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# Association of Circulating Monocyte Chemoattractant Protein-1 Levels With Cardiovascular Mortality

## A Meta-analysis of Population-Based Studies

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**IMPORTANCE** Human genetics and studies in experimental models support a key role of monocyte-chemoattractant protein-1 (MCP-1) in atherosclerosis. Yet, the associations of circulating MCP-1 levels with risk of coronary heart disease and cardiovascular death in the general population remain largely unexplored.

**OBJECTIVE** To explore whether circulating levels of MCP-1 are associated with risk of incident coronary heart disease, myocardial infarction, and cardiovascular mortality in the general population.

**DATA SOURCES AND SELECTION** Population-based cohort studies, identified through a systematic review, that have examined associations of circulating MCP-1 levels with cardiovascular end points.

**DATA EXTRACTION AND SYNTHESIS** Using a prespecified harmonized analysis plan, study-specific summary data were obtained from Cox regression models after excluding individuals with overt cardiovascular disease at baseline. Derived hazard ratios (HRs) were synthesized using random-effects meta-analyses.

**MAIN OUTCOMES AND MEASURES** Incident coronary heart disease (myocardial infarction, coronary revascularization, and unstable angina), nonfatal myocardial infarction, and cardiovascular death (from cardiac or cerebrovascular causes).

**RESULTS** The meta-analysis included 7 cohort studies involving 21 401 individuals (mean [SD] age, 53.7 [10.2] years; 10 012 men [46.8%]). Mean (SD) follow-up was 15.3 (4.5) years (326 392 person-years at risk). In models adjusting for age, sex, and race/ethnicity, higher MCP-1 levels at baseline were associated with increased risk of coronary heart disease (HR per 1-SD increment in MCP-1 levels: 1.06 [95% CI, 1.01-1.11]; $P = .01$), nonfatal myocardial infarction (HR, 1.07 [95% CI, 1.01-1.13]; $P = .02$), and cardiovascular death (HR, 1.12 [95% CI, 1.05-1.20]; $P < .001$). In analyses comparing MCP-1 quartiles, these associations followed dose-response patterns. After additionally adjusting for vascular risk factors, the risk estimates were attenuated, but the associations of MCP-1 levels with cardiovascular death remained statistically significant, as did the association of MCP-1 levels in the upper quartile with coronary heart disease. There was no significant heterogeneity; the results did not change in sensitivity analyses excluding events occurring in the first 5 years after MCP-1 measurement, and the risk estimates were stable after additional adjustments for circulating levels of interleukin-6 and high-sensitivity C-reactive protein.

**CONCLUSIONS AND RELEVANCE** Higher circulating MCP-1 levels are associated with higher long-term cardiovascular mortality in community-dwelling individuals free of overt cardiovascular disease. These findings provide further support for a key role of MCP-1-signaling in cardiovascular disease.

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Supplemental content

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The results of the recent Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial, Cardiovascular Inflammation Reduction Trial (CIRT), and Colchicine Cardiovascular Outcomes Trial (COLCOT)[1-3] emphasize the promise of targeting specific inflammatory pathways for lowering cardiovascular risk. While recent studies have focused on the interleukin-1β (IL-1β)-interleukin-6 (IL-6)-C-reactive protein (CRP) axis,[4] a range of proinflammatory cytokines have been implicated in atherosclerosis.[5] In a recent mendelian randomization study examining multiple cytokines, we found genetically predicted levels of monocyte-chemoattractant-protein-1 (MCP-1) to be associated with higher risk of coronary heart disease (CHD) and ischemic stroke.[6] The presence of MCP-1 recruits monocytes to the arterial wall, and experimental studies of atherosclerosis suggest that targeting MCP-1 signaling attenuates atherosclerosis progression and plaque destabilization.[7,8] Circulating MCP-1 levels have been associated with increased long-term risk of incident stroke,[9] but associations with other cardiovascular end points in the general population remain largely unexplored. We leveraged data from 7 population-based cohorts encompassing 21 401 individuals without overt cardiovascular disease and investigated associations of baseline circulating MCP-1 with incident CHD, nonfatal myocardial infarction, and cardiovascular death over a follow-up period extending beyond 20 years.

