**Incident clinical and mortality associations of myocardial native T1 in the UK Biobank: A prospective observational study**

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**Short title:** Myocardial native T1 and incident outcomes

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**Data sharing statement**

This research was conducted using the UK Biobank resource under access application 2964. UK Biobank will make the data (including image acquisition parameters) available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any persons. All researchers will be subject to the same application process and approval criteria as specified by UK Biobank. For more details on the access procedure, see the UK Biobank website: <http://www.ukbiobank.ac.uk/register-apply>.

**Abstract**

**Background:** Cardiovascular magnetic resonancenative T1-mapping provides non-invasive, quantitative, and contrast-free myocardial characterisation. However, its predictive value in population cohorts has not been studied.

**Objectives:** We evaluated associations of native T1 with incident events in 42,308 UK Biobank participants over 3.17 (±1.53) years of prospective follow-up.

**Methods:** Native T1-mapping was performed in one midventricular short-axis slice using the Shortened Modified Look-Locker Inversion recovery technique (ShMOLLI, WIP780B) in 1.5 Tesla scanners (Siemens Healthcare). Global myocardial T1 was calculated using an automated tool. We estimated T1 associations with: (1) prevalent risk factors (diabetes, hypertension, high cholesterol); (2) prevalent and incident diseases [any cardiovascular disease (CVD), any brain disease, valvular heart disease, heart failure, non-ischaemic cardiomyopathies, cardiac arrhythmias, atrial fibrillation (AF), myocardial infarction (MI), ischaemic heart disease (IHD), stroke]; (3) mortality (all-cause, CVD, IHD). We report odds ratio (OR) or hazard ratio (HR) per standard deviation increment of T1 value with 95% confidence intervals (CIs) and corrected p-values, from logistic and Cox proportional hazard regression models.

**Results:** Higher myocardial T1 was associated with greater odds of a range of prevalent conditions (any CVD, brain disease, heart failure, non-ischaemic cardiomyopathies, AF, stroke, diabetes). The strongest relationships were with heart failure (OR=1.41;CI=1.26-1.57; p=1.60x10-9) and non-ischaemic cardiomyopathies (OR=1.40;CI=1.16-1.66; p=2.42x10-4). Native T1 was positively associated with incident AF (HR=1.25;CI=1.10-1.43; p=9.19x10-4), incident heart failure (HR=1.47;CI=1.31-1.65; p=4.79x10-11), all-cause mortality (HR=1.24;CI=1.12-1.36, p=1.51x10-5), CVD mortality (HR=1.40;CI=1.14-1.73; p=0.0014), and IHD mortality (HR=1.36;CI=1.03-1.80; p=0.0310).

**Conclusions:** In this large population cohort, we demonstrate utility of myocardial native T1-mapping for disease discrimination and outcome prediction.

**Condensed abstract**

Cardiovascular magnetic resonance(CMR) native T1-mapping provides non-invasive, quantitative, and contrast-free myocardial characterisation. However, its predictive value in population cohorts has not been studied. We evaluated associations of native T1 with incident events in 42,308 UK Biobank participants over 3.17 (±1.53) years of prospective follow-up. We demonstrate associations of myocardial native T1 with a range of prevalent diseases, incident atrial fibrillation, incident heart failure, all-cause mortality, cardiovascular mortality, and ischaemic heart disease mortality. Our findings support high clinical utility for inclusion of myocardial native T1 measurement as a routine component of CMR studies.

**Abbreviations**

Atrial fibrillation (AF)

BMI: body mass index

CI: Confidence intervals

CMR: Cardiovascular magnetic resonance

CVD: cardiovascular disease

NHS: National Health Service

HES: Hospital Episode Statistics

HR: hazard ratio

ICD: international classification of disease

IHD: ischaemic heart disease

LVH: left ventricular hypertrophy

MI: myocardial infarction

OR: odds ratios

ShMOLLI: Shortened Modified Look-Locker Inversion

**Introduction**

Cardiovascular magnetic resonance (CMR) is the reference standard for evaluation of cardiac structure and function. CMR myocardial native T1 mapping provides quantitative, non-invasive, and contrast-free characterisation of myocardial tissue on a pixel-by-pixel basis, comparable to a virtual biopsy of the living heart(1,2).

