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

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Abstract

Objective: Previous evidences reported discrepancy effects of education and income on cardiovascular diseases (CVD). This systematic review and meta-analysis was therefore conducted which aimed to summarize effects of education and income on CVDs.

Methods: Studies were identified from Medline and Scopus until July 2016. Cohorts were eligible if they assessed associations between education/income and CVDs, had at least one outcome including coronary artery diseases (CAD), cardiovascular events (CVE), strokes and cardiovascular deaths (CD). 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, US, and Asia. Pooled risk ratios (RRs) of low and medium versus high education were 1.36 (95% CI: 1.11, 1.66) and 1.21 (1.06, 1.40) for CAD, 1.50 (1.17, 1.92) and 1.27 (1.09, 1.48) for CVE, 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 CD. Effects of educations on all CVDs were still present in US and Europe settings, except in Asia was present only CD. Effects of low and medium income versus high on these corresponding CVDs were 1.49 (1.16, 1.91) and 1.27 (1.10, 1.47) for CAD, 1.17 (0.96, 1.44) and 1.05 (0.98, 1.13) for CVE, 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 CD.

Conclusion: Social determinants are risk factors of CVDs 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

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Abbreviations

BMI Body mass index
CAD Coronary artery diseases
CHD Coronary heart disease
CI Confidence interval
CVD Cardiovascular diseases
CVE Cardiovascular events
CVRFs Cardiovascular risk factors
HF Heart failure
IHD Ischemic heart disease
LMICs Low- and middle-income developing countries
MI Myocardial infarction
NCD Non-communicable diseases
RR Relative risks
SDH Social determinants of health
SES Socioeconomic status

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**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.\(^1\) Majority are cardiovascular diseases (CVD) followed by cancers, respiratory diseases, and diabetes. CVD are a major public health problem accounting for about 30% of the annual global mortality (17.5 million annually) and 10% of the global disease burden.\(^1\)

Framingham Heart Study,\(^2\) WHO-MONICA Project,\(^3\) and INTERHEART\(^4\) studies provided evidences for the major risk factors of CVD. Interventions that modify these risk factors are known to reduce cardiovascular morbidity and mortality. Despite much effort 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 CVD. Recently, the fifth epidemiological transition proposed that social upheaval,\(^5\) a break down 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 influences CVD by impacting 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., low education was more likely to develop CVRFs (e.g., hypertension, diabetes, dyslipidemias, overweight, etc.), and have less healthy dietary habits.\textsuperscript{15,17} Evidences also showed that lower education is associated with atherosclerosis, ischemic heart disease (IHD), cerebrovascular diseases, CVD mortality and all-cause mortality.\textsuperscript{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.\textsuperscript{19,21} These effects of education and income are more consistent in developed countries, but results are still inconclusive in LMICs.\textsuperscript{22}

Several narrative and systematic reviews\textsuperscript{23-28} assessed the relationship between socioeconomic status (SES) and CVDs, including myocardial infarction (MI), strokes, heart failure (HF), and death. Two meta-analyses have reported the effects of education and income on MI\textsuperscript{23} and CVD mortality.\textsuperscript{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 few studies included participants from LMICs. We therefore conducted a systematic review and meta-analysis to pool the effects of low to high educations and incomes 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).\textsuperscript{29}
Search strategy

Relevant studies were identified from Medline and Scopus databases since inception to 31st 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 Appendix A.

Selection of studies

Retrospective/prospective cohorts published in English were selected if they met following criteria:

(1) assessed associations between education/income and cardiovascular outcomes in general adults or specific diseases; (2) measured education or income; (3) had at least one outcome of interest (i.e., coronary artery diseases (CAD), cardiovascular events (CVE), strokes and cardiovascular deaths);

(4) 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 3 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/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.\textsuperscript{30} Salary income was re-categorized as low, medium, and high for income ≤20,000, 20,001 to 40,000, and >40,000 US$\textsuperscript{30} year, respectively. If original studies reported income as quartiles, the 1\textsuperscript{st}, 2\textsuperscript{nd}, and 3\textsuperscript{rd} + 4\textsuperscript{th} quartiles were re-classified as low, medium, high incomes, respectively. If it was reported as quintiles, the 1\textsuperscript{st} + 2\textsuperscript{nd}, 3\textsuperscript{rd}, and 4\textsuperscript{th} + 5\textsuperscript{th} 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 strokes)), 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., risk ratio (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 (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. Total grade of seven or more stars was regarded as higher quality or lower risk of bias.

Statistical analysis

RRs of each outcome between low versus high (RR₁) and medium versus high (RR₂) 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 was applied for pooling two RRs simultaneously. Variance-covariance between RR₁ and RR₂ was assumed to be zero for those studies reporting summary RRs. Heterogeneity was assessed using Cochrane’s Q test and I² statistic. Heterogeneity was present if p-value of the Q test was <0.1 or I² ≥ 25%.

Subgroup analyses were performed to explore potential sources of heterogeneity by fitting each of co-variables (i.e., country, country income level, 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. If any of these indicated asymmetry, contour-enhanced funnel plot was constructed to distinguish whether asymmetry was due to publication bias or heterogeneity.

All analyses were performed using STATA version 14. P-values <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 1,335 studies from Scopus databases with 11 additional studies identified from reference lists. Of these 1,700 studies, 115 were duplicates, leaving 1,585 to be screened. After screening titles and abstracts, 1,399 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.

