

Title: Nitrous oxide and serious long-term morbidity and mortality in the ENIGMA-II trial

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Supplementary tables 1-10

Supplementary table 1. Odds ratios for the composite primary outcome of death or major cardiovascular events (nonfatal myocardial infarction, cardiac arrest, pulmonary embolism and stroke) ^a

| | n | n (%) with outcome | Univariate OR (95% CI) | P value | Multivariate ^b OR (95% CI) | P value |
|---------------------------|------|--------------------|------------------------|---------|---------------------------------------|---------|
| Age (years) | | | | <0.0005 | | <0.0005 |
| <50 | 166 | 17 (10.2) | 1.00 (reference) | | | |
| 50-59 | 842 | 102 (12.1) | 1.21 (0.70, 2.08) | | 1.19 (0.69, 2.05) | |
| 60-69 | 1610 | 234 (14.5) | 1.49 (0.89, 2.51) | | 1.42 (0.84, 2.40) | |
| 70-79 | 2353 | 396 (16.8) | 1.77 (1.06, 2.96) | | 1.67 (0.99, 2.80) | |
| ≥80 | 871 | 226 (25.9) | 3.08 (1.83, 5.21) | | 2.53 (1.49, 4.30) | |
| Sex | | | | 0.13 | | 0.15 |
| male | 3767 | 608 (16.1) | 1.00 (reference) | | | |
| female | 2075 | 367 (17.7) | 1.11 (0.97, 1.29) | | 1.12 (0.96, 1.30) | |
| Body mass index | | | | <0.0005 | | <0.0005 |
| <18.5 | 155 | 50 (32.3) | 1.91 (1.34, 2.72) | | 1.80 (1.25, 2.60) | |
| 18.5-24.9 | 1909 | 381 (20.0) | 1.00 (reference) | | | |
| 25-29.9 | 2052 | 303 (14.8) | 0.69 (0.59, 0.82) | | 0.68 (0.58, 0.81) | |
| ≥30 | 1726 | 241 (14.0) | 0.65 (0.55, 0.78) | | 0.64 (0.53, 0.77) | |
| ASA physical status | | | | <0.0005 | | <0.0005 |
| 1-2 | 1798 | 217 (12.1) | 1.00 (reference) | | | |
| 3 | 3633 | 643 (17.7) | 1.57 (1.33, 1.85) | | 1.49 (1.25, 1.78) | |
| 4 | 411 | 115 (28.0) | 2.83 (2.19, 3.66) | | 2.45 (1.85, 3.23) | |
| Exercise capacity ≥4 METS | | | | <0.0005 | | 0.001 |
| yes | 4378 | 659 (15.1) | 1.00 (reference) | | | |
| no | 1464 | 316 (21.6) | 1.55 (1.34, 1.80) | | 1.30 (1.11, 1.52) | |
| Coronary artery disease | | | | <0.0005 | | 0.018 |
| yes | 2213 | 420 (19.0) | 1.00 (reference) | | | |
| no | 3629 | 555 (15.3) | 0.77 (0.67, 0.89) | | 0.84 (0.72, 0.97) | |
| Emergency | | | | 0.001 | | 0.037 |

| | | | | | | |
|--------------------------------|------|------------|-------------------|---------|-------------------|---------|
| surgery | | | | | | |
| no | 5598 | 915 (16.3) | 1.00 (reference) | | | |
| yes | 244 | 60 (24.6) | 1.67 (1.24, 2.25) | | 1.40 (1.02, 1.91) | |
| Vascular surgery | | | | 0.016 | | 0.40 |
| no | 3575 | 563 (15.7) | 1.00 (reference) | | | |
| yes | 2267 | 412 (18.2) | 1.19 (1.03, 1.36) | | 1.07 (0.92, 1.24) | |
| Nitrous oxide | | | | 0.45 | | 0.37 |
| no | 2944 | 481 (16.3) | 1.00 (reference) | | | |
| yes | 2897 | 493 (17.0) | 1.05 (0.92, 1.21) | | 1.07 (0.93, 1.23) | |
| Propofol maintenance | | | | 0.012 | | 0.019 |
| yes | 188 | 44 (23.4) | 1.00 (reference) | | | |
| no | 5653 | 930 (16.5) | 0.64 (0.46, 0.91) | | 0.65 (0.46, 0.93) | |
| Regional LA block | | | | <0.0005 | | <0.0005 |
| yes | 1600 | 317 (19.8) | 1.00 (reference) | | | |
| no | 4241 | 657 (15.5) | 0.74 (0.64, 0.86) | | 0.75 (0.64, 0.87) | |
| BIS monitoring | | | | 0.25 | | 0.89 |
| yes | 2516 | 539 (16.2) | 1.09 (0.94, 1.25) | | 1.01 (0.87, 1.17) | |
| no | 3325 | 435 (17.3) | 1.00 (reference) | | | |
| MAC equivalents | | | | 0.12 | | 0.71 |
| ≥0.72 | 2819 | 445 (15.8) | 1.00 (reference) | | | |
| <0.72 | 2816 | 487 (17.3) | 1.12 (0.97, 1.29) | | 0.97 (0.81, 1.15) | |
| Duration of anesthesia (hours) | | | | <0.0005 | | <0.0005 |
| <2 | 703 | 80 (11.4) | 1.00 (reference) | | | |
| 2-3 | 1761 | 237 (13.5) | 1.23 (0.94, 1.60) | | 1.26 (0.96, 1.66) | |
| 3-4 | 1394 | 217 (15.6) | 1.49 (1.14, 1.95) | | 1.53 (1.15, 2.03) | |
| 4-5 | 837 | 150 (17.9) | 1.76 (1.32, 2.34) | | 1.89 (1.40, 2.56) | |
| ≥5 | 940 | 248 (26.4) | 2.84 (2.17, 3.71) | | 3.15 (2.37, 4.18) | |

^a unweighted analysis. ^b preoperative variables first adjusted for each other; then nitrous oxide, propofol maintenance, regional LA block and BIS monitoring adjusted for each other and preoperative variables; then MAC value in patients receiving volatile anesthetic maintenance and duration of anesthesia adjusted for each

other, preoperative variables, nitrous oxide and BIS monitoring (propofol maintenance not included because patients who received propofol for maintenance had missing data for volatile anesthetic administration). OR = odds ratio, CI = confidence interval, ASA = American Society of Anesthesiologists, METS = metabolic equivalents, LA = local anesthetic, BIS = bispectral index, MAC = minimum alveolar concentration.

