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1 **Socioeconomic Position and Incidence of Acute Myocardial Infarction: a Meta-Analysis**

2 Edison Manrique-Garcia^{a*}, Anna Sidorchuk^{abc*}, Johan Hallqvist^{ad}, Tahereh Moradi^b

3 * Both authors contributed equally

4 ^a Department of Public Health Sciences, Division of Social Medicine, Karolinska Institutet,
5 Stockholm, Sweden

6 ^b Institute of Environmental Medicine, Division of Epidemiology, Karolinska Institutet,
7 Stockholm, Sweden

8 ^c St. Petersburg State Medical Academy named after II. Mechnikov, Division of
9 Epidemiology, St. Petersburg, Russia

10 ^d Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden

11 **Correspondence to:** Anna Sidorchuk, MD, PhD

12 Karolinska Institutet

13 Department of Public Health Sciences, Division of Social Medicine

14 Norrbacka, Karolinska Hospital

15 SE-171 76, STOCKHOLM, SWEDEN

16 E-mail: Anna.Sidorchuk@ki.se

17 Phone: +46-524 80014, Fax: +46- 8-30 8008

18 **Key Words:** Acute Myocardial Infarction, socioeconomic position, meta-analysis.

19 **Word count:** 3989

20

21 **ABSTRACT:**

22 **Background:** Negative socioeconomic gradient is established for coronary heart disease
23 (CHD) mortality and survival, while socioeconomic patterning of disease incidence is less
24 investigated. To study socioeconomic inequalities in incidence of acute myocardial infarction
25 (AMI), the major component of CHD, we undertook meta-analysis to summarize existing
26 evidence on the issue. **Methods:** A systematic search was performed in PubMed and
27 EMBASE databases for observational studies on AMI incidence and socioeconomic position
28 (SEP), published in English through April 2009. Random-effects model was used to pool the
29 risks estimates from the individual studies. **Results:** Among 1,181 references, 70 studies
30 fulfilled inclusion criteria. An overall increased risk of AMI among the lowest SEP was
31 found for all three indicators: income (pooled RR=1.71, 95% CI 1.43 to 2.05), occupation
32 (pooled RR=1.35, 95% CI 1.19 to 1.53) and education (pooled RR=1.34, 95% CI 1.22 to
33 1.47). The strongest associations were seen in high-income countries such as US/Canada and
34 Europe, while the results were inconsistent for middle- and low-income regions. **Conclusion:**
35 AMI incidence is associated with low SEP. The nature of social stratification at the level of
36 economic development of a country could be involved in the differences of risk of AMI
37 between social groups.

38

39 INTRODUCTION

40 Acute Myocardial Infarction (AMI) is a major cause of death and disability
41 worldwide.[1] According to an estimate from the WHO, about 40% of all deaths will be
42 related to cardiovascular diseases (CVD) in 2020, with AMI being the main single cause.[2]
43 Projection of global mortality and burden of disease for 2030 presented that despite the
44 decline in mortality due to coronary heart disease (CHD) in high-income countries during the
45 last decades, it will remain the leading cause of mortality in low-and middle-income
46 countries.[3-5] Due to high mortality rate, severe damage to physical and mental health, long
47 rehabilitation periods and a high rate of disability, the burden of AMI is a highly significant
48 social issue.[6]

49 There is a considerable body of evidence linking socioeconomic position (SEP) with
50 the conventional risk factors for CHD, including AMI as the major component of CHD.[7-9]
51 Lower SEP is often associated with health-damaging lifestyle resulting in the development of
52 poor dietary habits as well as influencing behaviours related to smoking and physical
53 activity.[10] Individuals with low SEP are prone to be exposed to multiple risk factors and,
54 therefore, seem to suffer dramatically from excess burden of disease.[11]

55 Associations between SEP and CVD mortality and survival have been well discussed in
56 a number of reviews.[12-16] However, quantitative assessment of socioeconomic patterning of
57 CVD incidence and AMI incidence is presented to a lower extent. Use of incidence data
58 generally avoids problems with post-diagnosis SEP changes as well as with different survival
59 by socioeconomic groups.[17] Addressing the issue of social inequality in AMI further, it is
60 important to estimate the individual contribution of each SEP indicator rather than
61 interchangeable SEP measures as they affect health through different pathways and causal
62 mechanisms.[18] We undertook meta-analysis as a quantitative approach to summarize the

63 existing evidence on the issue[19, 20] to investigate the association between AMI incidence
64 and various SEP measures including educational attainment, income, and occupation
65 categories.

66

67

68 **SUBJECTS AND METHODS**

69 **Search strategy**

70 To identify eligible studies of associations between socioeconomic determinants and AMI
71 incidence, we conducted a systematic search in PubMed and EMBASE databases for articles
72 published in English-speaking, peer-reviewed journals from 1966 to April 01, 2009. For this
73 search, we used the relevant medical subject heading (MeSH) terms and key words related to
74 socioeconomic determinants *combined with specific outcome defined as “acute myocardial*
75 *infarction”*. *The details of electronic search are reported on-line in Appendix 1.* The
76 reference lists were scrutinized to identify additional studies.

77

78 **Study selection**

79 To be included in this meta-analysis, studies had to 1) use original data; 2) be designed as
80 case-control or cohort studies; 3) consider AMI incidence as an outcome; 4) present risk
81 estimates with 95% confidence intervals (CIs) on the association between incident cases of
82 AMI and at least one measure of SEP, or report sufficient information to compute these for
83 men, women or both.