The clinical utility of myocardial native T1 mapping has been demonstrated in select clinical cohorts, particularly for the diagnosis of acute myocardial injury, myocardial inflammation, myocardial iron overload, Fabry disease, and cardiac amyloidosis(3). However, the prognostic value of native T1 in large population cohorts, without pre-existing disease, has not been previously studied.

The UK Biobank is a very large population-based cohort study including detailed CMR and prospective tracking of incident health events through linkages to routine health data(4).

We studied demographic and clinical associations of myocardial native T1 in 42,308 UK Biobank participants. Importantly, we evaluated relationships with key incident diseases and mortality outcomes.

**Methods**

**Setting and study population**

The UK Biobank is a population-based cohort of over 500,000 participants recruited between 2006-2010. Postal invitations were sent to individuals aged 40-69 years old, identified through National Health Service (NHS) registers, living within 25 miles of one of 22 UK Biobank assessment centres. Individuals who were unable to consent or complete baseline assessment due to ill health or discomfort were not recruited. At baseline recruitment (2006-2010), there was detailed characterisation of participants’ demographic and clinical status, as well as a series of physical measures and blood sampling. The UK Biobank protocol is publicly available.(5) The UK Biobank imaging study, which is ongoing, was launched in 2015 and aims to scan a random 20% subset of the original cohort(4). The imaging protocol includes detailed CMR. Linkages to national health data, such as Hospital Episode Statistics (HES) and Office for National Statistics (ONS) death registration data, permit prospective tracking of incident health events for all UK Biobank participants.

**Ethics statement**

This study complies with the Declaration of Helsinki; the work was covered by the ethical approval for UK Biobank studies from the National Health Service (NHS) National Research Ethics Service on 17th June 2011 (Ref 11/NW/0382) and extended on 18 June 2021 (Ref 21/NW/0157) with written informed consent obtained from all participants.

**CMR image acquisition and analysis**

CMR scans were performed using 1.5 Tesla scanners (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany) in dedicated imaging centres with uniform equipment and staff training. The pre-defined UK Biobank acquisition protocol is available in a separate publication(6). Myocardial native T1 mapping was acquired in one midventricular short axis slice using the Shortened Modified Look-Locker Inversion recovery technique (ShMOLLI, WIP780B)~~.~~ The typical pulse sequence parameters are as published previously by Piechnik et al(7). Global myocardial native T1 was calculated from the entire short-axis slice using a fully automated quality-controlled analysis tool, excluding studies with a predicted Dice score of <0.7; technical details of the tool, including comparison of the manual and automated T1 measures, are described elsewhere(8).

**Ascertainment of clinical and mortality outcomes**

Diseases were defined based on a combination of UK Biobank baseline assessment records and HES international classification of disease (ICD) codes (Supplementary Table 1), as per previous publications using this cohort(9). We included the following prevalent outcomes: any cardiovascular disease (CVD), any brain disease, valvular heart disease, heart failure, non-ischaemic cardiomyopathies, cardiac arrhythmias, atrial fibrillation (AF), myocardial infarction (MI), ischaemic heart disease (IHD), stroke, hypertension, diabetes, high cholesterol. Mortality outcomes were defined according to the primary cause of death ascertained from death register data. We considered the following incident events: AF, heart failure, stroke, MI, IHD, all-cause mortality, CVD mortality, IHD mortality.

**Statistical analysis**

Statistical analysis was performed using R version 4.0.3 and RStudio Version 1.3.1093. We first examined myocardial native T1 values in a subset of healthy individuals (n=19,297), stratified by age and sex. Healthy status was defined as the absence of any CVD or classic vascular risk factors (diabetes, hypertension, high cholesterol, smoking) at the time of imaging. We took age as recorded at the imaging visit and sex from self-report. Within the healthy subset, we estimated the association of T1 with age using linear regression models, separately for men and women. We observed a sex differential trend of T1 with aging within the healthy subset. Thus, subsequent models are adjusted for age, sex, and age sex.

