolved through discussion with consultation by a third reviewer (MHJ). This scale is intended for non-randomised studies and consists of three domains that quantify various aspects of study quality. The Newcastle-Ottawa Scale is using a nine-star rating to assess the quality of the study based on the (i) participation selection; (ii) study group comparability; and (iii) ascertainment of desired outcomes domains. A scale of nine stars indicated that the study was of high quality, seven or eight stars indicated that the study was of medium quality, and the scale of less than seven stars indicated that the study was of low quality.

Assessment of Heterogeneity, Meta-Analysis and Certainty of Evidence Rating

Narrative analysis was conducted, and RevMan 5.4 used to pool the data when there were three or more study that reported the same conclusions (Campbell et al. 2020). In order to measure the degree of heterogeneity, I^2 statistic was performed with a cut-off level of 50% which was considered as significant (Higgins et al. 2011). Data was pooled and meta-analysis was performed where necessary, using the RevMan 5.4 software's random-effect model (The Cochrane Collaboration 2014), with the assumption that there may be large impact between the studies that they differ in terms of study population and study sample sizes. These findings were tabulated by using the standard mean difference (SMD) values for continuous outcomes and their respective confidence intervals (CI) at 95% level to measure the same outcome. However, two studies (Anonna et al. 2020; Cebi et al. 2011) results needed to be converted prior to the analysis to produce the same measurements. Then sensitivity analysis was conducted when the pooled effect exhibited a significant degree of heterogeneity (Higgins & Green 2011). Funnel plots were used to assessed publication biases.

RESULTS

There were six studies (Anonna et al. 2020; Cappelletti et al. 2016; Cebi et al. 2011; Ilyas & Shah 2015; Morfeld et al. 2017; Zengin et al. 2015) included in this review, all of which were published between 2011 and 2020. Table 4 summarised the characteristics of the studies that were included.

TABLE 4: Characteristics of reviewed studies

Author / Year	Country	Population source	Study design	Study duration	Age	Male gender (%)	Number of participants	Number of cases / CHD events / outcome / heart-related disease	Number of control	Analytic method	Samples, unit	Type of trace elements studied	Findings: level or concentration, mean (SD)/others	Adjustment factors	Recommendation
Cebi et al. (2011)	Turkey	Patients with CHD attending cardiology clinic at Yuzuncu Yil University Hospital	Case-control	NS	Mean age 58.3 years old	NS	50	30	20	Atomic absorption spectro-photometry (UNICAM-929)	Blood, mcg/dL	Zn	IG: 0.85 (0.55) CG:0.91 (0.18)	Age, BMI, smoking, comorbi-dities	Serum levels of iron and copper may be lower in patients with CHD
												Cu	IG: 1.02 (0.27) CG: 1.19 (0.42)		
												Fe	IG: 0.57 (0.24) CG: 1.07 (0.45)		
												Mn	IG: 0.06 (0.06) CG: 0.04 (0.06)		
												Pb	IG: 0.14 (0.09) CG: 0.10 (0.06)		
												Cd	IG: 0.01 (0.01) CG: 0.01 (0.01)		

Ilyas Shah (2015)	Pakistan	Patients admitted in Punjab Institute of Cardiology	Case-control	NS	Mean age 49.6 years old	60%	159	80	79	FAAS (Shimadzu AA-670, Kyoto, Japan)	Blood, mcg/L	Zn	IG: 4550 (2230) CG: 4930 (2150)	Age, gender, abode, food habit, tobacco use	Higher concentrations of Cr, Cu, Fe and Mn were observed in the blood of CAD patients than controls
												Cu	IG: 1170 (402) CG: 902 (430)		
												Fe	IG: 470000 (117000) CG: 375000 (137000)		
												Mn	IG: 7.1 (13.6) CG: 5.64 (7.80)		
												Pb	IG: 58.1 (47.14) CG:39.2 (28.68)		
												Cd	IG: 0.55 (0.381) CG: 0.45 (0.273)		
												Mg	IG: 39900 (25300) CG: 35400 (20400)		
												Co	IG: 0.69 (0.392) CG: 0.57 (0.38)		
												Cr	IG: 1.63 (1.157) CG: 0.79 (0.668)		
												Ca	IG: 88900 (51100) CG: 70000 (44800)		