Supplementary table 2. Odds ratios for the composite primary outcome of death or major cardiovascular events (nonfatal myocardial infarction, cardiac arrest, pulmonary embolism and stroke) associated with the use of nitrous oxide

| Characteristic | Unweighted | | Weighted ^a | |
|---------------------------|-------------------|---------------------|-----------------------|---------------------|
| | OR (95% CI) | Interaction P value | OR (95% CI) | Interaction P value |
| Age (years) | | 0.061 | | 0.046 |
| <50 | 1.23 (0.45, 3.42) | | 1.17 (0.41, 3.31) | |
| 50-59 | 0.74 (0.49, 1.13) | | 0.77 (0.50, 1.18) | |
| 60-69 | 1.46 (1.10, 1.93) | | 1.52 (1.14, 2.01) | |
| 70-79 | 0.94 (0.76, 1.17) | | 0.94 (0.75, 1.16) | |
| ≥80 | 1.09 (0.81, 1.48) | | 1.12 (0.82, 1.52) | |
| Sex | | 0.75 | | 0.82 |
| male | 1.07 (0.90, 1.28) | | 1.08 (0.91, 1.29) | |
| female | 1.03 (0.82, 1.29) | | 1.05 (0.83, 1.32) | |
| BMI | | 0.042 | | 0.070 |
| <18.5 | 0.84 (0.43, 1.64) | | 0.94 (0.47, 1.87) | |
| 18.5-24.9 | 1.05 (0.84, 1.32) | | 1.06 (0.84, 1.33) | |
| 25-29.9 | 0.85 (0.66, 1.08) | | 0.87 (0.68, 1.11) | |
| ≥30 | 1.43 (1.09, 1.89) | | 1.43 (1.08, 1.89) | |
| ASA physical status | | 0.55 | | 0.63 |
| 1-2 | 0.95 (0.72, 1.27) | | 0.97 (0.72, 1.29) | |
| 3 | 1.07 (0.90, 1.27) | | 1.09 (0.91, 1.29) | |
| 4 | 1.26 (0.82, 1.94) | | 1.23 (0.80, 1.91) | |
| Exercise capacity ≥4 METS | | 0.64 | | 0.67 |
| yes | 1.07 (0.91, 1.27) | | 1.09 (0.92, 1.28) | |
| no | 1.00 (0.78, 1.28) | | 1.02 (0.79, 1.31) | |
| Coronary artery disease | | 0.97 | | 0.95 |
| yes | 1.06 (0.85, 1.31) | | 1.07 (0.86, 1.32) | |
| no | 1.06 (0.89, 1.27) | | 1.08 (0.90, 1.29) | |
| Emergency surgery | | 0.84 | | 0.80 |
| no | 1.06 (0.92, 1.22) | | 1.07 (0.93, 1.23) | |

| | | | | |
|--------------------------------|-------------------|-------|-------------------|-------|
| yes | 1.00 (0.56, 1.79) | | 1.16 (0.64, 2.10) | |
| Vascular surgery | | 0.72 | | 0.70 |
| no | 1.08 (0.90, 1.29) | | 1.09 (0.91, 1.31) | |
| yes | 1.03 (0.83, 1.27) | | 1.04 (0.83, 1.29) | |
| Propofol maintenance | | 0.83 | | 0.97 |
| yes | 0.98 (0.50, 1.93) | | 1.08 (0.54, 2.14) | |
| no | 1.06 (0.92, 1.22) | | 1.07 (0.93, 1.23) | |
| Regional LA block | | 0.49 | | 0.49 |
| yes | 1.14 (0.89, 1.45) | | 1.15 (0.90, 1.48) | |
| no | 1.02 (0.87, 1.21) | | 1.04 (0.88, 1.23) | |
| BIS monitoring | | 0.071 | | 0.081 |
| no | 0.94 (0.78, 1.13) | | 0.96 (0.79, 1.15) | |
| yes | 1.21 (0.99, 1.49) | | 1.23 (1.00, 1.51) | |
| MAC equivalents | | 0.45 | | 0.57 |
| ≥0.72 | 1.07 (0.84, 1.35) | | 1.06 (0.83, 1.34) | |
| <0.72 | 0.94 (0.75, 1.18) | | 0.96 (0.77, 1.21) | |
| Duration of anesthesia (hours) | | 0.20 | | 0.18 |
| < 2 | 0.97 (0.61, 1.53) | | 0.97 (0.61, 1.53) | |
| 2-3 | 0.86 (0.66, 1.13) | | 0.86 (0.65, 1.12) | |
| 3-4 | 1.12 (0.84, 1.48) | | 1.14 (0.86, 1.52) | |
| 4-5 | 1.47 (1.03, 2.08) | | 1.48 (1.04, 2.11) | |
| ≥5 | 1.04 (0.78, 1.38) | | 1.08 (0.81, 1.44) | |

^a each observation weighted by the probability of being non-missing at one year. OR = odds ratio, CI = confidence interval, ASA = American Society of Anesthesiologists, METS = metabolic equivalents, LA = local anesthetic, BIS = bispectral index, MAC = minimum alveolar concentration.

Supplementary table 3. Odds ratios for disability or death ^a

| | n | n (%) with outcome | Univariate OR (95% CI) | P value | Multivariate ^b OR (95% CI) | P value |
|---------------------------|------|--------------------|------------------------|---------|---------------------------------------|---------|
| Age (years) | | | | <0.0005 | | <0.0005 |
| <50 | 165 | 13 (7.9) | 1.00 (reference) | | | |
| 50-59 | 837 | 74 (8.8) | 1.13 (0.61, 2.10) | | 1.12 (0.60, 2.09) | |
| 60-69 | 1591 | 132 (8.3) | 1.06 (0.58, 1.92) | | 1.03 (0.56, 1.88) | |
| 70-79 | 2330 | 258 (11.1) | 1.46 (0.81, 2.60) | | 1.33 (0.74, 2.40) | |
| ≥80 | 862 | 159 (18.4) | 2.66 (1.47, 4.81) | | 2.11 (1.15, 3.86) | |
| Sex | | | | 0.63 | | 0.14 |
| male | 3728 | 404 (10.8) | 1.00 (reference) | | | |
| female | 2057 | 232 (11.3) | 1.04 (0.88, 1.24) | | 0.87 (0.73, 1.05) | |
| Body mass index | | | | <0.0005 | | <0.0005 |
| <18.5 | 154 | 43 (27.9) | 2.33 (1.60, 3.39) | | 2.08 (1.41, 3.07) | |
| 18.5-24.9 | 1895 | 270 (14.2) | 1.00 (reference) | | | |
| 25-29.9 | 2024 | 185 (9.1) | 0.61 (0.50, 0.74) | | 0.61 (0.50, 0.75) | |
| ≥30 | 1712 | 138 (8.1) | 0.53 (0.42, 0.65) | | 0.53 (0.43, 0.67) | |
| ASA physical status | | | | <0.0005 | | 0.012 |
| 1-2 | 1784 | 170 (9.5) | 1.00 (reference) | | | |
| 3 | 3598 | 400 (11.1) | 1.19 (0.99, 1.44) | | 1.18 (0.96, 1.45) | |
| 4 | 403 | 66 (16.4) | 1.86 (1.37, 2.53) | | 1.66 (1.19, 2.33) | |
| Exercise capacity ≥4 METS | | | | <0.0005 | | <0.0005 |
| yes | 4338 | 389 (9.0) | 1.00 (reference) | | | |
| no | 1447 | 247 (17.1) | 2.08 (1.75, 2.48) | | 1.95 (1.63, 2.34) | |
| Coronary artery disease | | | | 0.62 | | 0.84 |
| yes | 2183 | 246 (11.3) | 1.00 (reference) | | | |
| no | 3602 | 390 (10.8) | 0.96 (0.81, 1.13) | | 0.98 (0.82, 1.18) | |
| Emergency surgery | | | | <0.0005 | | <0.0005 |
| no | 5542 | 582 | 1.00 (reference) | | | |