### Key Points

**Question** Are circulating monocyte-chemoattractant protein-1 (MCP-1) levels associated with the risk of cardiovascular disease in the general population?

**Findings** In this meta-analysis of 7 population-based studies involving 21 401 individuals who were free of overt cardiovascular disease, higher baseline circulating MCP-1 levels were associated with higher risk of cardiovascular mortality over a follow-up extending beyond 20 years.

**Meaning** By complementing evidence from previous genetic and experimental studies, these results provide additional support for a key role of MCP-1 in cardiovascular disease development.

## Methods

Studies included in this meta-analysis were identified through systematic review, as previously described (eMethods in the Supplement).[9] Specifically, PubMed was searched for population-based cohort studies examining associations between MCP-1 levels and incident vascular outcomes up to July 2019. The corresponding authors of identified studies were contacted and agreed on a harmonized analysis plan. Contributing studies are described in eTable 1 in the Supplement. Baseline data were collected from 1984 to 2002, with the range of data collection dates varying between studies. Outcomes of interest included incident CHD (a composite of fatal and nonfatal myocardial infarction, unstable angina, and coronary revascularization), nonfatal myocardial infarction (no death within 28 days after an event), and cardiovascular mortality (death from any cardiac or cerebrovascular cause). Individuals with a baseline history of CHD, heart failure, stroke, or peripheral artery disease were excluded from the analyses. Study quality was assessed with the Newcastle-Ottawa scale.[10] Studies fulfilled all quality criteria (eTable 2 in the Supplement).

Cox regression models were fitted in each study. Natural log-transformed MCP-1 levels were incorporated in the models as continuous (in 1-SD increments) and also categorized in quartiles. Because of the different MCP-1 quantification assays, absolute MCP-1 values were not considered. Two main models were applied: model 1 was adjusted for age, sex, and race/ethnicity; model 2 was additionally adjusted for baseline vascular risk factors, including hypertension (documented diagnosis; systolic blood pressure, ≥140 mm Hg; diastolic blood pressure, ≥90 mm Hg; or antihypertensive medication use), low-density lipoprotein cholesterol levels, use of statins, diabetes (documented diagnosis; hemoglobin $A_{1c}$, ≥6.5% [to convert to proportion of total hemoglobin, multiply by 0.01]; fasting glucose, ≥126 mg/dL [to convert to millimoles per liter, multiply by 0.0555]; random glucose, ≥200 mg/dL; or glucose-lowering medication use), body mass index (calculated as weight in kilograms divided by height in meters squared), smoking (current vs noncurrent), estimated glomerular filtration rate, physical activity, and alcohol consumption. In subsequent models, additional adjustments for circulating IL-6 and high-sensitivity CRP levels were applied. The hazard ratios (HRs) derived from each study were pooled with random-effects meta-analyses (preselected because of differences in MCP-1 assays). Heterogeneity was assessed with the $I^2$ and Cochran Q statistics ($I^2$ > 50% and $P$ < .10 were considered significant). We further performed subgroup analyses by age (<50, 50-64, and ≥65 years), sex, hypertension status, diabetes status, and body mass index (<30 and ≥30). To minimize reverse-causation risk, sensitivity analyses were restricted to incident events occurring 5 or more years after MCP-1 measurements by censoring individuals with events at earlier points. Statistical significance was set at 2-sided $P$ < .05. Meta-analyses were conducted with Stata version 13.0 (StataCorp). Statistical analysis was carried out from August 2019 to February 2020.

## Results

Seven population-based cohort studies contributed data for this meta-analysis. A total of 21 401 individuals (mean [SD] age, 53.7 [10.2] years; 10 012 men [46.8%]; **Table**) without overt cardiovascular disease at baseline were followed for a mean (SD) interval of 15.3 (4.5) years (326 392 person-years at risk). A total of 3283 incident cases of CHD, 1221 cases of nonfatal myocardial infarction, and 1568 cardiovascular deaths were recorded during follow-up.

