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## Supplemental Material

# Long-Term Exposure to Ambient Ozone and Progression of Subclinical Arterial Disease: The Multi-Ethnic Study of Atherosclerosis and Air Pollution

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**Figure S2.** Concentration-response curves for associations of long-term exposure to $O_3$ with progression of intima-media thickness of common carotid artery ($IMT_{CCA}$, μm/year) in mixed model (left) and carotid plaque (CP) formation (log-transformed odds ratio) in logistic model (right) smoothed by a natural spline with 4 degree of freedom. Full models were adjusted for age, sex, race/ethnicity, study region, body mass index, smoking status, pack-years, second-hand smoke exposure, alcohol consumption, physical activity, employment status, high-density lipid, total cholesterol, statin use, neighborhood SES index, income, education, systolic and diastolic blood pressure, hypertension, anti-hypertensive medication, diabetes.

## SUPPLEMENTAL MATERIAL

**Table S1. Number of participants included in each exam with $O_3$ exposure data.**

| Exam | 1 (2000-01) | 2 (2002-03) | 3 (2004-05) | 4 (2005-07) | 5 (2010-12) |
|---|---|---|---|---|---|
| CAC (N) | 6374 | 2839 | 2723 | 1569 (245 new MESA recruitment) | 3219 |
| IMT and CP(N) | 3147 | - | - | 951 (245 new MESA recruitment) | 3276 |

CAC: coronary artery calcification.
IMTCCA: Intima-media thickness of common carotid artery.
CP: Carotid plaque burden.

**Table S2. Participant characteristics with coronary artery calcification (CAC) measurement at baseline and during follow-up by study regions. Values provided are mean ± standard deviation for continuous variables or number (%) for categorical variables.**