Zengin et al. (2015)	Germany	Patients who underwent coronary angiography at the Department of Medicine II of the Johannes Gutenberg-University Mainz or the Federal Armed Forces Central Hospital Koblenz	Cohort	June 1996 - April 2004	Median age 64 old years	83%	2239	103	Nil	NS	Blood, NS	Cu / Zn	103 cases of cardiovas-cular deaths, p=0.045	Gender, age, BMI, comorbi-dity, family history	SOD activity of the copper/ zinc type was a predictor of an adverse course in patients with known CHD
Capelletti et al. (2016)	Italy	Male steel workers at an electric arc furnace	Cohort	19 March 1979 - 31 Dec 2009	Mean age at entry was 31.1 years and mean age at death was 54 years	All	331	Nil	Nil	NS	Nil	PM 2.5, Fe, Aluminum, Zinc, Mn, Pb, Cr, Ni, Cd, Hg, Ar, PAHs, Polychlo-rinated Biphe-nyls and Dioxins	Mortality study: SMR 1.27; 95 % CI: 0.35–3.26; 4 cases for ischeamic heart disease Morbidity study: there was a statistically significant increase of cardiovas-cular diseases in exposed workers	Age, duration of exposure, type of work, comorbi-dity	Reliable method for measuring metal PM in tissue was needed for better exposure assessment in future studies
Morfeld et al. (2017)	Germany	Workers at hardmetal industry plant	Cohort	1 Jan 1975 - 31 Dec 2012	Mean age at end of follow-up was 54.1 years	75%	6865	187	Nil	NS	Total cumula-tive environ-mental exposure, NS	Co, Ni, Tungsten, respirable & inhalable dust	SMR 1.56; 95% CI: 1.35- 1.81; 187 cases for all heart diseases	Gender, age, smoking, comorbi-dity, duration of exposure, type of work	Heart diseases showed excesses in SMR analyses

Anonna et al. (2020)	Bangladesh	IHD patients at Department of Cardiology, Cumilla Sadar Hospital & Lakshmipur Sadar Hospital	Case-control	July 2015 - March 2016	Mean age 43.83 years old	53.85%	113	52	61	FAAS; Varian Spectra AA 220) and GFAAS	Blood, mg/L	Zn	IG: 2.5 (0.19) CG: 4.02 (0.29)	Age, gender, BMI, comorbidity	Strong association of the pathogenesis of IHD with depleted serum levels of Zn and Cu and elevated Fe and Mn levels
												Cu	IG: 2.52 (0.167) CG: 3.63 (0.32)		
												Fe	IG: 148.97 (1.25) CG: 59.94 (7.28)		
												Mn	IG: 7.32 (1.23) CG: 7.32 (1.55)		

IHD: ischaemic heart disease; CHD: coronary heart disease; PM: particulate matter; NS: not stated; mg/L: miligrams per litre; mcg/dL: micrograms per decilitre; mcg/L: micrograms per litre; IG: intervention group; CG: control group; SOD: Superoxide dismutase; FAAS: Flame atomic absorption spectrometry; GFAAS: Graphite furnace atomic absorption spectrometry; Zn: zinc; Cu: copper; Fe: iron; Mn: manganese; Pb: lead; Cd: cadmium; Mg: magnesium; Co: cobalt; Cr: chromium; Ca: calcium; Al: aluminium; PAHS: polycyclic aromatic hydrocarbon; Ar: arsenic; Hg: mercury; Ni: nickel; PM: particulate matter