84 The articles were selected for inclusion if the study event was originally defined as AMI
85 either nonfatal or in combination with fatal or reported as a composite outcome of AMI and

86 death attributed to CHD / ischemic heart disease (IHD), including sudden death. We also
87 considered studies where the outcome definition composed AMI with congestive heart
88 failure[21, 22] or unstable angina (UA).[23] In order to avoid the inclusion of chronic
89 ischemic disease, we did not include studies if the outcome of interest was presented as CHD
90 event corresponding to codes 410-414 in ICD-9 or I21-I25 in ICD-10 with no further
91 specification. **Neither** did we include studies if AMI was combined with angina pectoris,
92 coronary atherosclerosis **or stroke** with no possibility to extract data on AMI alone. We
93 sought data on the first AMI event to assess the impact of social inequality on development of
94 the disease in people apparently free from acute ischemic disease. Studies focusing
95 exclusively on mortality and survival were not included.

96 SEP indicators were included only if they were based on income, educational
97 attainment or occupational categories. Studies utilizing a social indicator constructed as a
98 combination of two or more standard socioeconomic indicators were not included. Neither
99 did we include studies where the SEP measure was based on ownership of car/houses/health
100 insurance or presented as categories of deprivation. Only the studies with **adult** individual-
101 level measure of SEP were included. No restrictions were made by the type of SEP, personal
102 or household.

103 When overlap was identified from various studies, the original data were included only
104 once, prioritizing datasets providing maximally-adjusted risk estimates. If not, we used the
105 most up-to-date information or studies with greater number of participants. Two co-authors
106 (EM, AS) independently extracted relevant studies following the inclusion criteria. In case of
107 missing data we contacted the corresponding authors. All authors[24-29] from whom the
108 additional information was requested provided us with data we asked for. Discrepancies were
109 resolved by consensus in a panel meeting (TM, EM, AS).

110

111 **Data extraction**

112 The following information was extracted from each publication: the first author's last
113 name, the year of publication, the country where the study was performed, study design,
114 years of data collection and type of controls (population-based / hospital-based) in case-
115 control studies, duration of follow-up in cohort studies, the sample size, indicators of SEP,
116 source **and type** of SEP data, definition **and status** of the outcome, status of event, sex and age
117 along with the risk estimates for AMI associated with SEP with corresponding 95% CIs, and
118 the variables controlled for. The information on country where the study was performed was
119 then classified both according to the geographical area (US/Canada, Europe, Asia, Latin
120 America, Middle East) and country's income level (high-, middle-, or low-income
121 countries).[5] From each study, we extracted the risk estimate both minimally-and
122 maximally-adjusted for the potential confounders. Unless otherwise stated, we included in the
123 analysis the maximally-adjusted estimates in order to overcome inconsistency in handling
124 confounding and mediating variables. We considered the study risk estimates to be
125 minimally-adjusted if unadjusted or adjusted for age, sex and residence, either one or all, by
126 matching, restriction, stratification or statistical adjustment, and to be maximally-adjusted if
127 in addition adjusted for any of the classical well-recognised AMI-specific risk factors. If the
128 original study reported risk estimates in association with more than one measure of SEP, each
129 estimate was extracted and then analysed as its own association with the specific SEP.

130

131 **Statistical analysis**

132 Relative risk (RR) was used as the measure for summary statistic of associations
133 between SEP and AMI incidence. To simplify the procedure, RRs represented all reported
134 study-specific results derived from cohort studies and odds ratios (ORs) from case-control
135 studies.[30] Due to the initial assumption of between-study heterogeneity, a random-effects
136 model of DerSimonian-Laird,[31] which incorporates both within- and between-study
137 variability, was applied to combine log RRs across the studies. To augment comparability
138 between the studies **using different SEP categories**, we compared the **lowest versus** the
139 highest SEP category. If the original study reported the risk estimates not in this order, we
140 back-calculated the point estimate and 95% CIs. For the articles that did not report estimates
141 in form of RRs or ORs, the risk estimates and 95% CIs were recalculated from the **presented**
142 raw data by using standard equations. If the original study reported separate RRs for different
143 sexes[32-37] or different races[34] or if RRs were reported separately for two subcohorts
144 with rheumatoid arthritis and non-inflammatory rheumatoid disorders within same
145 cohort,[38] the risk estimates were pooled (weighted by inverse of their variance) to obtain a
146 single estimate per SEP from each study.

147 To evaluate the statistical heterogeneity among studies we used the Cochran's Q
148 test.[39] This test examines the null hypothesis that heterogeneity across the study estimates
149 of RRs is due to chance by using a chi-square test with degrees of freedom equal to the
150 number of studies minus one. For Q statistic we considered $P < 0.1$ as a representative of
151 statistically significant heterogeneity. To describe the proportion of total variance in study
152 estimates explained by heterogeneity between study variation rather than chance, we
153 calculated the I^2 statistic.[40]

154 Random-effect meta-regression analyses were performed to identify study-level factors
155 contributing to heterogeneity between studies. The explanatory variables included study

156 design, geographical area, country's income level, publication year (before 2000 / 2000 and
157 after), type of adjustment with respect to AMI-specific risk factors, type of controls in case-
158 control studies, personal or household SEP, and status of the event and the natural logarithm
159 of RR was the dependent variable.[41-43] An univariate meta-regression was performed for
160 each study-level factors for studies on income, education and occupation. A backward
161 stepwise approach was used to select the significant variables to be included in a multivariate
162 analysis. **In addition**, a series of subgroup analyses were conducted by stratifying the original
163 studies by sex, country's income level and geographical region, study design, adjustment
164 strategy, publication period, personal or household SEP and type of study event. The stability
165 of the results was also evaluated in leave-one-out sensitivity analysis in which the influence
166 of the individual study on the overall pooled RR was estimated by omitting one study at a
167 time.[44]

168 We assessed publication bias by constructing funnel plots and using the Egger's
169 regression asymmetry test and the Begg-Mazumdar adjusted rank correlation test.[45, 46].
170 All statistical analyses were performed using STATA version 10 (StataCorp, College Station,
171 TX). *P*-values that were less than 0.05 were considered statistically significant. All statistical
172 tests were two-sided.