Higher baseline MCP-1 levels were associated with increased risk of CHD (HR per 1-SD increment, 1.06 [95% CI, 1.01-1.11]; $P$ = .01), nonfatal myocardial infarction (HR, 1.07 [95% CI, 1.01-1.13]; $P$ = .02), and cardiovascular death (HR, 1.12 [95% CI, 1.05-1.20]; $P$ < .001) in models adjusted for age, sex, and race/ethnicity (**Figure**, A; eTable 3 in the Supplement). These associations showed stepwise increases across MCP-1 quar tiles. After additionally adjusting for vascular risk factors, the association

Table. Descriptive Baseline Characteristics of the 7 Included Population-Based Cohort Studies

| | No. (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| Cohort | ARIC | DHS | EPIC-Norfolk[a] | FHS Offspring | MONICA/KORA[b] | MDCS-CV[c] | Rotterdam Study |
| Geographical setting (baseline assessment) | United States | United States | United Kingdom | United States | Germany | Sweden | The Netherlands |
| Years | 1986-1989 | 2000-2002 | 1993-1997 | 1998-2001 | 1984-1995 | 1991-1994 | 1996-1999 |
| Individuals included in the analysis, No. | 1005 | 2800 | 2762 | 6899 | 2572 | 4610 | 753 |
| Age, mean (SD), y | 56.2 (5.1) | 43.6 (9.9) | 65.0 (7.9) | 48.9 (13.5) | 52.5 (10.5) | 57.4 (6.0) | 72.5 (7.1) |
| Male | 614 (61.1) | 1200 (42.9) | 1747 (63.3) | 3109 (45.1) | 1247 (45.5) | 1796 (39.0) | 299 (39.7) |
| Race/ethnicity | | | | | | | |
| Black | 249 (24.8) | 1388 (49.6) | 3 (0.1) | NA | NA | NA | 2 (0.3) |
| Hispanic | NA | 907 (32.4) | NA | NA | NA | NA | NA |
| White | 756 (75.2) | 446 (15.9) | 2756 (99.8) | 6899 (100) | 2572 (100) | 4610 (100) | 667 (98.2) |
| Other | NA | 59 (2.1) | 2 (0.1) | NA | NA | NA | 10 (1.5) |
| Follow-up, mean (SD), y | 22.1 (8.6) | 11.9 (1.9) | 17.6 (6.2) | 12.9 (3.5) | 12.6 (3.0) | 20.0 (4.4) | 11.6 (4.9) |
| Incident events, No. | | | | | | | |
| Coronary artery disease | 438 | 131 | 1179 | 324 | 568 | 544 | 99 |
| Nonfatal myocardial infarction | 200 | 62 | 285 | 195 | NA | 426 | 53 |
| Cardiovascular deaths | 360 | 77 | 590 | 130 | NA | 340 | 71 |
| Hypertension | 372 (37.1) | 855 (31.0) | 1663 (60.2) | 1812 (26.3) | 1091 (42.4) | 2867 (62.2) | 496 (65.9) |
| Blood pressure, mm Hg | | | | | | | |
| Systolic | 124 (20) | 124 (18) | 141 (18) | 121 (17) | 134 (19) | 141 (19) | 143 (21) |
| Diastolic | 75 (12) | 78 (10) | 85 (11) | 75 (10) | 82 (11) | 87 (9) | 75 (11) |
| Diabetes | 144 (14.3) | 267 (9.5) | 139 (5.0) | 377 (5.5) | 131 (5.1) | 175 (3.8) | 79 (10.5) |
| Cholesterol levels, mg/dL | | | | | | | |
| Total | 219 (41) | 181 (39) | 247 (46.0) | 194 (36.4) | 238 (44) | 240 (42) | 226 (35) |
| Low-density lipoprotein | 142 (39) | 108 (35) | 161 (39.4) | 116 (32.1) | NA | 163 (38) | NA |
| High-density lipoprotein | 50 (17) | 50 (14) | 53 (15.2) | 59 (16.6) | 57 (17) | 54 (14) | 55 (16) |
| BMI, mean (SD) | 27.3 (4.9) | 29.6 (7.0) | 26.6 (3.6) | 27.4 (5.5) | 27.1 (4.1) | 25.6 (3.9) | 26.7 (3.8) |
| Smoking status | | | | | | | |
| Never | 409 (40.7) | 1582 (56.6) | 1069 (38.7) | 3332 (48.3) | 1222 (47.5) | 1897 (41.1) | 273 (36.9) |
| Former | 274 (27.3) | 468 (16.7) | 1398 (50.6) | 2598 (37.7) | 715 (27.8) | 1714 (37.2) | 349 (47.2) |
| Current | 321 (32.0) | 746 (26.7) | 295 (10.7) | 966 (14.0) | 635 (24.7) | 993 (21.5) | 118 (15.9) |
| eGFR, mean (SD), mL/min/1.73 $m^2$ | 100.1 (15.6) | 99.9 (23.2) | 68.8 (19.4) | 94.4 (17.3) | 89.1 (17.8) | 76.9 (15.3) | 71.6 (12.8) |
| hsCRP levels, median (IQR), mg/dL | 0.37 (0.15-0.57) | 0.27 (0.11-0.66) | 0.20 (0.10-0.37) | 0.15 (0.07-0.37) | 0.14 (0.07-0.32) | 0.13 (0.07-0.27) | 0.14 (0.07-0.32) |
| Monocyte chemoattractant protein-1 | | | | | | | |
| Sample used for assessment | Plasma | Plasma | Serum | Serum | Serum | Plasma | Plasma |
| Levels, median (IQR), pg/mL | 394 (346-463) | 166 (123-223) | 57 (39-68) | 323 (258-395) | 206 (126-735) | 5.7 (4.6-7.0)[c] | 183 (151-224) |