Among the six included studies, three were cohorts (Cappelletti et al. 2016; Morfeld et al. 2017; Zengin et al. 2015) and three were case-controls (Anonna et al. 2020; Cebi et al. 2011; Ilyas & Shah 2015) study design. Two studies were conducted in Germany (Morfeld et al. 2017; Zengin et al. 2015), while the rest are conducted in Bangladesh (Anonna et al. 2020), Pakistan (Ilyas & Shah 2015), Italy (Cappelletti et al. 2016) and Turkey (Cebi et al. 2011). The number of participants ranged from 50 (Cebi et al. 2011) to 6865 (Morfeld et al. 2017). Individual-level blood serum was used to determine the levels of ETE and mostly were measured by atomic absorption spectrometry methods (Anonna et al. 2020; Cebi et al. 2011; Ilyas & Shah 2015).

Meanwhile, as shown in Table 5, study quality as measured by the Newcastle-Ottawa scale varied. The total score based on stars given for each study range between five to nine. There were four studies (three cohorts and one case-controls) that were rated as medium to high quality with a score of seven stars or more (Cappelletti et al. 2016; Ilyas & Shah 2015; Morfeld et al. 2017; Zengin et al. 2015), except for two studies (two case-controls) were of low quality (Anonna et al. 2020; Cebi et al. 2011). Of the studies included, all articles adequately explained the definition of case or controls in terms of Selection and able to assess the outcomes in terms of Exposure.

Quantitative Synthesis

Three case-controls studies (Anonna et al. 2020; Cebi et al. 2011; Ilyas

TABLE 5: Newcastle-Ottawa scale for assessing study quality (Wells et al. 2011)

Newcastle-Ottawa scale for assessing case-control study quality				
Author	**Selection (Max = 4)**	**Comparability (Max = 2)**	**Exposure (Max = 3)**	**Overall quality score (Max = 9)**
Cebi et al. (2011)	3	1	2	6
Ilyas et al. (2015)	4	1	3	8
Anonna et al. (2020)	2	1	2	5
Newcastle-Ottawa scale for assessing cohort study quality				
Author	**Selection (Max = 4)**	**Comparability (Max = 2)**	**Outcome (Max = 3)**	**Overall quality score (Max = 9)**
Zengin et al. (2015)*	3	1	3	7
Capelletti et al. (2016)*	4	2	3	9
Morfeld et al. (2017)*	3	1	3	7
*Studies not included in the meta-analysis				

& Shah 2015) with 322 participants were managed to pool the results in the meta-analysis of trace elements' level among patients with CHD. For the cohort studies (Cappelletti et al. 2016; Morfeld et al. 2017; Zengin et al. 2015), we were unable to pool their results for mortality comparison in view of different trace elements being studied with different outcomes. Table 6 showed the comparison of each outcome.

The trace elements pooled were blood serum level in microgram per litre (mcg/L). Among the included studies, Cu (SMD -0.13, 95% CI [-0.99, 0.73], I^2 = 92%, p = 0.77; Figure 2a) and Zn (SMD -0.38, 95% CI [-0.81, 0.06], I^2 = 71%, p = 0.09; Figure 2b) levels were observed not significant among the patients with CHD. While Fe (SMD 0.47, 95% CI [-1.19, 2.13], I^2 = 97%, p = 0.58; Figure 2c) and Mn (SMD 0.11, 95% CI [-0.11, 0.33], I^2 = 0%, p = 0.33; Figure 2d) levels were observed not significant among the controls.