173

174 **RESULTS**

175 **Study characteristics**

176 Total search in the electronic databases revealed 2,539 references and among those
177 1,358 were overlapping between different search categories. The search strategy for the 1,181
178 unique references is presented on Figure 1 as the QUOROM statement[47] flowchart where

179 the detailed procedure of the reference identification along with the information on exclusion
180 criteria applied on different stages of the selection is described. Briefly, 855 articles did not
181 address the issue of interest and were excluded after the screening the abstracts leaving us
182 with 326 full-text articles for further examination. Of these, only 64 articles fulfilled the pre-
183 defined inclusion criteria and were selected to be included in the analysis. The reference lists
184 of the selected articles were scrutinized and 19 articles were additionally identified fulfilling
185 the inclusion criteria. To mitigate overlapping in study populations, several studies being
186 initially considered relevant for the analysis[24, 26, 48-63] were excluded and substituted by
187 more recent ones, providing maximally-adjusted risk estimates or with greater number of
188 participants [18, 23, 33, 35, 64-71].

189 Two risk estimates for educational attainment and AMI incidence presented by
190 Chang C et al.[66] for women from Eastern Europe and those from non-European countries
191 (Latin America, Asia and Africa) were independently included in the analysis, referred as
192 Chang C (A) and Chang C (B), respectively. Similar to that, two substudies on occupational
193 SEP and AMI described in the article by Mattila K et al.[27] (series I and series II), were also
194 analysed separately. The same strategy was applied to data derived from the articles by Eaker
195 E et al.[72] and Qureshi A et al.,[73] where occupational and educational SEP were presented
196 among women at the age of 45-54 years (Eaker E (A)) and 55-64 years (Eaker E (B)) and
197 patients younger 50 years (Qureshi A (A)) and older 50 years (Qureshi A (B)), respectively.
198 Substudies from the articles by Bosma H et al.[74] originated from Lithuania (Bosma H (A))
199 and The Netherlands (Bosma H(B)) were included independently. Therefore, 70 original
200 studies from 65 articles, extending back to the year 1968, were finally included in the
201 analysis.

202 In total, there were 37 case-control studies in 35 articles[23, 25, 27, 28, 32, 33, 35,
203 65-67, 75-99] reporting associations with different SEP among 74,056 AMI cases and
204 619,652 controls and 33 cohort studies, including 2 studies nested in cohort, in 30 articles[18,
205 21, 29, 34, 36-38, 64, 68-74, 100-114] where association with SEP was studied for 28,629
206 incident cases among 3,869,270 participants. Supplementary table S1 presents data on
207 detailed study characteristics of the included studies.

208

209 **Overall result**

210 The overall results of this meta-analysis provided evidence of a significant increase in
211 risk of AMI among the lowest socioeconomic categories for all three socioeconomic
212 indicators (Fig. 2-4). Heterogeneity was observed for all three SEP indicators ($p < 0.001$)
213 (Table1).

214

Table 1 Pooled estimates for the lowest versus the highest socioeconomic category and incidence of acute myocardial infarction in series of subgroup analyses

Subgroup analysis	n = Number of studies, Pooled RR (95% CI), p-value for <i>Q</i> test for heterogeneity, <i>I</i> ² statistic (%)								
	n	Income	<i>Q</i> p-value	n	Education	<i>Q</i> p-value	n	Occupation	<i>Q</i> p-value
			<i>I</i> ² (%)			<i>I</i> ² (%)			<i>I</i> ² (%)
Summary pooled estimate	19	1.71 (1.43 to 2.05)	<0.001	47	1.34 (1.22 to 1.47)	<0.001	33	1.35 (1.19 to 1.53)	<0.001
			95.9			77.6			81.6
Sex									
Male	7	1.50 (1.31 to 1.72)	0.039	13	1.24 (1.04 to 1.48)	<0.001	18	1.34 (1.16 to 1.55)	<0.001
			54.8			83.7			77.3
Female	4	1.87 (1.48 to 2.36)	0.015	15	1.58 (1.25 to 2.00)	<0.001	11	1.87 (1.34 to 2.60)	<0.001

			71.3			66.5			77.6
Country's income group									
High	15	1.76 (1.46 to 2.12)	<0.001	34	1.39 (1.25 to 1.55)	<0.001	30	1.41 (1.25 to 1.59)	<0.001
			96.3			79.3			80.6
Middle or Low	4	1.46 (0.60 to 3.54)	<0.001	13	1.16 (0.97 to 1.39)	0.009	3	0.51 (0.27 to 0.99)	0.205
			81.3			54.9			37.0
Geographical region ^a									
US/Canada	4	1.49 (1.27 to 1.75)	0.350	10	1.42 (1.28 to 1.57)	0.340	6	1.44 (1.22 to 1.70)	0.988
			9.2			10.6			0.0
Europe ^b	11	1.80 (1.46 to 2.21)	<0.001	29	1.33 (1.17 to 1.50)	<0.001	26	1.37 (1.19 to 1.58)	<0.001

			97.0			82.6			84.4
Asia	3	1.52 (0.29 to 7.93)	<0.001	3	1.90 (0.48 to 7.58)	0.001	1	0.67 (0.41 to 1.09)	—
			88.0			86.3			
Latin America	1	1.27 (1.06 to 1.52)	—	3	1.23 (1.03 to 1.47)	0.086	0	—	
						59.2			
Middle East	0	—		1	1.18 (0.27 to 5.15)	—	0	—	
Adjustment strategy ^c									
Unadjusted for AMI	10	1.79 (1.44 to 2.24)	<0.001	29	1.37 (1.21 to 1.56)	<0.001	19	1.27 (1.05 to 1.54)	<0.001
risk factors ^d			97.5			81.3			68.1
Adjusted for AMI	9	1.58 (1.20 to 2.08)	0.001	16	1.26 (1.06 to 1.49)	<0.001	14	1.41 (1.19 to 1.68)	<0.001
risk factors ^e			70.1			68.4			80.5