| | | | | | | |
|--------------------------------|------|------------|-------------------|---------|-------------------|---------|
| | | (10.5) | | | | |
| yes | 243 | 54 (22.2) | 2.43 (1.78, 3.33) | | 1.87 (1.34, 2.61) | |
| Vascular surgery | | | | 0.12 | | 0.003 |
| no | 3550 | 408 (11.5) | 1.00 (reference) | | | |
| yes | 2235 | 228 (10.2) | 0.87 (0.74, 1.04) | | 0.76 (0.63, 0.91) | |
| Nitrous oxide | | | | 0.40 | | 0.42 |
| no | 2915 | 311 (10.7) | 1.00 (reference) | | | |
| yes | 2869 | 325 (11.3) | 1.07 (0.91, 1.26) | | 1.07 (0.91, 1.27) | |
| Propofol maintenance | | | | 0.059 | | 0.12 |
| yes | 183 | 28 (15.3) | 1.00 (reference) | | | |
| no | 5601 | 608 (10.9) | 0.67 (0.45, 1.02) | | 0.71 (0.46, 1.09) | |
| Regional LA block | | | | 0.045 | | 0.076 |
| yes | 1590 | 196 (12.3) | 1.00 (reference) | | | |
| no | 4194 | 440 (10.5) | 0.83 (0.70, 1.00) | | 0.85 (0.70, 1.02) | |
| BIS monitoring | | | | 0.70 | | 0.58 |
| yes | 3290 | 358 (10.9) | 1.03 (0.88, 1.22) | | 1.05 (0.88, 1.25) | |
| no | 2494 | 278 (11.1) | 1.00 (reference) | | | |
| MAC equivalents | | | | 0.15 | | 0.58 |
| ≥0.72 | 2789 | 287 (10.3) | 1.00 (reference) | | | |
| <0.72 | 2794 | 322 (11.5) | 1.13 (0.96, 1.34) | | 0.94 (0.77, 1.16) | |
| Duration of anesthesia (hours) | | | | <0.0005 | | <0.0005 |
| <2 | 701 | 57 (8.1) | 1.00 (reference) | | | |
| 2-3 | 1750 | 159 (9.1) | 1.16 (0.85, 1.58) | | 1.18 (0.85, 1.63) | |
| 3-4 | 1387 | 151 (10.9) | 1.41 (1.03, 1.92) | | 1.48 (1.06, 2.05) | |
| 4-5 | 824 | 98 (11.9) | 1.59 (1.14, 2.22) | | 1.72 (1.21, 2.46) | |
| ≥5 | 921 | 144 (15.6) | 2.14 (1.55, 2.93) | | 2.32 (1.66, 3.25) | |

^a unweighted analysis. ^b preoperative variables first adjusted for each other; then nitrous oxide, propofol maintenance, regional LA block and BIS monitoring adjusted for each other and preoperative variables; then MAC value in patients receiving volatile anesthetic maintenance and duration of anesthesia adjusted for each

other, preoperative variables, nitrous oxide and BIS monitoring (propofol maintenance not included because patients who received propofol for maintenance had missing data for volatile anesthetic administration). OR = odds ratio, CI = confidence interval, ASA = American Society of Anesthesiologists, METS = metabolic equivalents, LA = local anesthetic, BIS = bispectral index, MAC = minimum alveolar concentration.

Supplementary table 4. Odds ratios for disability or death associated with the use of nitrous oxide

| Characteristic | Unweighted | | Weighted ^a | |
|---------------------------|-------------------|---------------------|-----------------------|---------------------|
| | OR (95% CI) | Interaction P value | OR (95% CI) | Interaction P value |
| Age (years) | | 0.12 | | 0.15 |
| <50 | 1.40 (0.44, 4.49) | | 1.33 (0.41, 4.36) | |
| 50-59 | 0.64 (0.39, 1.03) | | 0.63 (0.38, 1.04) | |
| 60-69 | 1.42 (0.99, 2.04) | | 1.42 (0.98, 2.05) | |
| 70-79 | 1.12 (0.87, 1.46) | | 1.10 (0.85, 1.43) | |
| ≥80 | 1.00 (0.71, 1.40) | | 1.03 (0.73, 1.46) | |
| Sex | | 0.056 | | 0.094 |
| male | 1.21 (0.99, 1.49) | | 1.19 (0.96, 1.47) | |
| female | 0.87 (0.66, 1.14) | | 0.88 (0.67, 1.17) | |
| BMI | | 0.19 | | 0.25 |
| <18.5 | 0.97 (0.48, 1.97) | | 1.09 (0.53, 2.23) | |
| 18.5-24.9 | 0.92 (0.71, 1.19) | | 0.91 (0.70, 1.19) | |
| 25-29.9 | 1.05 (0.77, 1.41) | | 1.05 (0.77, 1.43) | |
| ≥30 | 1.49 (1.05, 2.12) | | 1.44 (1.01, 2.06) | |
| ASA physical status | | 0.68 | | 0.64 |
| 1-2 | 0.96 (0.70, 1.32) | | 0.94 (0.68, 1.30) | |
| 3 | 1.11 (0.90, 1.37) | | 1.12 (0.91, 1.38) | |
| 4 | 1.21 (0.71, 2.05) | | 1.16 (0.68, 1.99) | |
| Exercise capacity ≥4 METS | | 0.27 | | 0.30 |
| yes | 1.14 (0.93, 1.41) | | 1.13 (0.92, 1.40) | |
| no | 0.94 (0.72, 1.24) | | 0.94 (0.71, 1.25) | |
| Coronary artery disease | | 0.26 | | 0.23 |
| yes | 1.21 (0.93, 1.58) | | 1.22 (0.93, 1.60) | |
| no | 1.00 (0.81, 1.23) | | 0.98 (0.79, 1.22) | |
| Emergency surgery | | 0.78 | | 0.57 |
| no | 1.07 (0.90, 1.27) | | 1.06 (0.89, 1.26) | |
| yes | 1.17 (0.64, 2.15) | | 1.28 (0.69, 2.38) | |
| Vascular surgery | | 0.27 | | 0.20 |
| no | 1.15 (0.94, 1.41) | | 1.16 (0.94, 1.43) | |
| yes | 0.95 (0.72, 1.25) | | 0.92 (0.70, 1.22) | |