On further analysis using funnel

TABLE 6: Summary of outcome estimates levels of essential trace elements in patients with coronary heart disease versus controls

Outcome of Subgroup	Studies	Participants	Statistical Methods	Effect Estimates
1.1 Zinc	3	322	Std Mean Difference (IV, Random, 95% CI)	-0.38 [-0.81, 0.06]
1.2 Copper	2	163	Std Mean Difference (IV, Random, 95% CI)	-0.54 [-0.85, -0.22]
1.3 Iron	2	272	Std Mean Difference (IV, Random, 95% CI)	1.41 [0.08, 2.73]
1.4 Manganese	3	322	Std Mean Difference (IV, Random, 95% CI)	0.11 [-0.11, 0.33]

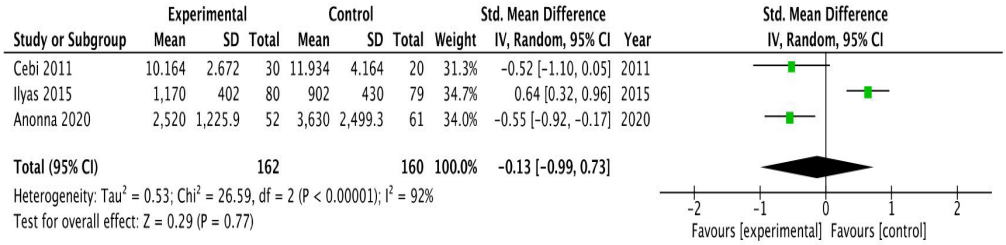

FIGURE 2a: The level of copper in patients with coronary heart disease versus controls (n=3)

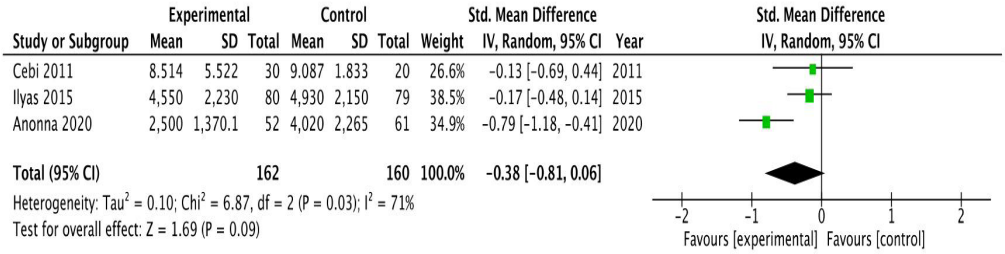

FIGURE 2b: The level of zinc in patients with coronary heart disease versus controls (n=3)

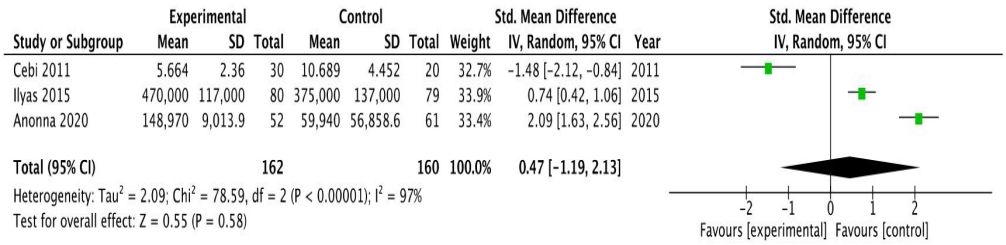

FIGURE 2c: The level of iron in patients with coronary heart disease versus controls (n=3)

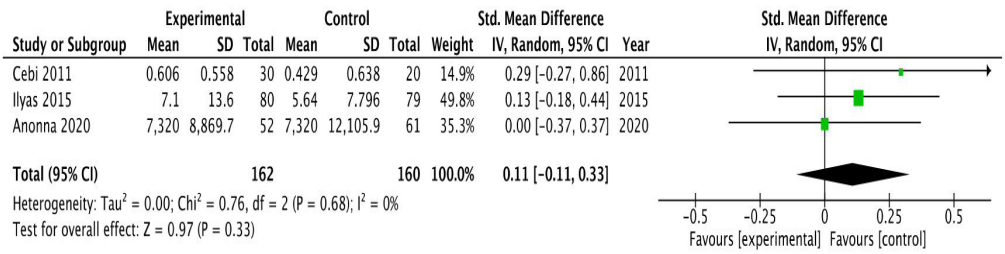

FIGURE 2d: The level of manganese in patients with coronary heart disease versus controls (n=3)

plots analysis, the outcomes were skewed because of limited number of studies and the heterogenous nature of the studies (Figure 3).