Design

Cohort ^f	10	1.59 (1.45 to 1.75)	0.016	23	1.45 (1.27 to 1.66)	<0.001	19	1.39 (1.24 to 1.56)	0.002
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			55.8			78.7			55.0
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Case-control	9	1.91 (1.37 to 2.66)	<0.001	24	1.23 (1.07 to 1.41)	<0.001	14	1.17 (0.88 to 1.55)	<0.001
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			91.3			74.1			82.8
--	--	--	------	--	--	------	--	--	------

Type of control for
case-control studies

Population ^g	6	2.36 (1.86 to 2.99)	0.005	12	1.41 (1.20 to 1.66)	<0.001	11	1.29 (0.95 to 1.76)	<0.001
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			69.9			77.0			80.5
--	--	--	------	--	--	------	--	--	------

Hospital	3	1.05 (0.41 to 2.69)	0.003	12	0.99 (0.78 to 1.27)	0.001	3	0.84 (0.61 to 1.17)	0.296
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			82.8			65.2			17.8
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Publication period

Before 2000	6	2.64 (2.16 to 3.22)	0.738	15	1.43 (1.12 to 1.82)	<0.001	16	1.34 (1.02 to 1.76)	0.005
			0.0			70.7			54.6
2000 or after	13	1.58 (1.29 to 1.93)	<0.001	32	1.31 (1.18 to 1.45)	<0.001	17	1.37 (1.18 to 1.59)	<0.001
			97.2			80.2			87.9

Personal or household

SEP

Personal	13	1.84 (1.49 to 2.26)	<0.001	47	1.34 (1.22 to 1.47)	<0.001	31	1.36 (1.20 to 1.55)	<0.001
			96.4			77.6			81.0
Household ^h	6	1.45 (1.00 to 2.08)	<0.001	0	—		2	1.35 (0.35 to 5.18)	0.002
			89.0						89.1

Event^c

Clearly first event	15	1.59 (1.30 to 1.94)	<0.001	38	1.29 (1.16 to 1.43)	<0.001	26	1.25 (1.09 to 1.43)	<0.001
ever			96.8			79.1			83.4
Potentially first event ⁱ	4	2.47 (2.12 to 2.88)	0.447	7	1.75 (1.14 to 2.67)	0.001	7	2.04 (1.28 to 3.25)	0.004
			0.0			74.4			68.5

^a Data from Chang C et al [66] are not included due to presenting combined results from Latin American and Asian countries

^b Corresponds to data from both Western European and Eastern European countries

^c On this item data from the study by Qureshi A et al. [73] are not available

^d Unadjusted or adjusted for age, sex and residence only (either one or all)

^e Adjusted for at least one AMI-specific risk factors such as smoking, diabetes, hypertension, hypercholesterolemia, physical activity and BMI

^f Corresponds to cohort studies and case-control studies nested in cohort

^g Corresponds to either population-based controls or relatives/neighbourhood controls

^h Corresponds to the family income SEP or husband's occupation for women or combination of women's and husband's occupation SEP

ⁱ Corresponds to the studies where less than <10% of cases may had had a prior AMI as well as the studies where information on cases' history on AMI was not clarified by the authors

242 The strongest pattern was seen for the lowest income group where the incidence of AMI
243 increased by 71% compared to high income group (RR=1.71, 95% CI 1.43 to 2.05) (Table 1).
244 Further stratification by sex, adjustment strategy, study design, status of event, personal or
245 household type of SEP or publication years did not alter the overall pooled results. No
246 association was seen for the case-control studies utilizing hospital controls, while studies with
247 population controls revealed statistically significant association between the lowest income
248 group and AMI (Table 1).

249 We observed a 34% increased risk of AMI for the lowest educational group (RR=1.34,
250 95% CI 1.22 to 1.47) (Table 1). The increase was apparent in subanalyses after stratifying by
251 the main study characteristics, i.e. sex, adjustment strategy, study design, publication period,
252 and status of event, apart from for the case-control studies with hospital controls (Table 1).

253 Increased incidence of AMI was observed when studies on occupational categories
254 were pooled (RR=1.35, 95% CI 1.19 to 1.53) (Table 1). The increase persisted for the lowest
255 occupational SEP when pooling studies within subgroups with different sex, status of event,
256 and publication years. Non-significant increase was seen in subanalysis for household SEP
257 measure (husband's occupation for women). The results were less consistent among case-
258 control studies (Table 1).

259 Increased incidence of AMI was evident for the lowest income-based, educational and
260 occupational SEP in high-income countries and in regional areas such as US/Canada and
261 Europe (Table 1). No significant associations were, however, apparent between any of the
262 SEP determinants and AMI incidence in studies carried out in the middle-or low income
263 countries, particularly in Asian region. In contrary, for middle-or low income countries an
264 inverse association was observed for the results combined across the studies on occupational
265 SEP.

266 There was a substantial heterogeneity in overall result among the studies on all SEP
267 determinants ($p < 0.001$) that remained significant for the results from most of the
268 subanalyses. However, no or low heterogeneity was present when analyses were restricted to
269 studies originated from US/Canada. There was a low heterogeneity among studies on
270 occupation when results were combined for middle-or low-income countries. Similar pattern
271 was seen when studies on income published before the year 2000 were analysed separately.