| **Site** | Winston-Salem | NYC | Baltimore | St. Paul | Chicago | LA |
|---|---|---|---|---|---|---|
| **$O_3$ concentrations (ppb)** | | | | | | |
| Baseline: annual mean 2000 | 27.8±2.4 | 14.7±1.3 | 22.0±2.1 | 25.4±2.3 | 21.4±1.4 | 16.0±2.0 |
| Follow-up: all-year mean | 27.9±2.5 | 14.8±1.3 | 21.9±2.2 | 25.6±1.9 | 21.3±1.4 | 16.1±2.2 |
| **Number of Participants** | | | | | | |
| Baseline | 1039 | 1083 | 1060 | 1030 | 1143 | 1264 |
| Follow-up | 944 | 975 | 905 | 928 | 1035 | 1076 |
| **Follow-up Time (years)** | 6.6±3.4 | 7.1±3.4 | 5.8±3.6 | 6.9±3.3 | 6.9±3.5 | 5.8±3.6 |
| **Average number of follow-up measurements per person** | 3±1 | 3±1 | 2±1 | 3±1 | 3±1 | 2±1 |
| **Outcomes** | | | | | | |
| Mean CAC at baseline (Agatston score) | 265±574 | 233±560 | 277±630 | 301±645 | 229±469 | 216±529 |
| Increase in CAC during follow-up (Agatston/year) | 28±1.8 | 23±1.7 | 26±1.9 | 28±1.8 | 23±1.7 | 23±1.6 |
| **Baseline demographics** | | | | | | |
| Age | 62±10 | 62±10 | 63±10 | 60±10 | 62±10 | 63±10 |
| Male N(%) | 488 (47) | 487 (45) | 498 (47) | 505 (49) | 537 (47) | 607 (48) |
| Race/Ethnicity N(%) | | | | | | |
| White | 561 (54) | 260 (24) | 530 (50) | 587 (57) | 537 (47) | 190 (15) |
| Chinese | - | - | - | - | 309 (27) | 430 (34) |
| Black | 468 (45) | 368 (34) | 530 (50) | | 297 (26) | 139 (11) |
| Hispanic | - | 455 (42) | - | 443 (43) | - | 493 (39) |
| Education N(%) | | | | | | |
| ≤High School | 83 (8) | 249 (23) | 117 (11) | 196 (19) | 80 (7) | 417 (33) |
| High School | 218 (21) | 206 (19) | 212 (20) | 227 (22) | 91 (8) | 228 (18) |
| Some College/Technical | 322 (31) | 303 (28) | 318 (30) | 361 (35) | 274 (24) | 329 (26) |
| College or Graduate | 416 (40) | 325 (30) | 413 (39) | 247 (24) | 697 (61) | 291 (23) |
| Employment N(%) | 662 (64) | 615 (57) | 631 (60) | 718 (70) | 762 (67) | 579 (46) |
| Neighborhood SES index | -0.7±4.6 | 0.4±7.9 | -0.2±4.5 | 0.2±3.3 | -6.4±6.7 | 0.6±5.9 |
| Income (USDx1000) | 56±34 | 43±31 | 52±34 | 45±30 | 71±40 | 36±31 |
| **Baseline risk factors** | | | | | | |
| Body mass index (kg/m$^2$) | 29±5 | 28±5 | 30±6 | 29±5 | 26±5 | 27±5 |
| Smoking Status | | | | | | |
| Never | 416 (40) | 531 (49) | 456 (43) | 433 (42) | 549 (48) | 771 (61) |
| Former | 447 (43) | 379 (35) | 445 (42) | 412 (40) | 446 (39) | 354 (28) |
| Current | 177 (17) | 173 (16) | 159 (15) | 185 (18) | 149 (13) | 139 (11) |
| Pack-years smoking | 14±24 | 10±18 | 14±23 | 12±21 | 12±23 | 7±15 |
| Second-hand smoking N(%) | 594 (57) | 475 (44) | 532 (50) | 629 (61) | 592 (52) | 363 (29) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Physical activity N(%) | | | | | | |
| Q1 | 253 (24) | 262 (24) | 288 (27) | 263 (26) | 205 (18) | 415 (33) |
| Q2 | 315 (30) | 248 (23) | 240 (23) | 262 (25) | 285 (25) | 383 (30) |
| Q3 | 234 (23) | 254 (23) | 243 (23) | 249 (24) | 316 (28) | 268 (21) |
| Q4 | 236 (23) | 318 (29) | 289 (27) | 256 (25) | 337 (29) | 198 (16) |
| Systolic Blood Pressure (mmHg) | 133±21 | 123±20 | 128±21 | 122±20 | 123±21 | 127±22 |
| Diastolic blood pressure (mmHg) | 74±10 | 73±10 | 72±10 | 70±10 | 72±10 | 72±10 |
| Hypertension[a] | 582 (56) | 509 (47) | 541 (51) | 350 (34) | 434 (38) | 544 (43) |
| High-density lipid (mg/dl)[b] | 50±15 | 53±15 | 52±15 | 49±14 | 54±16 | 49±14 |
| Total Cholesterol (mg/dl)[b] | 189±33 | 194±35 | 192±35 | 200±38 | 195±33 | 193±34 |
| Statin Use N(%)[c] | 166 (16) | 173 (16) | 201 (19) | 124 (12) | 160 (14) | 152 (12) |
| Anti-hypertensive medication N(%)[c] | 456 (44) | 453 (42) | 478 (45) | 292 (28) | 373 (33) | 420 (33) |
| Diabetes N(%)[d] | | | | | | |
| Normal | 790 (76) | 780 (72) | 763 (72) | 783 (76) | 903 (79) | 847 (67) |
| Impaired fasting glucose | 125 (12) | 152 (14) | 159 (15) | 134 (13) | 137 (12) | 202 (16) |
| Diabetic | 125 (12) | 152 (14) | 138 (13) | 113 (11) | 103 (9) | 215 (17) |
| Family history of premature CVD N(%)[e] | 315 (30) | 271 (25) | 339 (32) | 312 (30) | 280 (25) | 274 (22) |
| Fibrinogen (mg/dL) | 339±72 | 364±79 | 348±75 | 351±73 | 337±72 | 344±69 |
| C-reactive protein (mg/dL) | 4.4±6.5 | 3.6±5 | 4.3±6.6 | 3.9±5.4 | 3.2±5.9 | 3.4±5.6 |
| Creatinine (mg/dL) | 1±0.3 | 1±0.3 | 1±0.4 | 1±0.3 | 0.9±0.2 | 0.9±0.3 |

[a]Hypertension was defined as systolic blood pressure at least 140 mm Hg, diastolic blood pressure at least 90 mm Hg, or reported use of antihypertensive medication.