Sensitivity Analysis

Sensitivity analysis over studies with significant heterogeneity indicated that the ETE level may be related with differences in the timing of recruitment as Ilyas & Shah (2015) had newly diagnosed patients with CHD in comparison to the other two studies that recruited available patients with CHD from the respective cardiology departments. Meanwhile, differences in population ethnicity reflected upon (Cebi et al. 2011), which was a study conducted in Europe as compared to the other studies conducted in Asia. By removing these studies in the meta-analysis, the heterogeneity reduced and Cu level was significant in patients

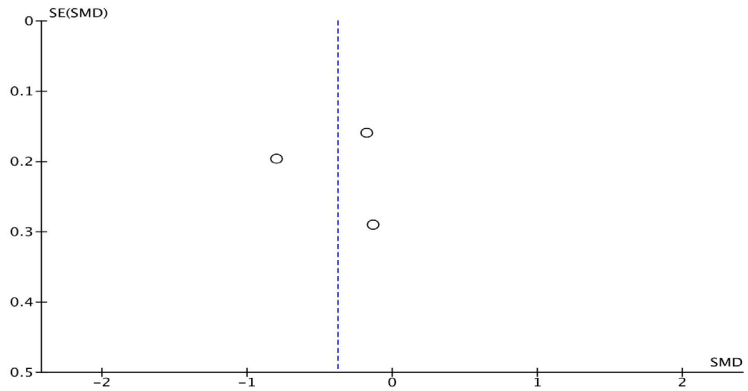

FIGURE 3a: Funnel plot comparison of zinc levels in patients with coronary heart disease versus controls (n=3)

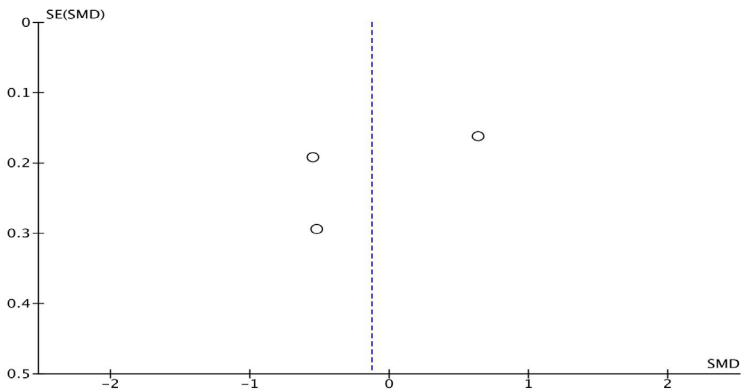

FIGURE 3b: Funnel plot comparison of copper levels in patients with coronary heart disease versus controls (n=3)

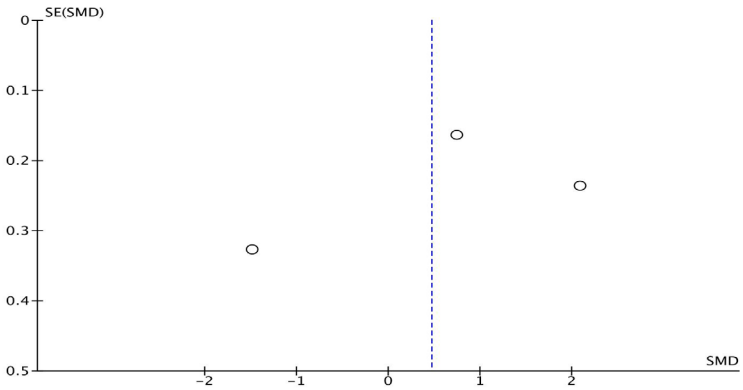

FIGURE 3c: Funnel plot comparison of iron levels in patients with coronary heart disease versus controls (n=3)