272 In random-effect meta-regression analyses the relation between SEP and AMI
273 incidence persisted irrespective to the design of original studies, though in case-control
274 studies **multivariate** regression indicated the association between type of control (**hospital vs.**
275 **population controls**) and RR of AMI for studies on all SEP indicators (for income β
276 **coefficient (β) = -2.76, 95% CI -4.77 to -0.76, $p = 0.007$; for education $\beta = -0.40$, 95% CI -
277 **0.75 to -0.05, $p = 0.02$; for occupation $\beta = -0.51$, 95% CI -1.00 to -0.02, $p = 0.04$). Pooling**
278 together the cohort studies and case-control studies with population controls only had no
279 effect on the overall results (pooled RR for income =1.80, 95% CI 1.50 to 2.16; pooled RR
280 for education =1.43, 95% CI 1.30 to 1.58; pooled RR for occupation =1.41, 95% CI 1.24 to
281 1.60). Type of AMI event (potentially first vs. clearly first event ever) was significantly
282 associated with outcome in **multivariate regression analyses in studies on income ($\beta = 0.24$,**
283 **95% CI 0.04 to 0.46, $p = 0.02$) and occupation ($\beta = 0.54$, 95% CI 0.27 to 0.82, $p < 0.001$).**
284 Among other study-level factors only two revealed associations with the outcome. For studies
285 on income SEP the publication period (published in year 2000 and after vs. published before
286 year 2000) reached statistical significance in univariate, **but not in multivariate** meta-
287 regression analysis (**data not shown**). For occupational SEP **in multivariate analysis** country's
288 income group (middle-or low-income countries vs. high-income countries) was associated
289 with RR of AMI (**$\beta = -1.24$, 95% CI -1.74 to -0.74, $p < 0.001$**). No other study-level**

290 characteristics for any of studied SEP indicators were found significant in meta-regression
291 analyses.

292 No publication bias were observed for educational SEP (Egger's test $p=0.49$) with
293 borderline significant result for occupational SEP ($p=0.05$), while selection of the studies
294 focusing on income introduced publication bias ($p=0.03$). The publication bias funnel plots
295 are presented as Supplementary material (Figure S1). No individual studies significantly
296 altered the overall estimates based on the results of the sensitivity analysis.

297

298 **DISCUSSION**

299 Our results indicated an increased incidence of myocardial infarction among the lowest
300 socioeconomic categories in income (71%), education (34%) and occupation (32%)
301 compared to the highest category of the corresponding SEP. The associations were significant
302 for both males and females and consistent for most of the results from the subgroup analyses.
303 The increased risk of AMI for the lowest categories of all SEP indicators was most evident in
304 high-income countries, while middle-or low-income countries revealed less consistent
305 associations probably due to a limited number of the studies included in the latter strata.

306 SEP is a surrogate measure for numerous factors that may affect health. There is an
307 increasing awareness that SEP indicators should not be used interchangeably because they
308 may represent different risk factors[115] and relate to different causal pathways.[18, 116]
309 Recent reviews discussed the new approach for health researchers to study the socioeconomic
310 inequalities in health by measuring the respective impact of separate socioeconomic
311 indicators on health outcomes along with the mediating mechanisms and adjustment
312 suggested by each indicator rather than studying an effect of a single composite SEP

313 variable.[18, 117, 118] In our analysis the attempt was made to identify the independent
314 contribution of each SEP indicator to AMI outcome across regions and over time. The results
315 must be interpreted with cautions because of the observational nature of the data.[19, 119,
316 120]

317 Several methodological issues are needed to be taken under consideration. One of the
318 limitations in our study was possible differences in the definition and classification of SEP
319 across studies. It was of particular importance for educational and income SEP categories
320 since differences in countries' general economy, educational systems and cultural issues
321 could cause the variability in the scales used to classify the exposure. The methodological
322 limitations for quantitative comparison of studies on SEP due to the substantial dissimilarity
323 in exposure measures used in different studies over time and geographical regions have been
324 discussed previously.[115] Lack of uniformity in reporting SEP data in original studies have
325 limited our ability to investigate a social gradient in AMI incidence. To reduce the
326 inconsistency in SEP stratification across the original studies and to obtain the meaningful
327 indicator of socioeconomic inequality in health, it has been suggested to measure the
328 difference between the extreme categories of SEP, i.e. to compare the highest and the lowest
329 SEP strata.[117, 118, 121] Studies selected for our analysis varied significantly in presenting
330 SEP categories that prevented us from collapsing the middle-level SEP categories in one. To
331 overcome the problem and to increase the comparability across the studies, we applied the
332 suggested approach and compared the extreme categories that, however, impaired the
333 possibility of studying the social gradient and could be considered as a limitation of the
334 analysis.

335 Due to significant heterogeneity observed across the selected studies, the pooled results
336 should be interpreted with cautions. The nature of observational studies introduces design-

337 related heterogeneity that basically reflects the disparity in the study characteristics.[122] In
338 our case the heterogeneity was probably boosted by the initial unevenness in study bases as
339 well as in outcome definitions and status of event used in the original studies along with
340 inconsistency in measures of exposure and variability in handling confounding and mediating
341 factors. The incidental manner of reporting SEP data in descriptive tables in a numerous
342 studies, resulted in using estimates adjusted neither by matching nor by statistical adjustment
343 and, probably influenced the completeness of the search. The result-related
344 heterogeneity[122] may be less pronounced in our meta-analysis due to non-substantial
345 variability between the original point estimates and considerable overlaps of the confidence
346 intervals. Meta-regression analyses indicated type of study controls in case-control studies as
347 potential sources of heterogeneity between studies for all SEP indicators. Several meta-
348 analyses discussed the limitations introduced by pooling the results of studies different in
349 study design or type of control groups as in hospital-based case-control studies the choice of
350 controls may affect the representativeness of exposure.[115, 123] In addition, characteristics
351 of hospital catchment area and presence of Berkson's bias, if study exposure is related to the
352 risk of being hospitalized for the control diseases, may jeopardize comparability of studies
353 selected for the analysis even further.[124] Socioeconomic inequalities may influence all
354 above mentioned conditions and, thus, be one of the reasons for type of controls to be a
355 source of heterogeneity. For income-based SEP overall results for studies published before
356 2000 yielded highly significant association with the outcome along with no heterogeneity
357 between studies, though in multivariable meta-regression the publication year was not
358 recognised as a potential source for heterogeneity. We must, however, acknowledge that in
359 meta-analysis of observational studies the results of multivariable meta-regression can also be
360 confounded by unidentified study-level factors.[41]