| | | | | |
|--------------------------------|-------------------|-------|-------------------|------|
| Propofol maintenance | | 0.69 | | 0.72 |
| yes | 0.91 (0.41, 2.04) | | 0.92 (0.41, 2.08) | |
| no | 1.08 (0.91, 1.28) | | 1.07 (0.90, 1.27) | |
| Regional LA block | | 0.54 | | 0.37 |
| yes | 1.16 (0.86, 1.56) | | 1.20 (0.89, 1.63) | |
| no | 1.04 (0.85, 1.26) | | 1.02 (0.83, 1.24) | |
| BIS monitoring | | 0.36 | | 0.41 |
| no | 1.00 (0.80, 1.25) | | 1.01 (0.80, 1.26) | |
| yes | 1.17 (0.91, 1.50) | | 1.16 (0.90, 1.49) | |
| MAC equivalents | | 0.093 | | 0.22 |
| ≥0.72 | 1.21 (0.92, 1.60) | | 1.17 (0.88, 1.56) | |
| <0.72 | 0.87 (0.67, 1.14) | | 0.92 (0.70, 1.20) | |
| Duration of anesthesia (hours) | | 0.22 | | 0.12 |
| < 2 | 1.43 (0.84, 2.44) | | 1.45 (0.84, 2.49) | |
| 2-3 | 0.79 (0.57, 1.09) | | 0.74 (0.54, 1.03) | |
| 3-4 | 1.22 (0.88, 1.71) | | 1.26 (0.90, 1.77) | |
| 4-5 | 1.25 (0.83, 1.89) | | 1.23 (0.81, 1.87) | |
| ≥5 | 1.06 (0.75, 1.50) | | 1.09 (0.77, 1.55) | |

^a each observation weighted by the probability of being non-missing at one year. OR = odds ratio, CI = confidence interval, ASA = American Society of Anesthesiologists, METS = metabolic equivalents, LA = local anesthetic, BIS = bispectral index, MAC = minimum alveolar concentration.

Supplementary table 5. Hazard ratios for death ^a

| | Death rate (95% CI) | Univariate OR (95% CI) | P value | Multivariate ^b OR (95% CI) | P value |
|----------------------------------|--------------------------------|-----------------------------------|----------------|--|----------------|
| Age (years) | | | <0.0005 | | <0.0005 |
| <50 | 49 (25, 99) | 1.00 (reference) | | | |
| 50-59 | 57 (43, 76) | 1.14 (0.54, 2.41) | | 1.13 (0.54, 2.41) | |
| 60-69 | 60 (50, 74) | 1.21 (0.59, 2.50) | | 1.20 (0.58, 2.47) | |
| 70-79 | 79 (68, 92) | 1.58 (0.78, 3.21) | | 1.42 (0.70, 2.89) | |
| ≥80 | 142 (118, 171) | 2.79 (1.36, 5.72) | | 2.14 (1.04, 4.40) | |
| Sex | | | 0.72 | | 0.19 |
| male | 78 (69, 87) | 1.00 (reference) | | | |
| female | 81 (69, 95) | 1.04 (0.85, 1.26) | | 0.87 (0.71, 1.07) | |
| Body mass index | | | <0.0005 | | <0.0005 |
| <18.5 | 307 (224, 420) | 2.52 (1.79, 3.55) | | 2.19 (1.55, 3.10) | |
| 18.5-24.9 | 120 (105, 137) | 1.00 (reference) | | | |
| 25-29.9 | 56 (46, 68) | 0.47 (0.38, 0.60) | | 0.49 (0.39, 0.61) | |
| ≥30 | 44 (35, 56) | 0.38 (0.29, 0.49) | | 0.38 (0.29, 0.50) | |
| ASA physical status | | | <0.0005 | | <0.0005 |
| 1-2 | 71 (59, 85) | 1.00 (reference) | | | |
| 3 | 76 (67, 86) | 1.08 (0.87, 1.34) | | 1.22 (0.97, 1.54) | |
| 4 | 144 (110, 188) | 2.04 (1.48, 2.82) | | 2.24 (1.58, 3.17) | |
| Exercise capacity ≥4 METS | | | <0.0005 | | 0.009 |
| yes | 71 (63, 79) | 1.00 (reference) | | | |
| no | 104 (88, 123) | 1.47 (1.20, 1.80) | | 1.33 (1.07, 1.64) | |
| Coronary artery disease | | | 0.37 | | 0.41 |
| yes | 74 (63, 87) | | | | |

| | | | | | |
|--------------------------------|----------------|-------------------|---------|-------------------|---------|
| no | 82 (73, 92) | 1.09 (0.90, 1.33) | | 1.09 (0.89, 1.34) | |
| Emergency surgery | | | <0.0005 | | 0.001 |
| no | 75 (68, 82) | 1.00 (reference) | | | |
| yes | 189 (139, 257) | 2.51 (1.81, 3.47) | | 1.79 (1.28, 2.50) | |
| Vascular surgery | | | 0.018 | | <0.0005 |
| no | 86 (77, 97) | 1.00 (reference) | | | |
| yes | 67 (57, 79) | 0.79 (0.64, 0.96) | | 0.68 (0.55, 0.84) | |
| Nitrous oxide | | | 0.19 | | 0.16 |
| no | 74 (64, 85) | 1.00 (reference) | | | |
| yes | 84 (74, 96) | 1.13 (0.94, 1.37) | | 1.14 (0.95, 1.38) | |
| Propofol maintenance | | | 0.079 | | 0.077 |
| yes | 122 (80, 188) | 1.00 (reference) | | | |
| no | 78 (70, 85) | 0.67 (0.43, 1.05) | | 0.66 (0.42, 1.05) | |
| Regional LA block | | | 0.087 | | 0.16 |
| yes | 90 (76, 106) | 1.00 (reference) | | | |
| no | 75 (67, 84) | 0.84 (0.68, 1.03) | | 0.86 (0.70, 1.06) | |
| BIS monitoring | | | 0.19 | | 0.63 |
| yes | 83 (73, 94) | 0.88 (0.73, 1.06) | | 0.95 (0.78, 1.16) | |
| no | 73 (63, 85) | 1.00 (reference) | | | |
| MAC equivalents | | | 0.032 | | 0.56 |
| ≥0.72 | 67 (58, 78) | 1.00 (reference) | | | |
| <0.72 | 89 (78, 101) | 1.24 (1.02, 1.50) | | 1.07 (0.85, 1.35) | |
| Duration of anesthesia (hours) | | | 0.046 | | <0.0005 |
| <2 | 49 (35, 69) | 1.00 (reference) | | | |
| 2-3 | 56 (45, 68) | 0.93 (0.63, 1.37) | | 1.16 (0.78, 1.72) | |

| | | | | | |
|-----|----------------|-------------------|--|-------------------|--|
| 3-4 | 73 (60, 89) | 1.06 (0.72, 1.56) | | 1.50 (1.01, 2.23) | |
| 4-5 | 94 (75, 118) | 1.29 (0.87, 1.93) | | 1.97 (1.30, 2.97) | |
| ≥5 | 144 (121, 172) | 1.34 (0.92, 1.95) | | 2.89 (1.97, 4.25) | |

^a unweighted analysis. ^b preoperative variables first adjusted for each other; then nitrous oxide, propofol maintenance, regional LA block and BIS monitoring adjusted for each other and preoperative variables; then MAC value in patients receiving volatile anesthetic maintenance and duration of anesthesia adjusted for each other, preoperative variables, nitrous oxide and BIS monitoring (propofol maintenance not included because patients who received propofol for maintenance had missing data for volatile anesthetic administration). OR = odds ratio, CI = confidence interval, ASA = American Society of Anesthesiologists, METS = metabolic equivalents, LA = local anesthetic, BIS = bispectral index, MAC = minimum alveolar concentration.

