SUPPLEMENTAL MATERIAL
Supplemental Methods

Data S1.

Cohort descriptions

DAN-MONICA

The DAN-MONICA study from the Research Center for Prevention and Health in Glostrup consists of three prospective cohorts with individuals randomly selected from eleven municipalities from the western part of the suburbs of Copenhagen, Denmark. Random sampling was based on the national population register, stratified by sex and year of birth. Cohort 1 (N=4,052; baseline survey 1982-1984) and 3 (N=1,504; 1991-1992) included inhabitants from 30 to 70 years, whereas age range for cohort 2 (N=1,624; 1986-1987) was set at 30 to 60 years. Follow-up was based on linkage to the Civil Registration System, the National Hospital Discharge Register and to the National Cause of Death Register using a unique personal identification number. At the present time, follow-up has been extended up to December 31st 2010.

https://www.thl.fi/publications/morgam/cohorts/full/denmark/den-gloa.htm

FINRISK

The FINRISK study is a large Finnish population-based survey on cardiovascular risk factors carried out every five years since 1972 by the National Public Health Institute in Helsinki, including individuals from up to six regions in eastern and south-western Finland. The cohorts were formed by random sampling based on the Nationwide Central Population Register, stratified by sex and 10-years age group. Baseline examinations were conducted in 1982 for cohort 1 (N=9,029), in 1987 for cohort 2 (N=5,811), in 1992 for cohort 3 (N=5,999), in 1997 for cohort 4 (N=8,444), and in 2002 for cohort 5 (N=9,291), respectively. Follow-up was achieved through linkage to the National Register of Cause of Death, the National Hospital Discharge Register and the National Drug Reimbursement Register. Follow-up for the cohort is completed up to December 31st 2010.

https://www.thl.fi/publications/morgam/cohorts/full/finland/fin-fina.htm

Moli-sani study

The cohort of the Moli-sani study was recruited from residents of the Molise region in Italy by multistage sampling based on the city-hall registries. First, townships were sampled in two
major areas by cluster sampling; then, within each township, individuals aged 35 years or older were selected by simple random sampling. Pregnancy at the time of recruitment, current polytrauma or coma, lack of understanding or refusal to sign the informed consent were exclusion criteria. Baseline examinations and questionnaires were administered by trained staff. Overall, 24,325 individuals were included from 2005 to 2010. Median follow-up for the total cohort was 4.2 years (with a maximum of 6.5 years) from the baseline examination until death or December 31st 2011 for those individuals who remained alive. Follow-up was achieved by record linkage to national mortality registers and hospital discharge registers.

https://moli-sani.org

Northern Sweden MONICA project
The Northern Sweden MONICA project consists of population-based surveys of individuals from the counties of Västerbotten and Norrbotten carried out every five years since 1986. Individuals were randomly selected from population registers, stratified for 10-years age group (with age range from 25 to 64 years in 1986 and 1990, and 25 to 74 years since 1994) and sex.

For every survey 250 men and 250 women were selected in each age group, totalling in 2,000 individuals for the first two surveys and 2,500 individuals from 1994 on, respectively. The participants of the 1986, 1990, and 1994 surveys were re-examined in 1999. Follow-up was achieved through linkage with the national death register and the National registers at the National Board of Health and Welfare (Cause of Death Register, Inpatient Diagnosis Register, Cancer Register, and Medication Register) as well as the MONICA stroke event and myocardial infarction registers, with endpoint diagnosis based on MORGAM criteria. Follow-up is completed until December 31st 2011.

https://www.thl.fi/publications/morgam/cohorts/full/sweden/swe-nswa.htm

https://snd.gu.se/en/catalogue/study/ext0042

Scottish Heart Health Extended Cohort (SHHEC)
The Scottish Heart Health Extended Cohort consists of two overlapping studies which share a common protocol and methods: the Scottish Heart Health Study randomly recruited men and women aged 40-59 across 22 Scottish districts in 1984-1987; Scottish MONICA similarly recruited men and women aged 25-64 in Edinburgh and North Glasgow in 1986, and in North Glasgow again in 1989, 1992 (age range 25-74 years), and in 1995 as part of the WHO MONICA Project. The cohorts comprise respondents of representative sample surveys of
the respective area. As the first sampling stage, a random sample of general practitioners was
selected based on a list of all general practitioners as the sampling frame. In the second stage,
the lists of persons registered with the selected general practitioners were used as sampling
frames. From each of these lists a sample of size proportional to the number of persons within
the target age and sex groups in the list was selected. The second stage sampling was stratified
by sex and 10-year age group. Follow-up was achieved by record linkage and extends through
2009. Of the original 18,107 individuals, complete data on 16,000 were transferred to
Helsinki in 2000 for the MORGAM collaboration and available serum and plasma to the
biomarker laboratory in Mainz/ Hamburg some years later, first for use in the MORGAM
biomarker study and then for the Biomarker for Cardiovascular Risk Assessment across
Europe (BiomarCaRE) project. A more detailed cohort description has been published
elsewhere 28. https://www.thl.fi/publications/morgam/cohorts/full/uk/unk-sco.htm