We estimated associations of myocardial native T1 in the entire cohort with prevalent disease and incident events (incident CVDs, mortality outcomes) using logistic regression and Cox proportional hazard regression, respectively. We investigated sex and age differential relationships of the associations with incident diseases and mortality using interaction terms added to models (T1 x age; T1 x sex) and stratified analyses by sex and median age where indicated by a significant interaction term. We examined for potential non-linearity by examining associations in strata of above/below the median T1 value. Prevalent diseases were considered as those present at time of imaging. Incident events were considered as first occurrence of the disease after imaging; that is, individuals with record of an outcome of interest before the index date were excluded from the analysis of that outcome. We selected haematocrit, body mass index (BMI), and heart rate as potential confounders of myocardial native T1, as per previous work(7). BMI and average heart rate were taken from the imaging visit; haematocrit percentage was measured at baseline recruitment. In secondary analyses, we included additional adjustment for BMI, haematocrit, and heart rate. Effect estimates are expressed as odds ratios (OR) and hazard ratios (HR) per one standard deviation increment of T1, and standardised beta coefficients and 95% confidence intervals (CIs). We present p-values corrected for multiple testing using the Benjamini-Hochberg procedure(10) setting the false discovery rate to 5%. The study is reported in accordance with the STROBE statement.

**Results**

**Participant characteristics**

Myocardial native T1 was available for 42,894 participants. From these, 586 studies (0.01%) with Dice score <0.7 were excluded. Thus, 42,308 participants with analysable native T1 were included in the analysis (Supplementary Figure 1); average age was 64.0 (±7.7) years and 51.9% (n=21,963) were women. For creation of the healthy subset (n=19,297), individuals with any CVD (n=4,855) or vascular risk factors (n=18,126) were further excluded.

Within the whole sample (n=42,308), the rates of diabetes, hypertension, and high cholesterol were 6.0% (n=2,528), 33.4% (n=14,136), and 35.6% (n=15,041), respectively (Table 1). There was record of CVD for 11.5% (n=4,885) of participants. As expected, IHD was the most common CVD (6.2%, n=2,604).

Over a follow-up period of 3.17 (±1.53) years, we observed 402 (1.0%) deaths; of these, 76 were attributed to CVD and 44 to IHD (Table 1). The most common incident diseases were IHD (n=649, 1.5%) and heart failure (n=243, 0.6%). There were 241 (1.0%) incident MIs and 215 (0.5%) incident cases each of AF and stroke (Table 1).

**Myocardial native T1 in healthy participants**

Within the healthy subset, women had, on average, higher myocardial native T1 than men across all age groups (range 44-84 years), with the greatest difference at younger ages (Table 2, Figure 1). With increasing age, myocardial native T1 decreased in women (Beta= -0.33; 95% CI= -0.41, -0.24; p<0.0001) and increased in men (Beta= 0.48; CI= 0.39, 0.57; p<0.0001;Figure 1, Supplementary Table 2).

**Associations of myocardial native T1 with prevalent disease**

Within the entire cohort, higher myocardial native T1 was associated with significantly greater odds of any CVD, any brain disease, heart failure, non-ischaemic cardiomyopathies, cardiac arrhythmias, AF, stroke, and diabetes (Table 3, Central illustration). Of these, the largest effect sizes were observed with heart failure (OR= 1.41; CI= 1.26, 1.57; p<0.0001) and non-ischaemic cardiomyopathies (OR= 1.40; CI= 1.16, 1.66; p=0.0002). Hypertension and high cholesterol were associated with significantly lower myocardial native T1, with a larger effect size observed with hypertension (OR= 0.88; CI= 0.86, 0.90; p<0.0001).

**Associations of myocardial native T1 with incident disease and mortality**

Within the entire cohort, higher myocardial native T1 was associated with significantly greater hazard of incident heart failure (HR= 1.47; CI= 1.31, 1.65; p<0.0001) and incident AF (HR= 1.25, CI= 1.10, 1.43; p= 0.0009). Higher myocardial native T1 was also associated with significantly greater hazard of all-cause mortality, CVD mortality, and IHD mortality (Table 4, Central illustration). There were no statistically significant associations of native T1 with incident MI, incident IHD, or incident stroke (Table 4, Central illustration).