Supplementary table 6. Hazard ratios for death associated with the use of nitrous oxide

| Characteristic | Unweighted | | Weighted ^a | |
|---------------------------|-------------------|---------------------|-----------------------|---------------------|
| | HR (95% CI) | Interaction P value | HR (95% CI) | Interaction P value |
| Age (years) | | 0.182 | | 0.158 |
| <50 | 1.45 (0.35, 6.07) | | 1.20 (0.28, 5.17) | |
| 50-59 | 0.62 (0.34, 1.12) | | 0.64 (0.35, 1.18) | |
| 60-69 | 1.53 (1.01, 2.31) | | 1.66 (1.09, 2.52) | |
| 70-79 | 1.11 (0.82, 1.49) | | 1.10 (0.82, 1.49) | |
| ≥80 | 1.18 (0.81, 1.71) | | 1.23 (0.85, 1.80) | |
| Sex | | 0.140 | | 0.203 |
| male | 1.26 (1.00, 1.60) | | 1.28 (1.00, 1.63) | |
| female | 0.94 (0.69, 1.28) | | 0.99 (0.72, 1.35) | |
| BMI | | 0.285 | | 0.274 |
| <18.5 | 1.07 (0.57, 2.01) | | 1.20 (0.63, 2.31) | |
| 18.5-24.9 | 1.04 (0.79, 1.37) | | 1.06 (0.80, 1.39) | |
| 25-29.9 | 1.01 (0.69, 1.46) | | 1.02 (0.70, 1.49) | |
| ≥30 | 1.72 (1.07, 2.77) | | 1.77 (1.10, 2.87) | |
| ASA physical status | | 0.679 | | 0.682 |
| 1-2 | 0.99 (0.69, 1.42) | | 1.01 (0.70, 1.46) | |
| 3 | 1.19 (0.94, 1.52) | | 1.23 (0.96, 1.57) | |
| 4 | 1.23 (0.72, 2.10) | | 1.23 (0.71, 2.15) | |
| Exercise capacity ≥4 METS | | 0.035 | | 0.053 |
| yes | 1.30 (1.03, 1.63) | | 1.31 (1.04, 1.66) | |
| no | 0.84 (0.60, 1.17) | | 0.87 (0.63, 1.22) | |
| Coronary artery disease | | 0.553 | | 0.497 |
| yes | 1.22 (0.89, 1.68) | | 1.27 (0.92, 1.74) | |
| no | 1.08 (0.86, 1.37) | | 1.10 (0.87, 1.40) | |
| Emergency surgery | | 0.999 | | 0.681 |
| no | 1.14 (0.94, 1.39) | | 1.15 (0.94, 1.41) | |
| yes | 1.14 (0.61, 2.12) | | 1.33 (0.69, 2.56) | |
| Vascular surgery | | 0.835 | | 0.843 |
| no | 1.15 (0.91, 1.44) | | 1.17 (0.93, 1.48) | |
| yes | 1.10 (0.79, 1.52) | | 1.13 (0.81, 1.57) | |

| | | | | |
|--------------------------------|-------------------|-------|-------------------|-------|
| Propofol maintenance | | 0.647 | | 0.621 |
| yes | 1.39 (0.57, 3.40) | | 1.45 (0.59, 3.56) | |
| no | 1.12 (0.92, 1.36) | | 1.15 (0.94, 1.40) | |
| Regional LA block | | 0.716 | | 0.647 |
| yes | 1.19 (0.85, 1.68) | | 1.24 (0.88, 1.76) | |
| no | 1.11 (0.88, 1.39) | | 1.13 (0.90, 1.42) | |
| BIS monitoring | | 0.245 | | 0.314 |
| no | 1.04 (0.81, 1.32) | | 1.07 (0.84, 1.37) | |
| yes | 1.30 (0.96, 1.76) | | 1.31 (0.97, 1.78) | |
| MAC equivalents | | 0.026 | | 0.065 |
| ≥0.72 | 1.27 (0.92, 1.76) | | 1.25 (0.90, 1.75) | |
| <0.72 | 0.78 (0.59, 1.03) | | 0.83 (0.62, 1.11) | |
| Duration of anesthesia (hours) | | 0.345 | | 0.276 |
| < 2 | 0.91 (0.47, 1.77) | | 0.94 (0.48, 1.84) | |
| 2-3 | 0.86 (0.58, 1.28) | | 0.84 (0.56, 1.26) | |
| 3-4 | 1.48 (0.99, 2.21) | | 1.54 (1.02, 2.32) | |
| 4-5 | 1.35 (0.85, 2.12) | | 1.36 (0.86, 2.16) | |
| ≥5 | 1.10 (0.78, 1.56) | | 1.17 (0.82, 1.66) | |

^a each observation weighted by the probability of being non-missing at one year. HR = hazard ratio, CI = confidence interval, ASA = American Society of Anesthesiologists, METS = metabolic equivalents, LA = local anesthetic, BIS = bispectral index, MAC = minimum alveolar concentration.