The Tromsø Study 29

The Tromsø Study is a prospective population-based health study carried out in the region of
Northern Norway with overall seven surveys taking place from 1974 to 2016. Residents of
specific age groups were invited to each survey based on the official population registry of the
municipality of Tromsø, enabling the gathering of information on the change of prevalent
diseases and risk factors in many individuals over time. The third and the fourth Tromsø
surveys, conducted in 1986/87 and 1994/95, participated in the current study. For the third
survey men aged 20-61 years, women aged 20-56 years, a randomly selected 10% sample
from the 12-19 years age group as well as a subsample, who were included in a family
intervention study, were invited, whereas for the fourth and largest survey all resident of
Tromsø aged 25 or elder were asked to participate. Analysis of the current study included all
individuals of the third survey aged 20-59 years, and all individuals from the fourth survey
who were not included from the third survey.

Follow-up for incident events was achieved by linkage to the discharge diagnosis registry at
the University Hospital of North Norway, the only hospital in the region of Tromsø, and to
the National Causes of Death Registry. Adjudication of all incident events was conducted.
Follow-up is completed up to December 31st 2010.
https://thl.fi/morgam/a/publications/cohorts/full/norway/nor-tro.htm
http://tromsoundersokelsen.uit.no/tromso/
Data S2.

Detailed outcome classification

*Incident atrial fibrillation* was defined as atrial fibrillation of any kind or duration. Self-reported diagnosis as the only information source was considered insufficient during follow-up. Clinical and death certificate diagnosis were scanned and the relevant ICD codes were 427.4 for ICD-8, 427.3 for ICD-9 and I48 for ICD-10, respectively. These codes comprise atrial fibrillation as well as atrial flutter, so that some cases classified as atrial fibrillation in this study might have actually been considered as atrial flutter.

*Incident myocardial infarction* was defined as first definite or possible fatal or non-fatal acute coronary event with or without cardiac revascularization according to MORGAM criteria\(^{30}\), excluding individuals with unstable angina pectoris in the cohort, in which angina pectoris could be reasonably separated from possible myocardial infarction (using cardiac troponin measurements).

The follow-up procedure for the assessment and validation of incident coronary events varied between the included cohorts.

In **DAN-MONICA** follow-up was achieved through linkage to the National Hospital Discharge Register (ICD codes 410 and 411 for ICD-8 and I21 and I22 for ICD-10, respectively) and the Causes of Death Register (ICD codes 410-414 for ICD-8 and I20-I25 for ICD-10, respectively).

In **FINRISK** events found in the FINMONICA or FINAMI register, two different diagnostic procedures were used. For events up to year 1996, the MONICA diagnostic category was used.

For an event to be classified as definite myocardial infarction according to MONICA criteria there had to be

- definite signs of myocardial infarction on electrocardiogram (ECG) or
- symptoms typical or atypical or inadequately described, together with probable ECG and abnormal enzymes, or
- symptoms typical and abnormal enzymes with ischaemic or non-codable ECG or ECG not available, or
- naked-eye appearance of fresh myocardial infarction and/or recent coronary occlusion found at necropsy in fatal cases.

Events were considered as a possible myocardial infarction if criteria for definite myocardial infarction were not met, but
the patient presented with typical symptoms without good evidence for another cause for the attack or

the case was fatal without good evidence for another cause of death (clinically or at autopsy).

For events from 1997 up to 2002, the AHA/WHF/ESC/CDC/NHLBI definition from year 2003 was used. For events found in the Hospital Discharge Register or the Register of Causes of Death but not in the FINMONICA or FINAMI register, and for all events after year 2002, the diagnostic classification was done using the relevant ICD-codes. For events found in the hospital discharge codes these were 410 for ICD-8/9 and 21 and I22 for ICD-10, respectively. For events identified through the Register of Causes of Death the relevant ICD codes were 410-414 for ICD-8/9 and I21-25 for ICD-10.