**Sex/age differential patterns and potential non-linearity**

Given that associations with incident disease and mortality outcomes are of the greatest clinical interest, we additionally evaluated age and sex differential dependencies of these relationships (Supplementary Table 5). There was no evidence of a sex differential relationship for any of the incident outcomes. For the mortality outcomes, we observed evidence of a significant interaction of T1 with age. Thus, for these outcomes we proceeded to examine associations with T1 stratified by median age (65 years); in doing so, we observed greater magnitude of association in older individuals (Supplementary Table 6). We additionally assessed for potential non-linearity of the associations of T1 with incident outcomes, by modelling in strata above and below the median T1 value. Overall patterns suggested that higher T1 values had stronger (larger magnitude of effect) associations with incident ouctomes (Supplementary Table 7).

**The importance of potential confounders**

Higher BMI and haematocrit were significantly associated with lower myocardial native T1, whilst faster average heart rate was associated with significantly higher native T1 (Supplementary Table 3). In models with additional confounder adjustment, all previously observed associations between higher native T1 and prevalent diseases remained robust, with additional significant relationships observed with valvular heart disease, MI, and IHD (Central illustration, Supplementary Table 4). The negative association with hypertension remained unchanged; however, the relationship with high cholesterol was attenuated. The positive association of native T1 with IHD mortality appeared stronger; relationships with other incident outcomes were unchanged (Central illustration, Supplementary Table 4).

**Discussion**

**Summary of findings**

In this large population-based cohort of 42,308 individuals, we describe associations of intrinsic myocardial tissue properties, as quantified by native T1-mapping, with key demographics, diseases, and incident health outcomes. Amongst healthy participants, women had, on average, higher global myocardial native T1 than men across all ages. There was a sex differential trend of myocardial native T1 with aging, with a significant positive association in men and a negative trend in women. In the whole sample, higher myocardial native T1 was associated with significantly greater likelihood of prevalent CVD, brain disease, heart failure, non-ischaemic cardiomyopathies, AF, stroke, and diabetes. We also observed significant positive associations between myocardial native T1 and risk of incident AF and incident heart failure. Importantly, we demonstrate significant associations of native myocardial T1 measures with all-cause mortality, CVD mortality, and IHD mortality. These relationships appeared more convincing with adjustment for potential confounders.

**Age and sex associations in healthy participants**

Within the healthy subset of 11,479 women and 7,818 men, we observed higher native T1 in women than men across all age groups. This observation is consistent with multiple previous reports in healthy cohorts(11–15). These findings may reflect genuine differences in the myocardial tissue character of men and women. Technical factors likely also play a role in augmenting any differences. In particular, the lower average wall thickness in women is expected to systematically shift the measurement error in global myocardial native T1 towards higher values through partial volume effects on magnetic resonance imaging. Indeed, previous work has described the negative associations of native T1 and myocardial thickness(7).

There are inconsistencies in existing literature on the age dependency of T1 and its variations by sex. In our study, we found that with increasing age, native T1 increased in men and decreased in women. Dong et al.(13) report no significant age trend of native T1 in 69 healthy Chinese adults. In a study of 625 women and 606 men from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, Liu et al. (12) demonstrate increasing myocardial native T1 with age in men, but no significant age-trend in women. Similarly, in a smaller study of 75 healthy individuals, Roy et al.(15) report positive association of native T1 with increasing age in men, but no significant age trend in women. However, Piechnik et al.(7) report no-age dependency of myocardial T1 in men and, similar to our observation, a declining trend of native T1 with increasing age in women. Whilst, Rosmini et al.(11) report lower native T1 with increasing age in both men and women (using MOLLI, and ShMOLLI sequences).