361 Publication bias is a concern in meta-analysis since it might lead to overestimation of
362 the relative risk. Since our meta-analysis was restricted to English-speaking peer reviewed
363 publications, our estimates may have been affected by missing data from the studies
364 performed in the low-or middle-income countries where SEP may be differently associated
365 with AMI. It may explain the presences of publication bias detected in our analysis for
366 combined estimates for studies on income-based SEP. In our study, publication bias may be
367 partially explained by variability in outcome definitions and SEP measures or if studies with
368 relatively smaller sample size and inconsistent results were lacking in the analysis
369 representing significance bias, size bias and suppression publication bias.[119]

370 Our selection criteria, particularly with respect to study definition, were rather tight that
371 resulted in a limited number of studies. We acknowledge the fact that numerous studies
372 potentially relevant for the analysis were, however, excluded if AMI was reported as a study
373 endpoint in combination with chronic heart diseases. In order to control highly heterogeneous
374 outcome and being mostly interested in social patterning of first acute coronary event, we
375 deliberately narrowed the analysis to AMI only.

376 Another restraint deals with the variety of confounders and/or mediators across the
377 original studies. It might mainly be crucial for the pooled results if the adjustment strategy
378 differs between the studies with respect to risk factors for myocardial infarction. The
379 complicated interplay between socioeconomic factors and risk factors for cardiovascular
380 diseases must be acknowledged while interpreting the results of meta-analysis. It is well-
381 known that standard risk factors explain more than half of association between SEP and CHD
382 mortality and morbidity and there is a pronounced socioeconomic gradient in CHD-related
383 behavioural and lifestyle factors.[125-128] Therefore, the choice of variables in the original
384 study to adjust for can influence the pooled results. Adjustment for risk factors acting as

385 intermediate steps in the causal pathways will result in underestimation of the relation
386 between SEP and the disease, while relation will be overstated if genuine confounders left
387 unadjusted. Evidence from the recent studies and reviews indicate that different SEP
388 measures can simultaneously be included in the multivariable models as they do not act as
389 proxy for each other,[117, 118, 129-131] while biological, behavioural and psychological
390 factors can mediate an association between SEP and AMI.[126-128, 131] To reduce the
391 influence of various adjustment we, therefore, performed separate subanalyses for studies
392 minimally-and maximally-adjusted that in our analysis yielded the similar results.

393 Our findings presented the overall increase in risk of AMI incidence among the
394 lowest SEP that has previously been reported for AMI mortality and CHD morbidity.[13, 16]
395 The aforementioned results corroborated the strong evidence of the relation between
396 socioeconomic deprivation and incidence of acute ischemic events. Further research
397 providing validated information is required to address public health strategies to reduce the
398 risk of AMI among the most vulnerable groups in different countries and among different
399 societies. It is imperative to emphasise the importance of such studies, particularly for the
400 regions with lower level of economic development, where the epidemic of CHD is becoming
401 a public health issue.

402

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414

What is already known?
Adverse socioeconomic position is related to coronary heart disease mortality and survival.
What does this study add?
<p>This meta-analysis reveals an association between low socioeconomic position (SEP) and increased incidence of acute myocardial infarction (AMI). The associations were consistent for both men and women.</p> <p>People from the lowest strata of income-based SEP have a 71% greater risk to develop myocardial infarction compared to those in the highest strata. An increased risk in AMI incidence of 34% and 35% was found for the lowest compared to the highest categories of educational and occupational SEP, respectively.</p> <p>The socioeconomic patterns in myocardial infarction incidence were seen to be most pronounced for high-income countries. The nature of social stratification at the level of economic development of a country could be involved in the differences of risk of AMI between social groups.</p>

415

Policy Implications

Public health policies aiming at reducing the risk of AMI should address socioeconomic position both in the promotion and the evaluation of preventive measures.

The potential for variation in the strength of AMI inequalities between different societies should be acknowledged by national and international policy makers.

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759 **FIGURE LEGENDS**

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761 **Figure 1.** The QUOROM^a statement [47] flowchart for study selection.

762 ^a Quality of Reports of Meta-Analyses of Randomised Controlled Trials

763

764 **Figure 2.** Relative Risk (RR) and 95% confidence intervals (CIs) for acute myocardial
765 infarction incidence and income categories (the lowest vs. the highest socioeconomic position
766 category) in individual studies and for all studies combined. RRs from the individual studies
767 are indicated by squares and the size of the squares represents the statistical weight that each
768 study contributed to the random-effect summary estimate. Horizontal lines indicate the study-
769 specific 95% CIs. Diamond represents the overall summary RR and its 95% CIs.