Supplementary table 7. Odds ratios for myocardial infarction ^a

| | n | n (%) with outcome | Univariate OR (95% CI) | P value | Multivariate ^b OR (95% CI) | P value |
|---------------------------|------|--------------------|------------------------|---------|---------------------------------------|---------|
| Age (years) | | | | <0.0005 | | <0.0005 |
| <50 | 161 | 9 (5.6) | 1.00 (reference) | | | |
| 50-59 | 815 | 44 (5.4) | 0.96 (0.46, 2.02) | | 0.91 (0.43, 1.92) | |
| 60-69 | 1549 | 133 (8.6) | 1.59 (0.79, 3.18) | | 1.42 (0.71, 2.87) | |
| 70-79 | 2239 | 203 (9.1) | 1.68 (0.85, 3.35) | | 1.56 (0.78, 3.13) | |
| ≥80 | 821 | 120 (14.6) | 2.89 (1.44, 5.82) | | 2.31 (1.14, 4.69) | |
| Sex | | | | 0.64 | | 0.17 |
| male | 3596 | 323 (9.0) | 1.00 (reference) | | | |
| female | 1989 | 186 (9.4) | 1.05 (0.87, 1.26) | | 1.15 (0.94, 1.41) | |
| Body mass index | | | | 0.28 | | 0.23 |
| <18.5 | 135 | 15 (11.1) | 1.12 (0.64, 1.96) | | 1.04 (0.59, 1.85) | |
| 18.5-24.9 | 1784 | 179 (10.0) | 1.00 (reference) | | | |
| 25-29.9 | 1981 | 167 (8.4) | 0.83 (0.66, 1.03) | | 0.80 (0.64, 1.00) | |
| ≥30 | 1685 | 148 (8.8) | 0.86 (0.69, 1.08) | | 0.85 (0.67, 1.08) | |
| ASA physical status | | | | <0.0005 | | <0.0005 |
| 1-2 | 1717 | 82 (4.8) | 1.00 (reference) | | | |
| 3 | 3481 | 358 (10.3) | 2.28 (1.78, 2.93) | | 1.82 (1.40, 2.36) | |
| 4 | 387 | 69 (17.8) | 4.33 (3.07, 6.09) | | 2.89 (2.00, 4.16) | |
| Exercise capacity ≥4 METS | | | | <0.0005 | | 0.001 |
| yes | 4196 | 328 (7.8) | 1.00 (reference) | | | |
| no | 1389 | 181 (13.0) | 1.77 (1.46, 2.14) | | 1.40 (1.15, 1.71) | |
| Coronary artery disease | | | | <0.0005 | | <0.0005 |
| yes | 2118 | 260 (12.3) | 1.00 (reference) | | | |
| no | 3467 | 249 (7.2) | 0.55 (0.46, 0.66) | | 0.66 (0.54, 0.80) | |
| Emergency surgery | | | | 0.024 | | 0.062 |
| no | 5361 | 479 (8.9) | 1.00 (reference) | | | |
| yes | 224 | 30 (13.4) | 1.58 (1.06, 2.34) | | 1.48 (0.98, 2.23) | |
| Vascular surgery | | | | <0.0005 | | <0.0005 |

| | | | | | | |
|--------------------------------|------|------------|-------------------|---------|-------------------|---------|
| no | 3414 | 256 (7.5) | 1.00 (reference) | | | |
| yes | 2171 | 253 (11.7) | 1.63 (1.36, 1.95) | | 1.43 (1.18, 1.74) | |
| Nitrous oxide | | | | 0.62 | | 0.71 |
| no | 2815 | 262 (9.3) | 1.00 (reference) | | | |
| yes | 2769 | 246 (8.9) | 0.95 (0.80, 1.15) | | 0.97 (0.80, 1.16) | |
| Propofol maintenance | | | | 0.19 | | 0.31 |
| yes | 176 | 21 (11.9) | 1.00 (reference) | | | |
| no | 5408 | 487 (9.0) | 0.73 (0.46, 1.17) | | 0.78 (0.48, 1.26) | |
| Regional LA block | | | | <0.0005 | | <0.0005 |
| yes | 1528 | 174 (11.4) | 1.00 (reference) | | | |
| no | 4056 | 334 (8.2) | 0.70 (0.58, 0.85) | | 0.69 (0.57, 0.85) | |
| BIS monitoring | | | | 0.001 | | 0.15 |
| no | 2419 | 253 (8.0) | 1.00 (reference) | | | |
| yes | 3165 | 255 (10.5) | 1.36 (1.13, 1.63) | | 1.15 (0.95, 1.39) | |
| MAC equivalents | | | | 0.82 | | 0.48 |
| ≥0.72 | 2700 | 247 (9.1) | 1.00 (reference) | | | |
| <0.72 | 2688 | 240 (8.9) | 0.98 (0.81, 1.18) | | 0.92 (0.73, 1.16) | |
| Duration of anesthesia (hours) | | | | <0.0005 | | <0.0005 |
| <2 | 677 | 40 (5.9) | 1.00 (reference) | | | |
| 2-3 | 1700 | 131 (7.7) | 1.29 (0.90, 1.85) | | 1.36 (0.94, 1.98) | |
| 3-4 | 1342 | 113 (8.4) | 1.53 (1.06, 2.20) | | 1.52 (1.04, 2.23) | |
| 4-5 | 795 | 79 (9.9) | 1.73 (1.17, 2.55) | | 1.89 (1.26, 2.84) | |
| ≥5 | 874 | 124 (14.2) | 2.62 (1.82, 3.77) | | 3.01 (2.05, 4.41) | |

^a unweighted analysis. ^b preoperative variables first adjusted for each other; then nitrous oxide, propofol maintenance, regional LA block and BIS monitoring adjusted for each other and preoperative variables; then MAC value in patients receiving volatile anesthetic maintenance and duration of anesthesia adjusted for each other, preoperative variables, nitrous oxide and BIS monitoring (propofol maintenance not included because patients who received propofol for maintenance had missing data for volatile anesthetic administration). OR = odds ratio, CI = confidence interval, ASA = American Society of Anesthesiologists, METS = metabolic equivalents, LA = local anesthetic, BIS = bispectral index, MAC = minimum alveolar concentration.

Supplementary table 8. Odds ratios for myocardial infarction associated with the use of nitrous oxide

| Characteristic | Unweighted | | Weighted ^a | |
|---------------------------|-------------------|---------------------|-----------------------|---------------------|
| | OR (95% CI) | Interaction P value | OR (95% CI) | Interaction P value |
| Age (years) | | 0.12 | | 0.087 |
| <50 | 1.08 (0.28, 4.19) | | 1.15 (0.29, 4.51) | |
| 50-59 | 0.86 (0.47, 1.58) | | 0.91 (0.49, 1.69) | |
| 60-69 | 1.43 (1.00, 2.05) | | 1.46 (1.02, 2.10) | |
| 70-79 | 0.76 (0.57, 1.02) | | 0.75 (0.56, 1.00) | |
| ≥80 | 0.95 (0.64, 1.40) | | 0.95 (0.65, 1.41) | |
| Sex | | 0.81 | | 0.91 |
| male | 0.97 (0.77, 1.22) | | 0.97 (0.77, 1.22) | |
| female | 0.93 (0.68, 1.25) | | 0.95 (0.70, 1.28) | |
| BMI | | 0.27 | | 0.29 |
| <18.5 | 0.90 (0.31, 2.65) | | 0.94 (0.32, 2.77) | |
| 18.5-24.9 | 1.00 (0.74, 1.37) | | 1.01 (0.74, 1.38) | |
| 25-29.9 | 0.75 (0.54, 1.03) | | 0.75 (0.54, 1.04) | |
| ≥30 | 1.18 (0.84, 1.65) | | 1.18 (0.84, 1.66) | |
| ASA physical status | | 0.36 | | 0.39 |
| 1-2 | 0.93 (0.60, 1.45) | | 0.93 (0.60, 1.46) | |
| 3 | 0.90 (0.72, 1.12) | | 0.91 (0.73, 1.13) | |
| 4 | 1.36 (0.81, 2.29) | | 1.35 (0.80, 2.29) | |
| Exercise capacity ≥4 METS | | 0.37 | | 0.37 |
| yes | 0.89 (0.71, 1.11) | | 0.90 (0.71, 1.12) | |
| no | 1.06 (0.77, 1.45) | | 1.07 (0.78, 1.46) | |
| Coronary artery disease | | 0.76 | | 0.87 |
| yes | 0.99 (0.76, 1.28) | | 0.98 (0.76, 1.27) | |
| no | 0.93 (0.72, 1.21) | | 0.95 (0.74, 1.24) | |
| Emergency surgery | | 0.99 | | 0.81 |
| no | 0.95 (0.79, 1.15) | | 0.96 (0.79, 1.16) | |
| yes | 0.96 (0.44, 2.07) | | 1.06 (0.49, 2.30) | |
| Vascular surgery | | 0.95 | | 0.94 |