*General Characteristics of included studies*

Characteristics of the 72 included cohorts published between 1982 and 2016 are described, see Supplement Table 1. Among them, 14, 39 and 19 studies were conducted in Asia, Europe, and the United States, respectively. Most studies were from high-income countries (93.1%); mean age and mean BMI ranged from 38.5 to 78 years and 23.02 to 30.33 kg/m², respectively. Percentages of
males, diabetes, smoking or hypertension varied from 35.9% to 78%, 1.3% to 42%, 7.28% to 72.64%, and 6.25% to 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 to 4,157,202.

Risk of bias assessment
Results of "risk of bias" assessment of the included studies are shown in Supplement Table 2. Total stars ranged from 5 to 9 with a median of 7. Among the included studies, 45 out of 72 (62%) had low risk of bias and 27 out of 72 (38%) had high risk of bias.

Education and cardiovascular outcomes
A total of 62 studies assessed the association between education and cardiovascular deaths (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 strokes (N=15 and 13 for low and medium vs high). Among these, only few studies assessed relative effects of education without adjusting co-variables, or frequency data were available (3 in cardiovascular deaths\(^{37,39}\) and CAD\(^{37,40,41}\), 2 in CVE\(^{38,39}\), and 2 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% to 99% (Table 1). Multivariate meta-analysis was applied indicating significant educational effects on all outcomes (Table 1 and Figure 2). 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 strokes when compared to high education level.

Sources of heterogeneity were next explored by meta-regression or subgroup analyses (Table 2 & Supplement Tables 3-6). Geographical regions were grouped as Asia, Europe, and US but few studies in the Asian setting were available for most outcomes. Effects of both low/medium education still remained for all 4 cardiovascular outcomes after pooling within Europe and US, 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 (≤60 vs >60 years), BMI (<25 kg/m² vs ≥25 kg/m²), percentage of males, diabetes, and smoking (Supplement 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 (Supplement Tables 3-6). Risk of cardiovascular deaths 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 ≤25 kg/m² (Supplement 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: t=2.33, p=0.008), for which funnel plots showed
asymmetry (Supplement Figures 1 & 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 (Supplement Figures 3 & 4). No individual study significantly changed the overall estimates based on results of the sensitivity analysis.

In *Income and cardiovascular outcomes*

Thirty-nine studies assessed income effects on cardiovascular deaths (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 strokes (both N=7 for low and medium vs high). Five studies (1, 3, 2, and 1 for cardiovascular deaths, CAD, CVE, and strokes) 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 deaths, with 76% and 34% higher risk of cardiovascular deaths 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 strokes compared to high income.

Sources of heterogeneity were explored by meta-regression or subgroup analyses (Table 2 & Supplement 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 deaths, CAD and CVE, in the studies with participants aged ≤60 years (Supplement 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: $t^2=2.98$, $p=0.009$), but funnel plots showed asymmetry (Supplement Figures 5 & 6). Contour-enhanced funnel plots suggested that asymmetry was more likely due to heterogeneity (Supplement Figures 7 & 8). Overall estimates were similar to the sensitivity analyses.

**Discussion**

We performed a systematic review and meta-analysis to pool effects of education and income on CVD outcomes. Our findings indicate that groups with low to medium education and income are higher risk of CAD, CVE, strokes and cardiovascular deaths than 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 respectively for CVE, 1.23 and 1.17 respectively for strokes, and 1.39 and 1.21 respectively for cardiovascular deaths. The pooled RRs for low and medium versus high income for these corresponding outcomes were 1.49 & 1.27, 1.17 & 1.05, 1.30 & 1.24, and 1.76 & 1.34, respectively.

Direct or indirect mechanisms linking education and income with CVD have been described showing behavioral risk factors, lifestyle or living environment conditions, health literacy and psychological factors play important roles. Those with low education or low income had a higher prevalence of risk behaviors (smoking, obesity, physical inactivity, unhealthy diet,
etc.), 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 combined and should not be interchangeable,52 because they may affect CVD outcomes through different, potentially independent, causal pathways. For example, Ahmed et al53 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 studies52,54 assessed education/income effect by comparing highest and lowest strata, which could not 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 strokes 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 educations/incomes 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 risk might be confounded.
Clinical Implications and further research

Braveman et al\textsuperscript{52} explained educational influence on general and health-related knowledge, health literacy, and problem-solving skills, which can change health outcome. Results of our meta-analysis provided some evidence of effects of education and income on CVD outcomes. However, whether education or income is directly associated with CVD outcomes,\textsuperscript{50} or education is indirectly associated with CVD outcomes through income as mediator,\textsuperscript{57} or both education and income are indirectly associated with CVD outcomes through other risk factors such as BMI,\textsuperscript{58} diabetes, 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.\textsuperscript{59}

Conclusion

In conclusion, low/medium education and income increased risk of CAD, CVE, strokes and cardiovascular deaths. Further studies should be conducted to assess causal pathway of education/income on cardiovascular outcomes to confirm our findings, especially in Asian countries.

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**Declaration of conflicting interests**

The Authors declared that there is no conflicts of interest.

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**Details of ethics approval**

There is no need for ethical approval for a systematic review.

**Contribution to authorships**

WK, SAV, AT contributed to conception and design, data analysis and interpretation of data, WK, SAV contributed to study selection, risk of bias assessment, and data extraction, WK, SAV, JA, MM, 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.
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