The heterogeneity in age-related T1 trends reported in existing literature may be influenced by several factors. Firstly, there are many technical variations in image acquisition and postprocessing between studies; this makes direct between-study comparisons difficult. Second, the small sample size in many studies limits power to detect trends that require stratification by both sex and age, may not capture more complex or subtle relationships, and has the potential to generate spurious trends. Third, to appreciate age-related trends there is need for samples which include a broad spectrum of ages, this is not always included in existing studies. Finally, the level of variation in direction of associations in existing work, suggests that the pattern of age-related myocardial alteration is not a simple linear trend which is consistent across all individuals.

Our findings, in the largest healthy cohort to date, support the positive aging trend of T1 in men (as per Liu et al.(12) in the MESA cohort), and additionally demonstrate a significant negative trend in women (similar to Piechnik et al.(7) towards the pre-menopausal stage). The sex differential age trends of native T1 in our study may indicate differences in cardiac aging patterns of men and women. They may also reflect technical factors which differentially influence measurement of T1 in men and women. Overall, it is likely that a range of biological and technical factors drive the sex differences in native T1.

**Associations with prevalent disease**

Previous work demonstrates associations of myocardial native T1 with a wide range of cardiovascular diseases in patient cohorts(3). These are mostly small studies of selected disease subtypes with highly heterogeneous methodologies, making direct comparisons challenging. Broadly, higher native T1 appears as an indicator of disease across the literature (except in myocardial iron overload, or significant myocardial fat e.g., Fabry disease, where the reverse is true). We examined these relationships in a population-based cohort, demonstrating association of higher native T1 with key prevalent diseases.

We observed strong associations of higher native T1 with prevalent heart failure and non-ischaemic cardiomyopathies. In keeping with our findings, Dass et al.(16), Puntmann et al.(17), and Puyol-Anton et al.(18) all report higher native T1 in individuals with non-ischaemic cardiomyopathies compared to healthy controls. These observations are consistent with the global myocardial remodelling characteristic of these conditions. We also found associations of higher native T1 with prevalent IHD and MI. These associations were comparatively weaker and, although the confounder adjusted models showed statistically significant relationships, the minimally adjusted models were non-significant. Previous studies indicate significantly higher myocardial native T1 in focal regions of myocardial injury compared to the remote myocardium in the setting of acute MI(19). It is likely that predominantly focal myocardial injuries in ischaemic disease are diluted within global native T1 measures.

We found higher native T1 to be linked to prevalent cardiac arrhythmias and, specifically, with prevalent AF. Previous literature on these associations is sparse, but broadly consistent. Kato et al.(20) report higher native T1 in 50 patients with paroxysmal AF compared to 11 healthy controls. Zhao et al.(21) demonstrate higher native T1 in individuals with greater AF burden in their analysis of 108 heart failure patients. In a study of patients with non-ischaemic dilated cardiomyopathy, Nakamori et al.(22) suggest links between native T1 and ventricular arrhythmias, reporting higher native T1 in patients with a history of complex ventricular arrhythmia (n=50) compared to those without (n=57).

Our findings of positive associations between native T1 and diabetes are in keeping with previous small studies demonstrating higher native T1 in people with diabetes compared to matched controls(23,24) and consistent with the pathophysiology of diabetic cardiomyopathy.

We observed significantly lower native T1 in participants with prevalent hypertension compared to those without hypertension. Previous studies report higher native T1 amongst hypertensives with LVH compared to those without LVH (25,26). Thus, existing studies make comparisons amongst cohorts of hypertensives with different remodelling patterns, whilst we compare hypertensives vs non-hypertensives. Furthermore, given that we studied a population-based cohort, our sample includes few individuals with severe hypertensive heart disease and pathologic LVH, whilst existing work is specifically focused on hypertensives with LVH. Given these fundamental differences in study design, it is not possible to make direct comparisons with our findings. Further work is required to better understand hypertension-related variations of native T1.

**Associations with incident disease**

We observed association of higher native T1 with incident AF and incident heart failure. Very few previous studies have examined the predictive value of native T1 for incident health events. In a study of 50 patients with paroxysmal AF, Kato et al.(20) report higher baseline native T1 in individuals with recurrence of AF after ablation (pulmonary vein isolation) compared to those who remained in sinus rhythm. Our findings indicate that higher native T1 is an indicator of first presentation of AF in a population setting without pre-existing AF.