[b]Plasma lipid measurements for high-density lipid and total cholesterol.

[c]Medication use was defined as any positive report of a statin and/or antihypertensive medication use on the medication inventory for the participants at each of the five clinical exams.

[d]Diabetes mellitus was defined as fasting glucose >125 mg/dl or the use of hypoglycemic medications. Among those not reporting use of hypoglycemic medications, we defined Impaired fasting glucose between 100 and 125mg/dl and normal fasting glucose as fasting blood glucose less than 100 mg/dl.

[e]Family history of premature cardiovascular disease was defined as myocardial infarction/heart attack, stroke/brain attack, or cardiovascular procedure (coronary bypass or balloon angioplasty) in a female primary relative (parent, sibling, or child) aged <65 years or a male primary relative aged <55 years) Outcome, demographic covariates and risk factors were available for all the participants.

**Table S3. Characteristics of air pollution distribution at baseline and follow-up period for intima-media thickness of common carotid artery ($IMT_{CCA}$) and carotid plaque (CP) burden.**

| | Mean | STD | Min | 25% | 50% | 75% | Max |
|---|---|---|---|---|---|---|---|
| **Baseline** | | | | | | | |
| $O_3$ Long-term | 21.0 | 5.0 | 10.5 | 16.0 | 21.2 | 25.1 | 42.3 |
| $O_3$ warm season[a] | 27.5 | 4.4 | 15.4 | 25.2 | 28.1 | 30.6 | 47.5 |
| $O_3$ 1-year[b] | 21.0 | 5.0 | 10.5 | 16.0 | 21.2 | 25.1 | 42.3 |
| $NO_x$ all years | 53.0 | 32.7 | 8.7 | 25.6 | 41.9 | 78.1 | 267.1 |
| $PM_{2.5}$ all years | 16.5 | 2.8 | 10.9 | 15.0 | 16.0 | 17.4 | 27.9 |
| **Follow-up** | | | | | | | |
| $O_3$ all years | 21.7 | 4.1 | 10.8 | 18.7 | 22.3 | 24.2 | 41.7 |
| $O_3$ warm season[a] | 27.5 | 4.4 | 15.2 | 25.1 | 28.1 | 30.6 | 47.6 |
| $O_3$ 1-year[b] | 22.8 | 4.6 | 11.1 | 18.9 | 23.3 | 26.1 | 44.3 |
| $NO_x$ Long-term | 39.3 | 25.2 | 6.6 | 20.2 | 31.8 | 52.7 | 246.2 |
| $PM_{2.5}$ all years | 13.6 | 2.4 | 8.6 | 12.6 | 13.5 | 14.8 | 22.3 |

[a]Long-term ozone exposure between April and September.

[b]1-year average prior to each exam.

**Table S4. Within-site correlation coefficients[a] between long-term air pollution exposures in the study period for intima-media thickness of common carotid artery ($IMT_{CCA}$) and carotid plaque (CP) burden.**

| | $O_3$ all years | $O_3$ warm season | $O_3$ 1-year | $NO_x$ all years | $PM_{2.5}$ all years |
|---|---|---|---|---|---|
| $O_3$ all years | 1.00 | | | | |
| $O_3$ warm season | 0.71 | 1.00 | | | |
| $O_3$ 1-year | 0.91 | 0.61 | 1.00 | | |
| $NO_x$ all years | -0.42 | -0.27 | -0.46 | 1.00 | |
| $PM_{2.5}$ all years | -0.29 | -0.17 | -0.42 | 0.67 | 1.00 |

[a]Within-Site: Calculated after subtracting the city-specific mean from each observation.

**Table S5. Estimates of the associations between $O_3$ exposure (3 ppb) and carotid plaque (CP) incidence from models with increasing amounts of adjustment for covariates.**

| Staged models | Odds Ratio (95% CI) CP incidence |
|---|---|
| Base | 1.3 (1.1, 1.4) |
| Moderate | 1.2 (1.1, 1.4) |
| Full | 1.2 (1.1, 1.4) |
| Extended | 1.2 (1.1, 1.4) |

Base model includes age, sex, race/ethnicity, study region.