Coronary events occurring within 28 days of each other were considered as one event. For events found both in the Hospital Discharge register and the Register of Causes of Death, a coronary event diagnosis was given if it was found in either of them.

In the Moli-sani study potential coronary events were selected for further validation if death certificates presented one of the following as the underlying cause of death:

- ischemic heart disease (ICD-9 codes 410-414)
- sudden death (ICD-9 code 798 and 799)
- diabetes as the underlying cause of death (ICD-9 code 250) or arterial hypertension (ICD-9 codes 401-405) or other form of heart disease (ICD-codes 420-429), associated with ischemic heart disease (ICD-9 codes 410-414) as a secondary cause of death.

Furthermore, events were selected for further evaluation if hospital discharge records revealed a hospitalization with ICD-9 code 410-414.

For all cases selected for further validation, the clinical records were searched and if clinical documentation was found, the event was validated using the procedure of the AHA, WHF, ESC, CDC and NHLBI definition for epidemiology and clinical research studies. If clinical documentation for a fatal event was not available, general practitioners were asked for information and on the basis of their patient description the diagnostic category was assigned.

The Northern Sweden MONICA project used the MONICA criteria (see above) to identify definite and possible myocardial infarctions through linkage to the myocardial infarction register. The cohort was further linked to the National Cause of Death Register, the National Inpatient Diagnosis Register and the Local Diagnosis Registers. For events not found in the myocardial infarction register and for non-fatal events found in the myocardial infarction
register with diagnostic category "possible MI", the MORGAM diagnostic category was derived using the corresponding ICD-codes. For an inpatient diagnosis these were 41000, 41007, and 41099 for ICD-8-SV, 410 and 411A for ICD-9-SV and I21-23 for ICD-10-SE, respectively. The relevant ICD-codes in the National Cause of Death Register were 410 and 412-4, 41007 for ICD-8-SV and ICD-9-SV and I21-25 for ICD-10-SE.

The Scottish Heart Health Extended Cohort used the combination of diagnostic codes found in the Scottish Record Linkage System or the NHS Central Register to assess incident acute coronary events and other coronary diagnoses. The relevant ICD-codes for incident definite or possible myocardial infarction were 410 for ICD-9 and I21-23 for ICD-10, respectively. If information from the official underlying or other death certificates were used, a coding of 410-414 for ICD-9 and I20-25 for ICD-10 were considered as incident myocardial infarction events.

In the Tromsø Study adjudication of hospitalized and out-of-hospital first-ever myocardial infarction was performed by an endpoint committee consisting of experienced physicians. Medical records have been validated for all persons with a relevant cardiovascular discharge diagnosis from the hospital (including visits in out-patient clinics) and/or from the national Causes of Death Registry. For out of hospital deaths, records from pre-hospital care (ambulance service, general practitioners, nursing homes) and/or death certificate were searched for diagnostic criteria (clinical presentation, diagnostic procedures, laboratory tests, and/or autopsy). To be accepted as definite myocardial infarction in the Tromsø Study one of the following had to be present:

- typical, atypical or inadequately described symptoms + a definite new infarction in ECG recordings.
- Typical symptoms + significantly higher myocardial enzyme and/or troponin levels.
- Atypical or inadequately described symptoms + significantly higher myocardial enzyme and/or troponin levels + a probable new infarction in ECG recordings.

To be accepted as probable myocardial infarction one of the following sets of conditions was required:

- Typical, atypical, or inadequately described symptoms + a probable new infarction in ECG recordings + moderately increased myocardial enzyme and/or troponin levels.
- Typical symptoms + moderately higher myocardial enzyme and/or troponin levels.
- Atypical or inadequately described symptoms + significantly higher myocardial enzyme and/or troponin levels.
• Fatal events with insufficient evidence for definite MI but a diagnosis of death due to coronary disease on the death certificate.

• Fatal events with a diagnosis of sudden death (ICD 7:795, ICD 8: 795-796, ICD 9: 798-799, ICD 10: I46, R96, R98, R99) on the death certificate with evidence of a history of coronary heart disease or where there is no good evidence for another cause of death and no concomitant diagnosis of cancer, chronic obstructive pulmonary disease, chronic alcoholism, alcohol-related liver disease and/or acute pneumonia. Furthermore, fatal events with a diagnosis of sudden death (please see above) when no information other than a diagnosis from the Causes of Death Registry was available were also accepted as cases of incident myocardial infarction in the Tromsø Study.