**Associations with mortality**

Our findings, over 3.17 (±1.53) years of prospective follow-up, demonstrate association of native T1 with all-cause mortality, CVD mortality, and IHD mortality. Associations of native T1 with IHD mortality appeared robust, despite the previously described weaker and non-significant associations with prevalent and incident IHD, respectively. This may suggest that the cohort who died from IHD comprised a large proportion of individuals with severe pre-existing (prevalent) IHD phenotypes (scarring, heart failure). These individuals would be expected to have more extensive myocardial abnormalities detectable by T1-mapping, which would predispose to death and drive the positive associations of T1 with IHD mortality. As individuals with severe disease phenotypes only comprise a minority of the prevalent IHD cohort, their influence on associations of T1 with prevalent IHD are diluted.

Previous studies have examined association of native T1 with incident mortality outcomes within specific disease cohorts, broadly demonstrating significant associations of these outcomes with higher native T1. In the largest such study, Puntmann et al.(27) prospectively studied 637 patients with hypertrophic cardiomyopathy, reporting association of higher native T1 with all-cause mortality and a composite of heart failure mortality and hospitalisation. Qin et al.(28) also demonstrate association of higher native T1 with adverse incident outcomes (composite of CVD death, ICD placement, cardiac transplantation, myocardial infarction, heart failure hospitalization) in 203 patients with hypertrophic cardiomyopathy. Similarly, Garg et al.(29) report association of higher native T1 with all-cause mortality in a retrospective study of 86 patients with heart failure with preserved ejection fraction. Consistently, amongst 108 heart failure patients with AF, Zhao et al.(21) report higher native T1 in patients who experienced an adverse event (composite of cardiac death, stroke, and heart failure hospitalisation) compared to those who did not. Furthermore, Martinez-Naharro et al.(30) observed association of higher native T1 with all-cause mortality in 227 patients with transthyretin amyloidosis, although this relationship was attenuated after adjustment for age. Our study adds important information to existing work, by demonstrating extension of these T1-mortality associations to predominantly healthy population cohorts.

Our findings demonstrate age differential pattern of T1-mortality relationships, with higher T1 values having stronger associations with the mortality outcomes in older ages. Furthermore, our results suggest potential non-linearity of T1 associations with both incident disease and mortality outcomes; indicating that the magnitude of T1 associations with these outcomes were increased with higher T1 values. We advise cautious interpretation of these findings given the small number of incident events in these stratified analyses. Further studies in larger samples and with longer follow-up are required to draw more definitive conclusions.

**Clinical Implications**

CMR is a key research and clinical tool providing non-invasive evaluation of cardiac structure and function. Myocardial native T1 measurement allows non-invasive assessment of myocardial tissue, providing a quantitative measure of increased free water content that can characterise abnormal myocyte pathophysiology and interstitial remodelling. Myocardial native T1 instils the impact of a multitude of local and systemic cardiovascular stressors on the myocardium into a single metric. Increased native T1 has been described in a range of non-ischaemic and ischaemic cardiomyopathies(3), including hypertrophic cardiomyopathy(31), dilated cardiomyopathy(32) and cardiac amyloid(30), whilst reduced native T1 is characteristic of Fabry disease(33) and iron overload(34).

In this study, we importantly extend existing observations in clinical cohorts to a population-based setting, demonstrating the value of myocardial native T1 for disease discrimination and outcome prediction in a very large predominantly healthy population cohort. Our findings support high clinical utility for inclusion of myocardial native T1 measurement as a routine component of CMR studies. There is now need for validation of these relationships in other large cohorts followed by concerted efforts towards standardisation of native T1-mapping techniques, which will underpin widespread clinical implementation. Furthermore, our studies lend additional weight to novel non-gadolinium machine learning-based approaches that assess myocardial scar and fibrosis that are largely based on native T1, such as the recently reported virtual native enhancement method(35).