Moderate model= Base model + body mass index, smoking status, pack-years, second-hand smoke exposure, alcohol consumption, physical activity, employment status, high-density lipid, total cholesterol, statin use.

Full model (primary analysis) = Moderate model + neighborhood SES index, income, education, systolic and diastolic blood pressure, hypertension, anti-hypertensive medication, diabetes; Full model is the primary model for report in the main text and discussion.

Extended model = Full model+family history of premature CVD, fibrinogen, c-reactive protein, creatinine.

**Table S6. Main and sensitivity analyses for estimates of the effect of a 3 ppb increase of O3 exposure on coronary artery calcification (CAC) progression over ten years from models with increasing amounts of covariate adjustment.**

| | Change of CAC ten years (Agatston units, 95% CI) |
|---|---|
| **Main Analyses** | |
| Base | -2 (-12, 8) |
| Moderate | -8 (-18, 2) |
| Full | -8 (-18, 2) |
| Extended | -8 (-19, 2) |
| **Sensitivity Analyses** | |
| $O_3$ warm seasons‡ | -6 (-15, 4) |
| $O_3$ 1-year mean | -12 (-19, 4) |
| Adjust for $NO_x$ | -18 (-38, 3) |
| Adjust for $PM_{2.5}$ | -22 (-41, 1) |

Main analyses (within-city IQR of $O_3$ exposure = 3ppb;):
Base model includes age, sex, race/ethnicity, study region and CT scanner types.
Moderate model= Base model + body mass index, smoking status, pack-years, second-hand smoke exposure, alcohol consumption, physical activity, employment status, high-density lipid, total cholesterol, statin use.
Full model = Moderate model + neighborhood SES index, income, education, systolic and diastolic blood pressure, hypertension, anti-hypertensive medication, diabetes; Full model is the primary model for report in the main text and discussion.
Extended model = Full model+family history of premature CVD, fibrinogen, c-reactive protein, creatinine
Sensitivity analyses: covariates in the sensitivity analyses are the same as those in the full model of the main analyses.
Long-term ozone exposure between April and September.
1-year average prior to exams.