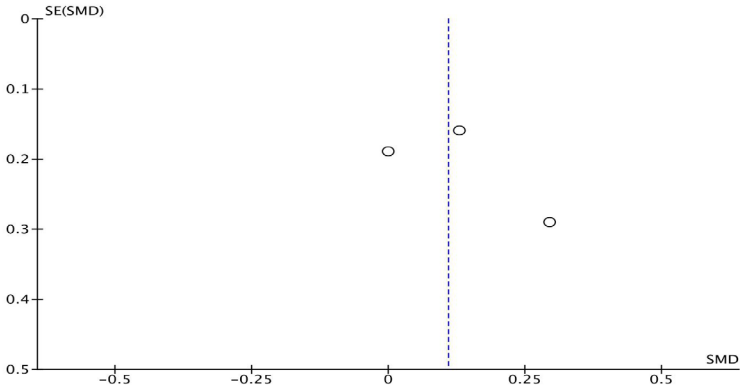

FIGURE 3d: Funnel plot comparison of manganese levels in patients with coronary heart disease versus controls (n=3)

with CHD (SMD -0.54, 95% CI [-0.85, -0.22], I^2 = 0%, p = 0.0008; Figure 4a), while Fe level was significant among the controls (SMD 1.41, 95% CI [0.08, 2.73], I^2 = 95%, p = 0.04; Figure 4b). Subgroup analysis was not possible for limited numbers of studies.

Qualitative Synthesis

In regard to Co and Cr, the significant effect of their levels was unable to be deduced as there was only two studies (Ilyas & Shah 2015; Morfeld et al. 2017). Thus, they were discussed narratively. Ilyas & Shah (2015) discovered that vegetarian controls had significantly higher mean ($p<0.05$) Co levels, among them, smokers had significantly higher ($p<0.05$) Co levels. Dietary sources contributed the majority of this element (Ilyas & Shah 2015). The standardised mortality ratios (SMRs) for all heart diseases were statistically significant elevated by about 50% in the full analytical cohort and the

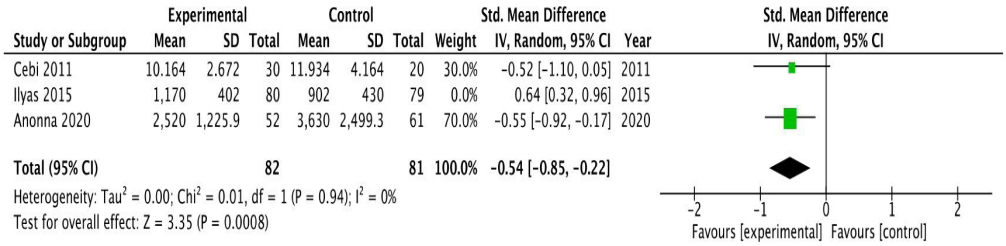

FIGURE 4a: Sensitivity analysis on the levels of copper in patients with coronary heart disease versus controls (n=2)

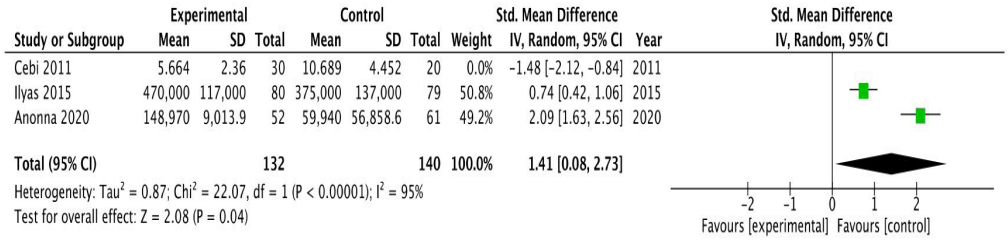

FIGURE 4b: Sensitivity analysis on the levels of iron in patients with coronary heart disease versus controls (n=2)

excess was observed in both men and women (with almost a doubling of risk) (Morfeld et al. 2017).