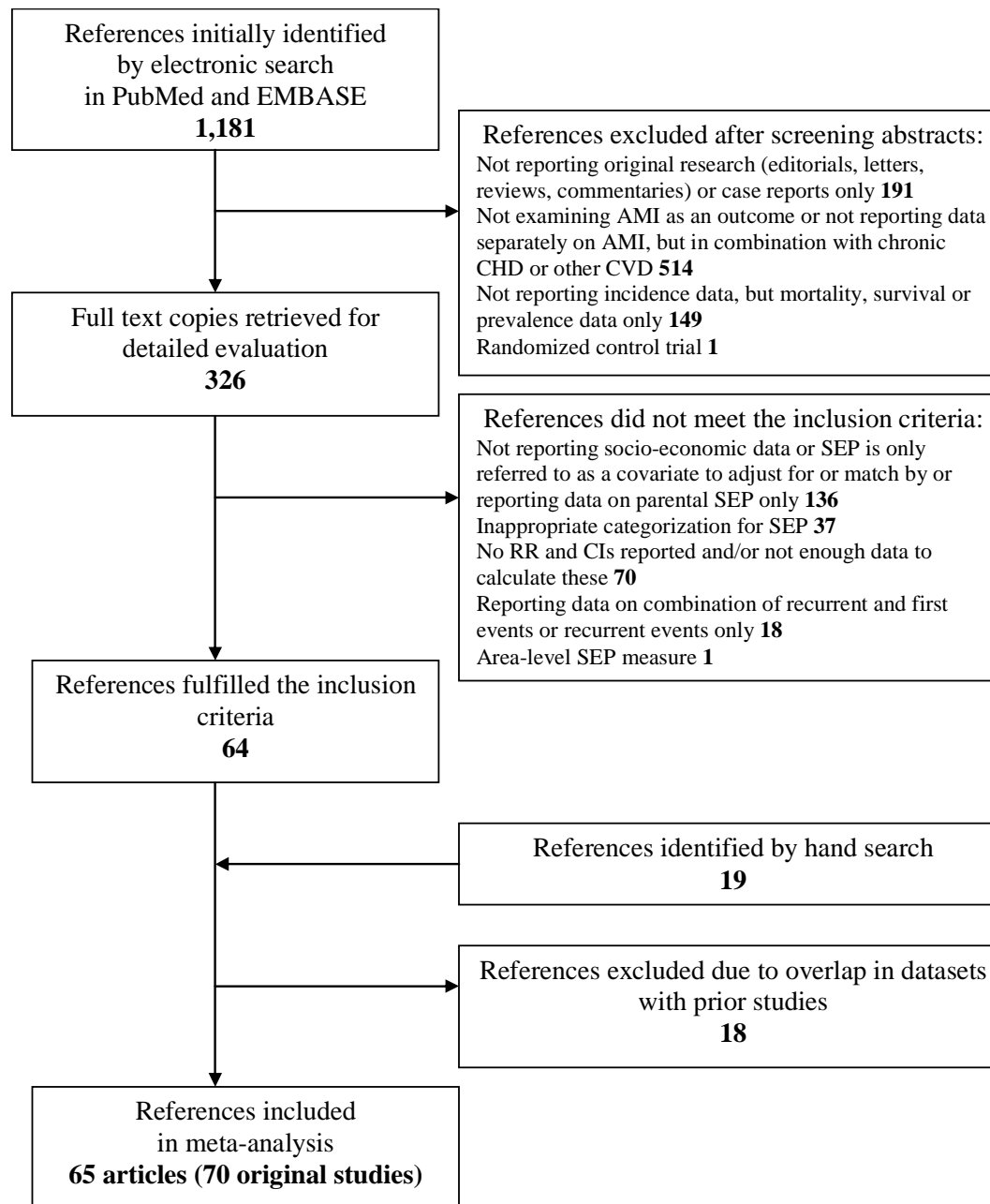
770

771 **Figure 3.** Relative Risk (RR) and 95% confidence intervals (CIs) for acute myocardial
772 infarction incidence and educational attainment (the lowest vs. the highest socioeconomic
773 position category) in individual studies and for all studies combined. RRs from the individual
774 studies are indicated by squares and the size of the squares represents the statistical weight
775 that each study contributed to the random-effect summary estimate. Horizontal lines indicate
776 the study-specific 95% CIs. Diamond represents the overall summary RR and its 95% CIs.

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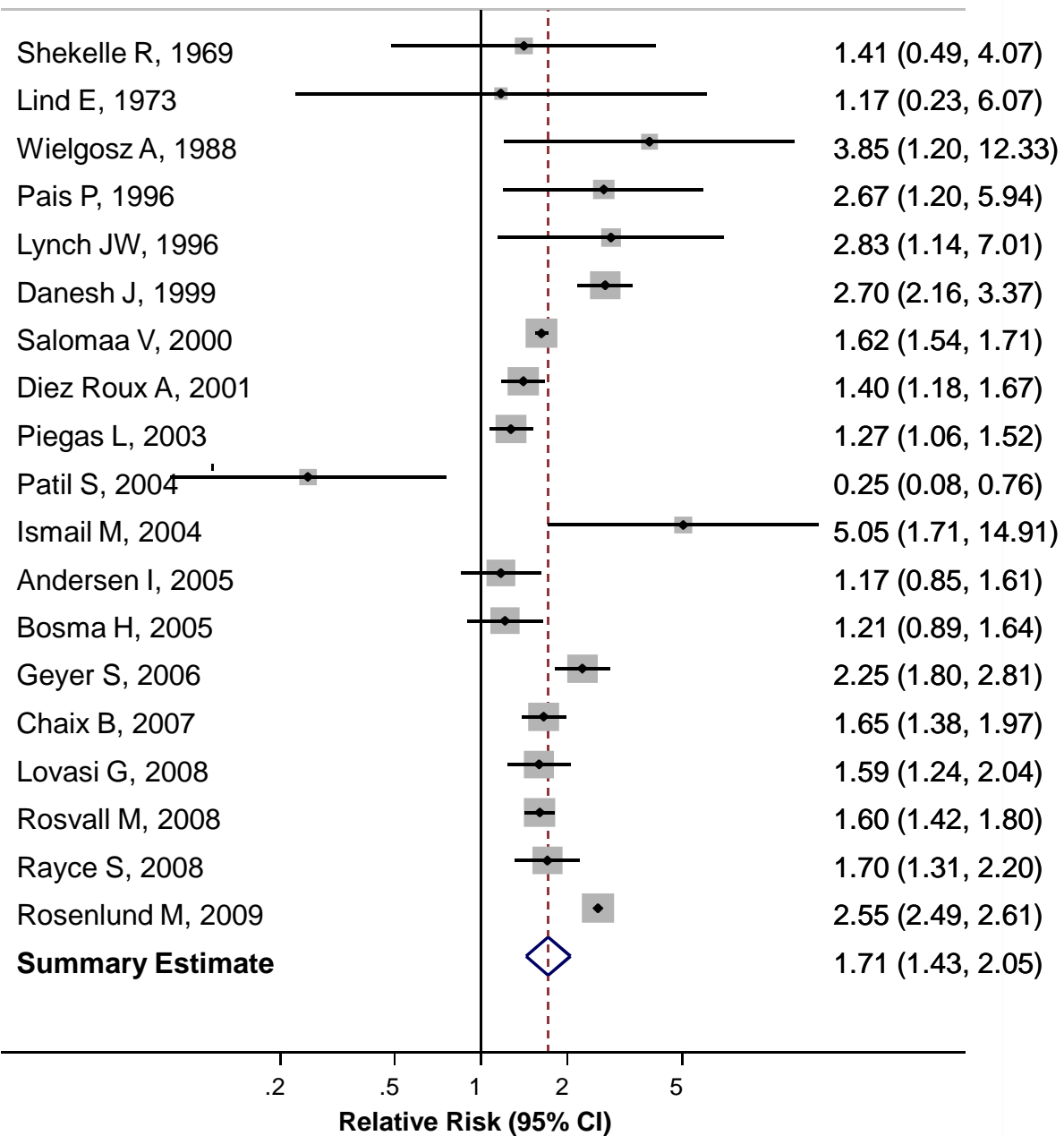
778 **Figure 4.** Relative Risk (RR) and 95% confidence intervals (CIs) for acute myocardial
779 infarction incidence and occupational categories (the lowest vs. the highest socioeconomic
780 position category) in individual studies and for all studies combined. RRs from the individual