*Overall mortality* was defined as mortality due to any cause during the follow-up time.

Further details of the follow-up and diagnostic procedures of each participating study have been published elsewhere.

**Data S3.**

**Supplementary statistical methods**

As outlined in the main manuscript the statistical significance of all possible second-order interactions and quadratic terms of the variables in the model was assessed and an interaction was included as additional covariate if its Bonferroni-corrected p-value was smaller than 0.05 in order to avoid non-linearity in all multivariable Cox proportional hazards models. The number of tests for these Bonferroni corrections was taken each time as the total number of estimable interactions plus the total number of estimable quadratic terms. Interactions with time since baseline were added when needed to avoid violations of the proportional hazard assumption, which were identified using the R function `cox.zph` with parameter “global” set to false. When included in an interaction, continuous variables were centered on their overall mean. In the analyses were hazard ratios for AF and MI were compared, the interactions and quadratic terms added to the AF model were also added to the MI model and vice versa. After the addition of the interactions with time, a few further changes were implemented:

(i) The interaction of MI and time since MI was added to the model with outcome AF and the interaction of AF and time since AF was added to the model with outcome MI.

(ii) All possible age interactions and the quadratic age term were tested and included in the model when the Bonferroni-corrected p-value was smaller than 0.05. The number of tests
in this Bonferroni-correction was the number of estimable age interactions plus one (to account for the quadratic age term).

(iii) In a final step, it was again assured that all interactions in the model with AF as the outcome were also present in the model with MI as the outcome. Interactions which became non-significant (p≥0.05) in both models were removed from both models.
Table S1. Characteristics of the study population by cohort.

| Cohort                      | DANMONICA | FINRISK | Moli-sani | TROMSØ | NORTHERN SWEDEN | SHHEC |
|-----------------------------|-----------|---------|-----------|--------|-----------------|-------|
| General characteristics     | N=7167    | N=33,420| N=16,136  | N=26,364| N=10,121        | N=15,155 |
| Years of baseline examinations | 1982-1992 | 1982-2002 | 2005-2010 | 1986-1995 | 1986-2009 | 1984-1995 |
| Age at baseline, years      | 50.0 (20.2) | 45.1 (21.6) | 53.6 (17.5) | 37.3 (18.6) | 47.9 (21.8) | 49.4 (12.7) |
| Men, No. (%)                | 3540 (49.4) | 15874 (47.5) | 7556 (46.8) | 12857 (48.8) | 4903 (48.4) | 7520 (49.6) |
| Cardiovascular characteristics |          |         |           |        |                 |       |
| Systolic blood pressure, mmHg | 121 (23) | 134 (26) | 137 (27) | 130 (22) | 126 (26) | 129 (26) |
| Body mass index, kg/m²      | 24.4 (5.0) | 25.8 (5.6) | 27.5 (6.1) | 23.8 (4.4) | 26.2 (5.9) | 25.3 (5.0) |
| Total cholesterol, mmol/L   | 5.7 (1.5) | 5.6 (1.5) | 5.5 (1.5) | 5.6 (1.8) | 5.8 (1.7) | 6.2 (1.6) |
| Diabetes mellitus, No. (%)  | 155 (2.2) | 1423 (4.3) | 957 (5.9) | 329 (1.2) | 329 (3.3) | 229 (1.5) |
| Daily smoker, No. (%)       | 3198 (44.6) | 8268 (24.7) | 3311 (20.5) | 10585 (40.1) | 1875 (18.5) | 5815 (38.4) |
| Antihypertensive treatment, No. (%) | 481 (6.7) | 3919 (11.7) | 4371 (27.1) | 1111 (4.2) | 1181 (11.7) | 1000 (6.6) |
| Prevalent stroke, No. (%)   | 72 (1.0) | 476 (1.4) | 97 (0.6) | 258 (1.0) | 163 (1.6) | 116 (0.8) |
| Endpoints during follow-up  |           |         |           |        |                 |       |
| Atrial fibrillation, No. (%) | 249 (3.5) | 550 (1.6) | 185 (1.1) | 849 (3.2) | 384 (3.8) | 196 (1.3) |
| Myocardial infarction, No. (%) | 405 (5.7) | 1062 (3.2) | 91 (0.6) | 1329 (5.0) | 487 (4.8) | 675 (4.5) |
| Death, No. (%)              | 1043 (14.6) | 1721 (5.1) | 245 (1.5) | 2059 (7.8) | 728 (7.2) | 1137 (7.5) |