Meanwhile, average Cr levels in patients with CHD were significantly higher ($p<0.001$) than controls, which in non-vegetarian patients, the mean levels of Cr were significantly higher ($p<0.05$) (Ilyas & Shah 2015).

DISCUSSION

The review identified robust evidence on ETE level among patients with CHD versus controls. Empirical studies revealed the significance of these ETE at varying level for many chronic non-communicable diseases, predominantly CHD (Choi et al. 2019; Mohamed et al. 2019; Morais et al. 2020; Ramesh & Kulkarni 2016). This highlighted the elements' unique role in the development of the CHD disease is important in terms of prevention and management. This study found significant level of Cu in patients with CHD and Fe among the controls. From the meta-analysis, it was evident that these elements were considered as contributory factors towards CHD.

Descriptively, a noteworthy finding was the observed gender distribution discrepancy among the studied groups. Most participants, especially those with CHD (Anonna et al. 2020; Cebi et al. 2011; Ilyas & Shah 2015; Zengin et al. 2015), and also among industry workers (Cappelletti et al.

2016; Morfeld et al. 2017), were predominantly male. Consider the gender imbalance, as biological and hormonal differences between men and women may impact the observed associations. CHD is generally common in men than women, except in women aged more than 65 years (Majidi et al. 2021). The delay in CHD onset in women may be linked to the protective effects of endogenous oestrogen and menopausal hormonal changes (Bugiardini et al. 2019; Clerc Liaudat et al. 2018; Schmidt et al. 2018). At the cellular level, male mitochondria are less resilient to ischaemic reperfusion injury due to higher reactive oxygen species production and lesser antioxidant capacity (Beale et al. 2018). The link between serum Cu levels and cardiovascular disease death risk in Finnish men was seen after 25.8 years of follow-up, revealed a continuous increase in cardiovascular deaths with rising Cu levels (Isiozor et al. 2023).

Regarding to the distinct regional distribution between Asian (Anonna et al. 2020; Ilyas & Shah 2015) and European (Cappelletti et al. 2016; Cebi et al. 2011; Morfeld et al. 2017; Zengin et al. 2015) populations, notable differences surfaced, highlighting the intricate interplay of various factors. Global variations, such as genetic variability among populations, can complicate essential trace element status by affecting trace element metabolism (Himoto & Masaki 2020). Also, factors such as cultural practices, lifestyle variations, and dietary differences, might contribute to observed variations, potentially influencing trace element distributions (Zhu et al. 2019). Examples include genetics, body composition, and size reveal an inverse relationship between iron status and body composition, suggesting a potential need for higher iron requirements in individuals with a high body mass index, a globally escalating condition (Alshwaiyat et al. 2021). Excessive fat presence can trigger inflammation, impacting iron status (Laudisio et al. 2023). The Fe-containing protein hepcidin is a mediator in this process, contributing to iron deficiency in individuals with high body fat (Qiu et al. 2022). Cultural practices profoundly influence global food choices and preparation, like some customs in Hinduism, Buddhism, and Jainism promoting vegetarianism due to religious beliefs (Prakash 2020). Plant-based diets are linked to a high prevalence of iron-deficiency anaemia and reduced cognitive performance (Bhatnagar & Padilla-Zakour 2021). Diet-related factors vary across countries, can impact nutrient bioavailability, leading to interactions among trace elements, such as competitive interactions between Cu and Fe. Ceruloplasmin and hephaestin are Cu-dependent enzymes vital for releasing Fe from specific tissues and facilitating Fe transport from enterocytes into the circulation (Doguer et al. 2018).