| | | | | |
|--------------------------------|-------------------|-------|-------------------|-------|
| no | 0.95 (0.74, 1.23) | | 0.96 (0.74, 1.24) | |
| yes | 0.96 (0.74, 1.25) | | 0.97 (0.74, 1.26) | |
| Propofol maintenance | | 0.41 | | 0.61 |
| yes | 0.65 (0.26, 1.63) | | 0.75 (0.29, 1.94) | |
| no | 0.97 (0.80, 1.17) | | 0.97 (0.80, 1.17) | |
| Regional LA block | | 0.86 | | 0.94 |
| yes | 0.98 (0.71, 1.34) | | 0.97 (0.71, 1.33) | |
| no | 0.94 (0.75, 1.18) | | 0.96 (0.76, 1.20) | |
| BIS monitoring | | 0.051 | | 0.045 |
| no | 0.79 (0.61, 1.02) | | 0.79 (0.61, 1.03) | |
| yes | 1.14 (0.88, 1.48) | | 1.16 (0.89, 1.50) | |
| MAC equivalents | | 0.67 | | 0.64 |
| ≥0.72 | 0.94 (0.69, 1.29) | | 0.94 (0.68, 1.29) | |
| <0.72 | 1.04 (0.76, 1.42) | | 1.04 (0.76, 1.43) | |
| Duration of anesthesia (hours) | | 0.13 | | 0.13 |
| < 2 | 0.73 (0.39, 1.38) | | 0.72 (0.38, 1.35) | |
| 2-3 | 0.71 (0.50, 1.02) | | 0.73 (0.51, 1.04) | |
| 3-4 | 0.92 (0.64, 1.33) | | 0.92 (0.63, 1.33) | |
| 4-5 | 1.45 (0.91, 2.31) | | 1.45 (0.91, 2.33) | |
| ≥5 | 1.13 (0.78, 1.64) | | 1.15 (0.79, 1.66) | |

^a each observation weighted by the probability of being non-missing at one year. OR = odds ratio, CI = confidence interval, ASA = American Society of Anesthesiologists, METS = metabolic equivalents, LA = local anesthetic, BIS = bispectral index, MAC = minimum alveolar concentration.

Supplementary table 9. Odds ratios for stroke ^a

| | n | n (%) with outcome | Univariate OR (95% CI) | P value | Multivariate ^b OR (95% CI) | P value |
|---------------------------|------|--------------------|------------------------|---------|---------------------------------------|---------|
| Age (years) | | | | <0.0005 | | 0.007 |
| 50-59 | 809 | 9 (1.1) | 0.26 (0.12, 0.55) | | 0.34 (0.16, 0.72) | |
| 60-69 | 1529 | 25 (1.6) | 0.39 (0.23, 0.65) | | 0.47 (0.28, 0.82) | |
| 70-79 | 2206 | 43 (1.9) | 0.46 (0.29, 0.73) | | 0.55 (0.34, 0.88) | |
| ≥80 | 799 | 33 (4.1) | 1.00 (reference) | | | |
| Sex | | | | 0.24 | | 0.13 |
| male | 3447 | 65 (1.9) | 1.00 (reference) | | | |
| female | 1896 | 45 (2.4) | 1.26 (0.86, 1.85) | | 1.37 (0.91, 2.06) | |
| Body mass index | | | | 0.003 | | 0.035 |
| <18.5 | 127 | 7 (5.5) | 2.21 (0.97, 5.00) | | 1.95 (0.84, 4.55) | |
| 18.5-24.9 | 1707 | 44 (2.6) | 1.00 (reference) | | | |
| 25-29.9 | 1911 | 39 (2.0) | 0.79 (0.51, 1.22) | | 0.82 (0.52, 1.27) | |
| ≥30 | 1598 | 20 (1.3) | 0.47 (0.28, 0.80) | | 0.55 (0.32, 0.96) | |
| ASA physical status | | | | 0.036 | | 0.43 |
| 1-2 | 1648 | 25 (1.5) | 1.00 (reference) | | | |
| 3 | 3329 | 72 (2.2) | 1.44 (0.91, 2.28) | | 1.16 (0.71, 1.91) | |
| 4 | 366 | 13 (3.6) | 2.42 (1.23, 4.78) | | 1.63 (0.77, 3.42) | |
| Exercise capacity ≥4 METS | | | | 0.027 | | 0.30 |
| yes | 4023 | 73 (1.8) | 1.00 (reference) | | | |
| no | 1320 | 37 (2.8) | 1.57 (1.05, 2.34) | | 1.25 (0.82, 1.91) | |
| Coronary artery disease | | | | 0.61 | | 0.48 |
| yes | 2040 | 39 (1.9) | 1.00 (reference) | | | |
| no | 3303 | 71 (2.1) | 1.11 (0.75, 1.64) | | 1.16 (0.77, 1.77) | |
| Emergency surgery | | | | 0.36 | | 0.58 |
| no | 5141 | 104 (2.0) | 1.00 (reference) | | | |
| yes | 202 | 6 (3.0) | 1.47 (0.64, 3.40) | | 1.28 (0.54, 3.02) | |
| Vascular surgery | | | | <0.0005 | | 0.003 |
| no | 3278 | 48 (1.5) | 1.00 (reference) | | | |
| yes | 2065 | 62 (3.0) | 2.08 (1.42, 3.05) | | 1.87 (1.24, 2.82) | |