Characteristics of the six cohorts are presented as absolute and relative frequencies for categorical variables, and medians and interquartile range for continuous variables.
Table S2. Secular trends in the association of cardiovascular risk factors with incident myocardial infarction and atrial fibrillation and the risk of sequential disease diagnosis

| Variable                                | Atrial fibrillation | Myocardial infarction |
|-----------------------------------------|---------------------|-----------------------|
|                                         | HR (95% CI)         | HR (95% CI)           |
| Age, per 5 years increase               | 1.00 (1.00 - 1.00)  | 0.99 (0.99 - 0.99)    |
| Male sex                                | 0.99 (0.98 - 1.00)  | 0.94 (0.94 - 0.95)    |
| Systolic blood pressure, per 10 mmHg   | 1.00 (1.00 - 1.00)  | 0.99 (0.99 - 0.99)    |
| Body mass index, per 5 kg/m²            | 1.00 (0.99 - 1.01)  | 0.98 (0.98 - 0.99)    |
| Total cholesterol, mmol/L              | 1.00 (0.99 - 1.00)  | 0.98 (0.98 - 0.99)    |
| Diabetes mellitus                       | 1.01 (0.99 - 1.03)  | 0.97 (0.95 - 0.98)    |
| Daily smoker                            | 0.98 (0.97 - 0.99)  | 0.96 (0.95 - 0.96)    |
| Prevalent stroke                        | 0.99 (0.96 - 1.03)  | 0.96 (0.93 - 0.98)    |
| Antihypertensive treatment              | 1.00 (0.98 - 1.01)  | 0.95 (0.94 - 0.96)    |
| Incident myocardial infarction *        | 0.98 (0.95 - 1.01)  | -                     |
| Incident atrial fibrillation *          | -                   | 0.93 (0.90 - 0.96)    |

This table shows the impact of the date of baseline examination on the strength of the association of the specific risk factors with incident atrial fibrillation or myocardial infarction (per 1 year increase). * For incident myocardial infarction/atrial fibrillation the table shows the relative risk for the subsequent diagnosis of the respective other disease over time (per 1 year increase).

Table S3. Multivariable adjusted hazard ratio for overall mortality after incident atrial fibrillation

| Variables                                | Hazard ratio (95% CI) | p-value |
|------------------------------------------|-----------------------|---------|
| Subsequent myocardial infarction         | -                     | -       |
| … overall*                               | 1.68 (1.03 - 2.74)    | 0.04    |
| … within the first 2 years after AF      | 3.27 (2.26 - 4.74)    | <0.01   |
| … 2 to 4 years after AF                  | 1.11 (0.70 - 1.75)    | 0.66    |
| … 4 to 6 years after AF                  | 1.39 (0.76 - 2.55)    | 0.29    |
| … 6 to 8 years after AF                  | 2.92 (1.11 - 7.69)    | 0.03    |
| … 8 to 10 years after AF                 | 0.90 (0.12 - 6.79)    | 0.92    |
| Age, per 5 years increase                | 1.55 (1.47 - 1.64)    | <0.01   |
| Sex (men)                                | 1.69 (1.39 - 2.06)    | <0.01   |
| Systolic blood pressure, per 10 mmHg increase | 1.04 (0.99 - 1.08)    | 0.09    |
| Body mass index, per 5 kg/m² increase    | 0.77 (0.69 - 0.86)    | <0.01   |
| Total cholesterol, per 1 mmol/L increase | 1.10 (1.03 - 1.17)    | <0.01   |
| Diabetes mellitus                        | 1.54 (1.13 - 2.10)    | <0.01   |
| Daily smoker                             | 1.67 (1.35 - 2.06)    | <0.01   |
| Antihypertensive treatment               | 1.06 (0.85 - 1.32)    | 0.62    |
| Prevalent stroke                         | 1.65 (1.20 - 2.26)    | <0.01   |

AF, atrial fibrillation; CI, confidence interval; * The reported hazard ratio is the geometric mean of the five hazard ratios: exp((log(3.27)+log(1.11)+log(1.39)+log(2.92)+log(0.90))/5) = 1.68