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DHS, Dallas Heart Study; eGFR, estimated glomerular filtration rate; EPIC-Norfolk, European Prospective Investigation of Cancer-Norfolk; FHS Offspring, Framingham Heart Study-Offspring Cohort; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; MDCS-CV, Malmö Diet and Cancer Study-Cardiovascular subcohort; MONICA/KORA, Monitoring of Trends and Determinants in Cardiovascular Disease-Kooperative Gesundheitsforschung in der Region Augsburg; NA, not applicable.

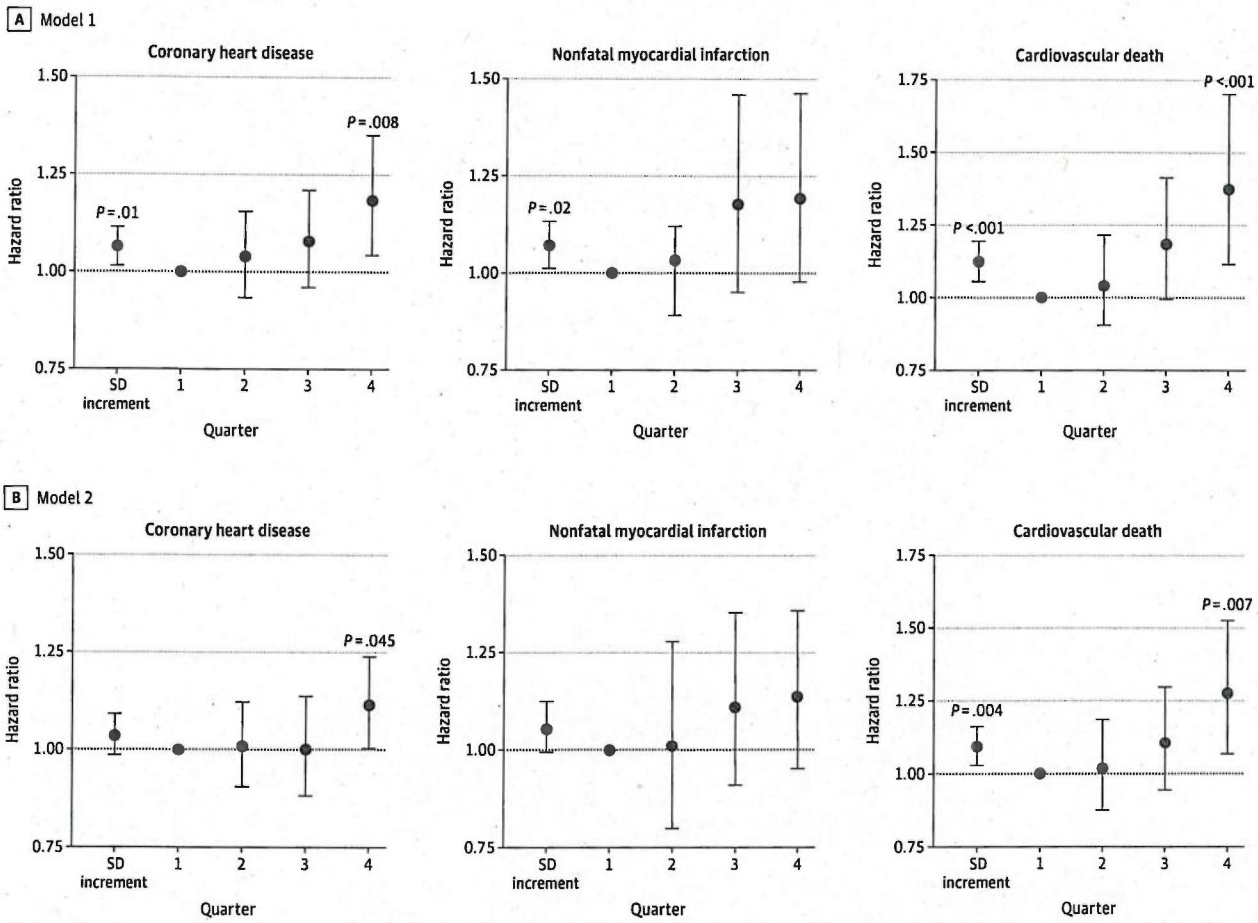
SI conversion factors: To convert C-reactive protein to mg/L, multiply by 10; high-density lipoprotein cholesterol to mmol/L, multiply by 0.0259; low-density lipoprotein cholesterol to mmol/L, multiply by 0.0259.

[a] EPIC-Norfolk data were obtained using a nested case-control design.

[b] MONICA/KORA data were obtained using a case-cohort design and not included in analyses for the outcomes of nonfatal myocardial infarction and cardiovascular death.

[c] The used assay in MDCS-CV did not provide monocyte chemoattractant protein-1 measurements as absolute values, but as relative expression levels obtained by proximity extension assay.

Figure. Associations Between Baseline Circulating Monocyte-Chemoattractant Protein-1 Levels and Risk of Coronary Heart Disease, Nonfatal Myocardial Infarction, and Cardiovascular Death