**Strengths and limitations**

The large study sample, uniform standardised image acquisition and analysis, and linked health data in the UK Biobank provided an ideal platform for the present study. Ascertainment of mortality outcomes through data linkage with death register data is highly reliable. Similarly, incident diseases such as MI and stroke are reliably ascertained through HES records. We demonstrated sex-differential trends of T1 with aging amongst healthy participants. However, the narrow age range within our sample (44-84 years at the time of imaging) precluded examination of trends across the whole spectrum of ages; this is a particular limitation when evaluating relationships in women in whom the onset of menopause may alter the trajectory of myocardial alterations. Furthermore, we were underpowered to adequately assess sex-specific disease associations, which have relevance given major heterogeneities in CVD patterns in men and women. The purpose of this study is to provide a broad overview of clinical associations of native T1; it is possible that the observed relationships may have specificity within disease subtypes, and future work dedicated to elucidating these more granular associations is required. As outcomes accrue in the UK Biobank, it will be possible to examine more disease specific associations and to consider relationships in sex-stratified models. The reported findings have been derived from a fraction of the planned UK Biobank cohort, pending confirmation on the complete total 100,000 studies, including possible use of independent methods for automatic segmentation, e.g. Puyol-Anton et al.(17).The UK Biobank CMR protocol does not include contrast administration; as such, broader comparison of our findings with tissue characterisation methods requiring contrast, such as late gadolinium enhancement or extracellular volume (ECV), was not possible. Another key question for future work is to determine whether native T1 measurement provides incremental risk information over existing standard morphological CMR metrics. Finally, these modern in-vivo T1 measurements are subject to multiple confounders and great care needs to be exercised when applying the observations to other techniques until the ongoing standardization effort is successfully completed(36).

**Conclusions**

In this large population cohort of 42,308 UK Biobank participants, we demonstrate significant associations of intrinsic properties of the living myocardial tissue, as measured by myocardial native T1, with a wide range of prevalent and incident CVDs. Critically, we demonstrate novel associations of myocardial T1 with all-cause mortality, CVD mortality, and IHD mortality. Our findings support wider use of myocardial native T1 in routine clinical practice.

**Clinical perspectives**

**Competency in medical knowledge**

In this analysis of 42,308 UK Biobank participants, we illustrate associations of higher native T1 with a range of cardiovascular risk factors and diseases. Importantly, we demonstrate the value of native T1 as a reliable indicator of incident cardiovascular disease and mortality outcomes in a predominantly healthy population-based cohort.

**Translational outlook**

Our findings significantly extend the remit of native T1 outside of very specific diseases contexts (reported in previous work) into wider populations. Our results support clinical utility for wider use of native T1 sequences and their inclusion in routine CMR protocols. Given this hugely expanded remit, there is now urgent need for standardisation of native T1 techniques to establish universal reference distributions and to ensure globally comparability.