781 studies are indicated by squares and the size of the squares represents the statistical weight
782 that each study contributed to the random-effect summary estimate. Horizontal lines indicate
783 the study-specific 95% CIs. Diamond represents the overall summary RR and its 95% CIs.



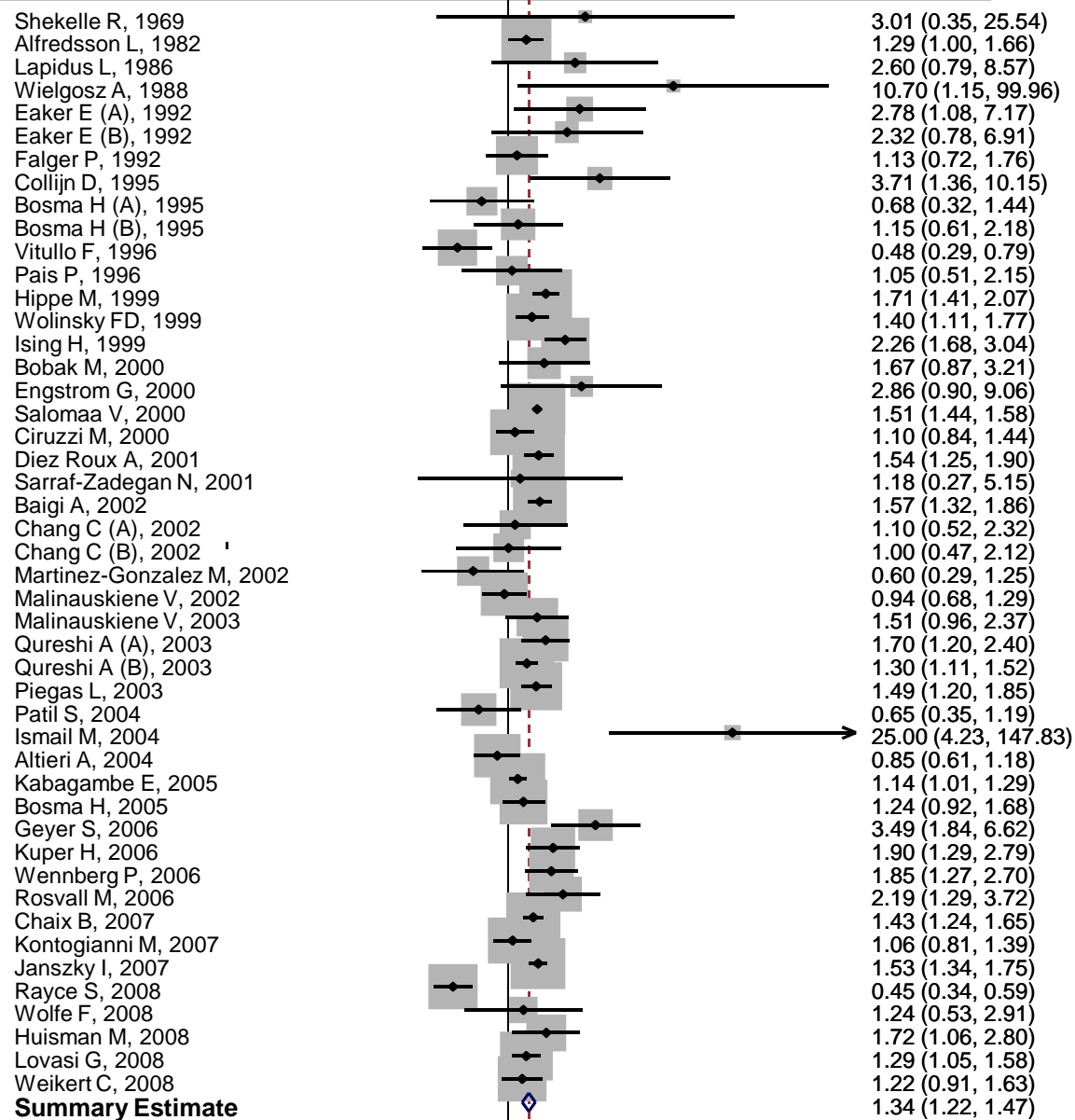
First author, Publication Year

RR (95% CI)



First author, Publication Year

RR (95% CI)



Relative Risk (95% CI)