Shown are the results from random-effects meta-analyses of the pooled sample consisting of 7 population-based studies, as derived from model 1 (adjusted for age, sex, and race/ethnicity) (A) and model 2 (adjusted for age, sex, race/ethnicity, and vascular risk factors) (B). The vascular risk factors adjusted for in model 2 include hypertension, low-density lipoprotein cholesterol levels, use of statins, diabetes mellitus, body mass index (per 1-kg/m$^2$ increment), smoking (current vs noncurrent), estimated glomerular filtration rate (per 1-mL/min/1.73 m$^2$ increment), physical activity, and alcohol consumption at baseline. Analyses for 1-SD increment correspond to natural log-transformed MCP-1 levels. The Monitoring of Trends and Determinants in Cardiovascular Disease–Kooperative Gesundheitsforschung in der Region Augsburg (MONICA/KORA) study is not included in any of the analyses for nonfatal myocardial infarction and cardiovascular death.

between MCP-1 levels and cardiovascular death remained significant (HR per 1-SD increment, 1.09 [95% CI, 1.03-1.16]; $P$ = .004), as did the association between MCP-1 levels in the upper quartile with CHD (Figure, B). There was no evidence of significant heterogeneity ($I^2$ < 50%, $P$ > .10; eFigures 1-6 in the Supplement). The MCP-1 levels were also associated with noncardiovascular death, but the association was nonsignificant after additional adjustments for vascular risk factors (eFigures 7 and 8 in the Supplement).