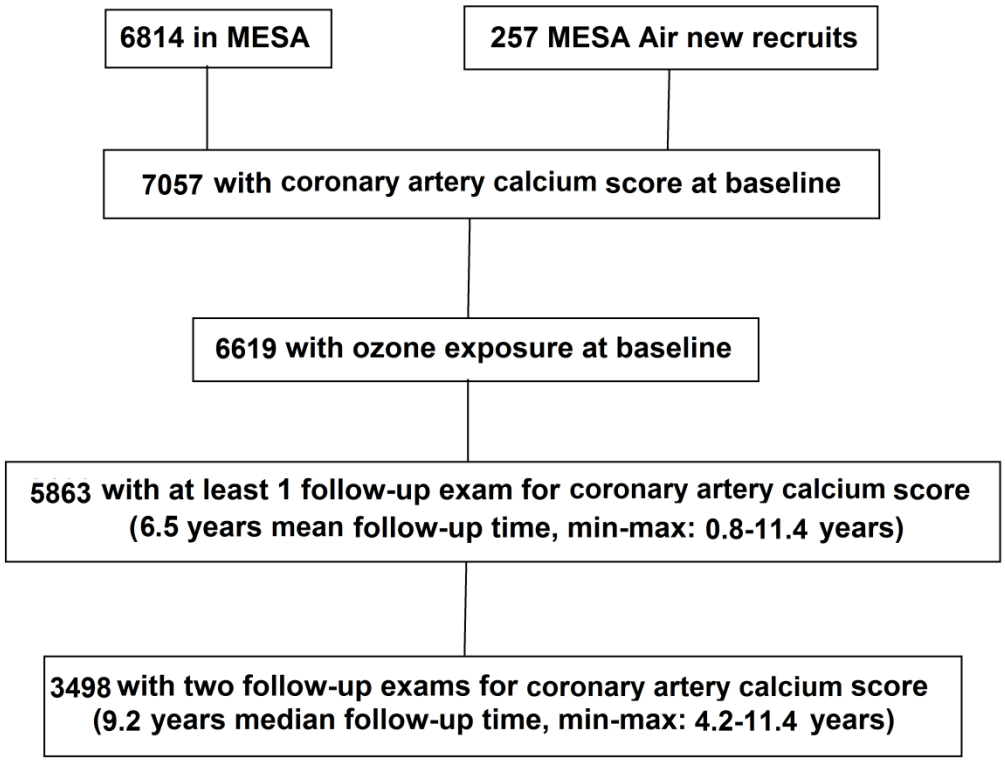


**Figure S1.** Description of study design and data characteristics for coronary artery calcification.

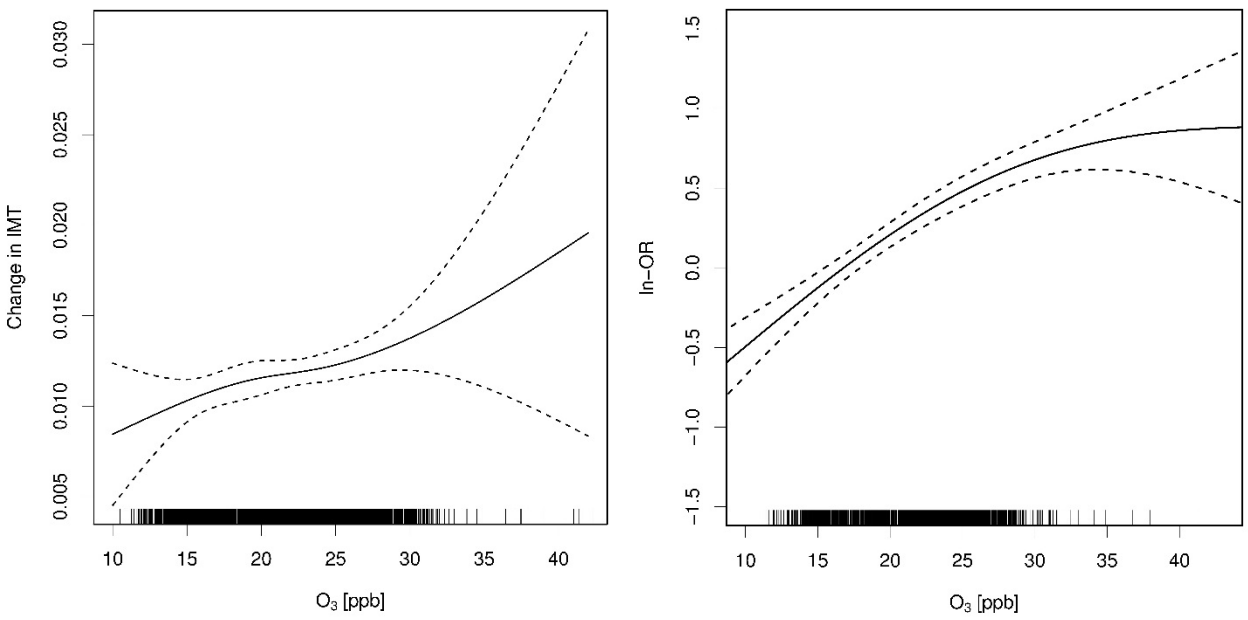


**Figure S2.** Concentration-response curves for associations of long-term exposure to $O_3$ with progression of intima-media thickness of common carotid artery ($IMT_{CCA}$, µm/year) in mixed model (left) and carotid plaque (CP) formation (log-transformed odds ratio) in logistic model (right) smoothed by a natural spline with 4 degree of freedom. Full models were adjusted for age, sex, race/ethnicity, study region, body mass index, smoking status, pack-years, second-hand smoke exposure, alcohol consumption, physical activity, employment status, high-density lipid, total cholesterol, statin use, neighborhood SES index, income, education, systolic and diastolic blood pressure, hypertension, anti-hypertensive medication, diabetes.