Trace element Cu, needed only in trace amounts, an essential micronutrient for human bodily functions (Bagheri et al. 2015; Dinicolantonio et al. 2018; Godswill et al. 2020; Liu & Miao 2022). Cu toxicity can affect in a variety of ways, including cardiac arrhythmia (Al-Fartusie &

Mohssan 2017; Bost et al. 2016; Bulska & Ruszczy ska 2017; Kunutsor et al. 2021; Liu & Miao 2022). The current review revealed high circulating Cu level in patients with CHD. This high level of Cu can stimulate superoxide dismutase types 1 and 3 that causes oxidative stress by generating reactive oxygen species, which are linked to cardiovascular mortality in patients with CHD (Chowdhury et al. 2018; Prashanth et al. 2015; Zengin et al. 2015). Several studies utilising in-vivo and in-vitro methods have shown copper-mediated lipid peroxidation (Chowdhury et al. 2018) and the harmful mechanism effects of copper-homocysteine complex, that causes endothelial dysfunction and vascular injury (Prashanth et al. 2015; Shi et al. 2021). Furthermore, the current review discovered that controls had significantly higher levels of circulatory Fe, indicating that patients with CHD have low Fe levels. Iron serves as an oxygen carrier in the blood and muscles (Banach et al. 2020; Haehling et al. 2015). Chronic iron deficiency is well known to accelerate the development of CHD which can lead to coronary atherosclerosis and acute myocardial infraction. This low level of iron can be considered as one of the biological and prognostic marker of coronary atherosclerosis (Meng et al. 2022). Supported by medium to high quality assessment of the studies, the generalisability of findings is applicable to other populations despite limited number of studies.

Other non-significant findings of Zn and Mn may be possibly due to small sample sizes or lacking comparable studies. The outcome of the funnel plots analysis also had shown the presence of publication bias which was due to limited studies. This type of bias is induced by the fact that research with statistically significant result is more likely to be accepted for publication than those with insignificant results. Hence, this may compromise the validity of the analyses that possibly lead to an incorrect and over optimistic conclusions (Nissen et al. 2016).

The limited or traces findings of Co and Cr may be related to a variety of factors. One factor to consider is the analysation method of these elements. Atomic absorption spectrometry lacks the detection limits necessary to analyse these metals at the trace levels required for biomonitoring, and it also does not permit simultaneous measurement of multiple analytes, which this technique may vary between studies (Georgi et al. 2017). Sensitivity, multi-elemental analysis, high sample throughput, and the ability to efficiently reduce interferences caused by collision or reaction cells are required for detection of low level trace elemental analysis (Bulska & Ruszczyńska 2017). Behavioural factors on types of diet and smoking may contributed to how these elements are being metabolised in the body (Al-Fartusie & Mohssan 2017; Balali-Mood et al. 2021; Banihani et al. 2019).

This study had included the majority of relevant literature by conducting a comprehensive search across multiple databases, in regard to ETE levels among patients with CHD. The findings are relevant in understanding the preventable determinants of CHD,

which is important in developing appropriate intervention strategies for prevention and control.

Additionally, this study had some limitations, from the small number of the studies included in this meta-analysis to confirm our findings. The time of onset of CHD and population ethnicity were important variables in studies examining the effect of ETE metabolism on CHD. Furthermore, this meta-analysis did not account for confounding variables such as chemical forms, exposure times, doses, and routes to heavy metals, dietary habits, lifestyles, and smoking habits, all of which influence the cardiotoxic effects of these toxicants. Finally, majority of studies included were conducted on patients with CHD from specific regions of Europe and Asia. It was unknown at this point whether the findings can be generalised to other populations.

CONCLUSION

With evidence of medium-to-high quality, Cu was significantly found in patients with CHD and Fe was significantly found among the controls. Other findings are inconclusive given the study limitations, the ETE levels in patients with CHD has to be interpreted cautiously. These findings emphasise the role of monitoring the levels of ETE, indicating that these elements may be involved in the human metabolic cycle, and that any disruption in their homeostasis is frequently associated with adverse health consequences. Due to the small number of studies retrieved, additional studies in different countries and population groups are necessary to obtain more comprehensive and reliable results.

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