| | | | | | | |
|--------------------------------|------|-----------|-------------------|---------|-------------------|---------|
| Previous stroke/TIA | | | | <0.0005 | | <0.0005 |
| yes | 989 | 43 (4.3) | 2.91 (1.98, 4.30) | | 2.41 (1.61, 3.59) | |
| no | 4354 | 67 (1.5) | 1.00 (reference) | | | |
| Nitrous oxide | | | | 0.77 | | 0.71 |
| no | 2701 | 54 (2.0) | 1.00 (reference) | | | |
| yes | 2641 | 56 (2.1) | 1.06 (0.73, 1.54) | | 1.08 (0.73, 1.58) | |
| Propofol maintenance | | | | 0.39 | | 0.33 |
| yes | 165 | 5 (3.0) | 1.00 (reference) | | | |
| no | 5177 | 105 (2.0) | 0.67 (0.27, 1.67) | | 0.63 (0.25, 1.60) | |
| Regional LA block | | | | 0.40 | | 0.18 |
| yes | 1464 | 34 (2.3) | 1.00 (reference) | | | |
| no | 3878 | 76 (2.0) | 0.84 (0.56, 1.26) | | 0.75 (0.49, 1.14) | |
| BIS monitoring | | | | 0.14 | | 0.046 |
| no | 3024 | 70 (2.3) | 1.00 (reference) | | | |
| yes | 2318 | 40 (1.7) | 0.74 (0.50, 1.10) | | 0.66 (0.44, 0.99) | |
| MAC equivalents | | | | 0.58 | | 0.78 |
| ≥0.72 | 2575 | 50 (1.9) | 1.00 (reference) | | | |
| <0.72 | 2585 | 55 (2.1) | 1.11 (0.76, 1.64) | | 0.93 (0.58, 1.49) | |
| Duration of anesthesia (hours) | | | | 0.32 | | 0.034 |
| <2 | 658 | 14 (2.1) | 1.00 (reference) | | | |
| 2-3 | 1637 | 28 (1.7) | 0.78 (0.42, 1.46) | | 0.78 (0.40, 1.51) | |
| 3-4 | 1296 | 27 (2.1) | 0.95 (0.51, 1.80) | | 0.97 (0.50, 1.90) | |
| 4-5 | 751 | 11 (1.5) | 0.75 (0.36, 1.59) | | 0.71 (0.32, 1.61) | |
| ≥5 | 818 | 25 (3.1) | 1.34 (0.70, 2.55) | | 1.80 (0.90, 3.57) | |

^a unweighted analysis. ^b preoperative variables first adjusted for each other; then nitrous oxide, propofol maintenance, regional LA block and BIS monitoring adjusted for each other and preoperative variables; then MAC value in patients receiving volatile anesthetic maintenance and duration of anesthesia adjusted for each other, preoperative variables, nitrous oxide and BIS monitoring (propofol maintenance not included because patients who received propofol for maintenance had missing data for volatile anesthetic administration). OR = odds ratio, CI = confidence interval, ASA = American Society of Anesthesiologists, METS = metabolic equivalents, LA = local anesthetic, BIS = bispectral index, MAC = minimum alveolar concentration.

Supplementary table 10. Odds ratios for stroke associated with the use of nitrous oxide

| Characteristic | Unweighted | | Weighted ^a | |
|---------------------------|-------------------|---------------------|-----------------------|---------------------|
| | OR (95% CI) | Interaction P value | OR (95% CI) | Interaction P value |
| Age (years) | | 0.71 | | 0.71 |
| 50-59 | 0.75 (0.20, 2.82) | | 0.71 (0.19, 2.66) | |
| 60-69 | 0.82 (0.37, 1.82) | | 0.79 (0.36, 1.76) | |
| 70-79 | 1.07 (0.59, 1.96) | | 1.06 (0.58, 1.95) | |
| ≥80 | 1.45 (0.72, 2.93) | | 1.38 (0.68, 2.82) | |
| Sex | | 0.76 | | 0.76 |
| male | 1.11 (0.68, 1.81) | | 1.08 (0.66, 1.78) | |
| female | 0.99 (0.55, 1.79) | | 0.96 (0.53, 1.74) | |
| BMI | | 0.11 | | 0.098 |
| <18.5 | 0.99 (0.41, 2.40) | | 0.89 (0.36, 2.17) | |
| 18.5-24.9 | 0.83 (0.45, 1.51) | | 0.82 (0.45, 1.49) | |
| 25-29.9 | 2.14 (1.09, 4.18) | | 2.11 (1.07, 4.14) | |
| ≥30 | 0.99 (0.41, 2.40) | | 0.89 (0.36, 2.17) | |
| ASA physical status | | 0.38 | | 0.41 |
| 1-2 | 1.12 (0.51, 2.46) | | 1.12 (0.51, 2.47) | |
| 3 | 1.19 (0.74, 1.90) | | 1.15 (0.72, 1.85) | |
| 4 | 0.48 (0.14, 1.58) | | 0.48 (0.14, 1.60) | |
| Exercise capacity ≥4 METS | | 0.59 | | 0.65 |
| yes | 1.13 (0.71, 1.79) | | 1.08 (0.68, 1.73) | |
| no | 0.90 (0.47, 1.74) | | 0.90 (0.47, 1.74) | |
| Coronary artery disease | | 0.53 | | 0.52 |
| yes | 1.24 (0.66, 2.35) | | 1.22 (0.64, 2.30) | |
| no | 0.96 (0.60, 1.54) | | 0.94 (0.58, 1.50) | |
| Emergency surgery | | 0.45 | | 0.43 |
| no | 1.10 (0.74, 1.62) | | 1.07 (0.72, 1.58) | |
| yes | 0.55 (0.10, 3.08) | | 0.52 (0.09, 2.93) | |
| Vascular surgery | | 0.80 | | 0.82 |
| no | 1.00 (0.57, 1.77) | | 0.98 (0.55, 1.74) | |
| yes | 1.11 (0.67, 1.84) | | 1.07 (0.64, 1.79) | |
| Propofol maintenance | | 0.75 | | 0.76 |

| | | | | |
|--------------------------------|-------------------|------|-------------------|------|
| yes | 1.41 (0.23, 8.67) | | 1.36 (0.22, 8.34) | |
| no | 1.04 (0.71, 1.53) | | 1.01 (0.69, 1.50) | |
| Regional LA block | | 0.76 | | 0.77 |
| yes | 1.16 (0.59, 2.29) | | 1.12 (0.56, 2.22) | |
| no | 1.02 (0.65, 1.60) | | 0.99 (0.63, 1.57) | |
| BIS monitoring | | 0.32 | | 0.30 |
| no | 0.92 (0.57, 1.47) | | 0.89 (0.55, 1.43) | |
| yes | 1.37 (0.73, 2.57) | | 1.35 (0.72, 2.55) | |
| MAC equivalents | | 0.24 | | 0.25 |
| ≥0.72 | 1.29 (0.69, 2.41) | | 1.22 (0.66, 2.29) | |
| <0.72 | 0.78 (0.43, 1.40) | | 0.74 (0.41, 1.34) | |
| Duration of anesthesia (hours) | | 0.78 | | 0.77 |
| < 2 | 1.25 (0.45, 3.50) | | 1.23 (0.44, 3.45) | |
| 2-3 | 1.24 (0.59, 2.59) | | 1.17 (0.55, 2.47) | |
| 3-4 | 1.00 (0.47, 2.11) | | 0.94 (0.44, 1.99) | |
| 4-5 | 1.58 (0.51, 4.87) | | 1.65 (0.53, 5.11) | |
| ≥5 | 0.70 (0.31, 1.58) | | 0.70 (0.31, 1.58) | |

^a each observation weighted by the probability of being non-missing at one year. OR = odds ratio, CI = confidence interval, ASA = American Society of Anesthesiologists, METS = metabolic equivalents, LA = local anesthetic, BIS = bispectral index, MAC = minimum alveolar concentration