In sensitivity analyses excluding events occurring in the first 5 years of follow-up, there were significant associations of MCP-1 levels with incident nonfatal myocardial infarction (HR per 1-SD increment, 1.08 [95% CI, 1.001-1.16]; $P$ = .048) and cardiovascular death (HR per 1-SD increment, 1.10 [95% CI, 1.02-1.18]; $P$ = .02) after adjusting for demographics and vascular risk factors (eTable 4 in the Supplement). In subgroup analyses stratifying for age, sex, hypertension, diabetes mellitus, and body mass index, there was no indication for between-subgroup heterogeneity, except for a stronger association with cardiovascular death in individuals without hypertension (HR, 1.17 [95% CI, 1.08-1.27]; $P$ = .045; eFigures 9-11 in the Supplement). Additional adjustments for IL-6 and high-sensitivity CRP levels (subset of 5 studies; 16 621 individuals) did not substantially attenuate the risk estimates (eFigure 12 in the Supplement). When exploring the additive predictive value of MCP-1, we found no significant increment on top of vascular risk factors (C statistic for cardiovascular death with MCP-1, 0.779 vs without MCP-1, 0.774; eTable 5 in the Supplement).

## Discussion

Among 21 401 community-based individuals without overt cardiovascular disease at baseline, higher MCP-1 levels were

associated with increased long-term cardiovascular mortality. The results were present after adjusting for known vascular risk factors, followed a dose-response pattern, and remained stable after additional adjustments for serum IL-6 and high-sensitivity CRP levels.

Our results add to previous data showing significant associations of MCP-1 levels with cardiovascular mortality after acute coronary syndromes,[11,12] by also demonstrating an association with cardiovascular mortality in the general population. While attenuated in the multivariable model, we also found significant associations with risk of CHD and nonfatal myocardial infarction in models adjusted for age, sex, and race/ethnicity.

The magnitude of the examined associations was modest, and there was no increment in C-statistics for MCP-1 on top of other vascular risk factors for prognosticating cardiovascular disease. Thus, MCP-1 measurement is unlikely to be a valuable risk marker for cardiovascular end points. However, the aim of this study was to provide additional support for MCP-1 as a promising therapeutic target in atherosclerosis. In fact, the point estimates of the associations with CHD and nonfatal myocardial infarction matched those previously obtained for genetically predicted MCP-1 levels.[6] Together, the genetic and biomarker findings support a key role of MCP-1 signaling in cardiovascular disease.

Most studies in this analysis used a broader definition of cardiovascular death that included death from ischemic heart disease, stroke, and other vascular conditions. The more prominent associations compared with CHD and nonfatal myocardial infarction might be explained by differences in the effects of MCP-1 across different vascular beds, in line with our previous findings for stronger associations with stroke.[6,9] The observed outcomes of MCP-1 on cardiovascular mortality might be further associated with additive outcomes of MCP-1 on atherosclerosis risk[7,8,13,14] and inflammatory responses critical to healing from myocardial infarction.[15]

### Limitations

As a limitation, the lack of a standardized assay to quantify MCP-1 and the differences in assays between studies precluded analyses using absolute MCP-1 values. While previous studies have shown available anti-inflammatory medications to differentially influence MCP-1 levels,[16] this could not be examined in this meta-analysis.

## Conclusions

In conclusion, higher circulating levels of MCP-1 are associated with higher long-term cardiovascular mortality in community-based individuals free of overt cardiovascular disease. Our findings triangulate previous genetic and experimental evidence supporting a key role of MCP-1-signaling in cardiovascular disease.

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*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* Georgakis, Sun, Dichgans.
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