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**Table 1. Participant characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Whole set** | **Men** | **Women** |
| Number of participants | 42,308 | 20,345 (48%) | 21,963 (52%) |
| Age at imaging (years) | 64.0 (±7.7) | 64.8 (±7.8) | 63.4 (±7.6) |
| Body mass index (kg/m2) | 25.9 [23.5, 28.8] | 26.4 [24.3, 29.0] | 25.2 [22.7, 28.5] |
| Heart rate (bpm) | 62.6 (±10.5) | 61.5 (±10.7) | 63.7 (±10.2) |
| Haematocrit (%) | 41.1 (±3.5) | 43.3 (±2.8) | 39.0 (±2.7) |
| Myocardial native T1 (ms) | 932.3 (±35.7) | 919.6 (±33.0) | 943.9 (±34.0) |
| **Prevalent disease** |  |  |  |
| Hypertension | 14,136 (33.4%) | 8,231 (40.5%) | 5,905 (26.9%) |
| Diabetes | 2,528 (6.0%) | 1,606 (7.9%) | 922 (4.2%) |
| High cholesterol | 15,041 (35.6%) | 8,683 (42.7%) | 6,358 (28.9%) |
| Any cardiovascular disease | 4,885 (11.5%) | 3,070 (15.1%) | 1,815 (8.3%) |
| Any brain disease | 2,967 (7.0%) | 1,541 (7.6%) | 1,426 (6.5%) |
| Valvular heart disease | 802 (1.9%) | 409 (2.0%) | 393 (1.8%) |
| Heart failure | 278 (0.7%) | 220 (1.1%) | 58 (0.3%) |
| Non-ischaemic cardiomyopathies | 104 (0.2%) | 74 (0.4%) | 30 (0.1%) |
| Cardiac arrhythmias | 2,271 (5.4%) | 1,397 (6.9%) | 874 (4.0%) |
| Atrial fibrillation | 753 (1.8%) | 534 (2.6%) | 219 (1.0%) |
| Myocardial infarction | 1,061 (2.5%) | 854 (4.2%) | 207 (0.9%) |
| Ischaemic heart disease | 2,604 (6.2%) | 1,851 (9.1%) | 753 (3.4%) |
| Stroke | 852 (2.0%) | 568 (2.8%) | 284 (1.3%) |
| **Incident events** |  |  |  |
| Incident cardiovascular disease (any) | 1,256 (3.0%) | 788 (3.9%) | 468 (2.1%) |
| Incident atrial fibrillation | 215 (0.5%) | 145 (0.7%) | 70 (0.3%) |
| Incident stroke | 215 (0.5%) | 132 (0.6%) | 83 (0.4%) |
| Incident myocardial infarction | 241 (0.6%) | 169 (0.8%) | 72 (0.3%) |
| Incident ischaemic heart disease | 649 (1.5%) | 430 (2.1%) | 219 (1.0%) |
| Incident heart failure | 243 (0.6%) | 162 (0.8%) | 81 (0.4%) |
| All-cause mortality | 402 (1.0%) | 263 (1.3%) | 139 (0.6%) |
| Cardiovascular disease mortality | 76 (0.2%) | 56 (0.3%) | 20 (0.1%) |
| Ischaemic heart disease mortality | 44 (0.1%) | 36 (0.2%) | 8 (0.0%) |

**Table 1 footnote.** Continuous variables are summarised as mean (±standard deviation) or median [interquartile range], depending on skew. Count variables are expressed as number (percentage).

**Table 2. Global myocardial native T1 in healthy men and women stratified by age**

|  |  |  |
| --- | --- | --- |
| **Age group (years)** | **Mean (SD) global myocardial T1 (ms)** | |
|  | **Women (n= 11,479)** | **Men (n= 7,818)** |
| 44-45 | 952.1 (35.0) | 913.2 (31.2) |
| 55-64 | 945.3 (33.1) | 917.2 (31.1) |
| 65-74 | 944.8 (33.5) | 921.2 (32.6) |
| 75-84 | 944.5 (33.1) | 926.4 (31.9) |
| Overall mean | 946.6 (33.7) | 918.3 (31.9) |

**Table 2 footnote.** ms: milliseconds; SD: standard deviation.

**Table 3. Associations of myocardial native T1 with prevalent disease**

|  |  |  |
| --- | --- | --- |
|  | **OR [95% CI]** | **p-value** |
| Any cardiovascular disease | 1.04\* [1.00, 1.07] | 0.0260 |
| Any brain disease | 1.11\* [1.07, 1.16] | <0.0001 |
| Valvular heart disease | 1.04 [0.96, 1.12] | 0.3094 |
| Heart failure | 1.41\* [1.26, 1.57] | <0.0001 |
| Non-ischaemic cardiomyopathies | 1.40\* [1.16, 1.66] | 0.0002 |
| Cardiac arrhythmias | 1.15\* [1.10, 1.20] | <0.0001 |
| Atrial fibrillation | 1.22\* [1.13, 1.31] | <0.0001 |
| Myocardial infarction | 1.05 [0.99, 1.12] | 0.1243 |
| Ischaemic heart disease | 0.98 [0.93, 1.02] | 0.2839 |
| Stroke | 1.13\* [1.06, 1.22] | 0.0005 |
| Hypertension | 0.88\* [0.86, 0.90] | <0.0001 |
| Diabetes | 1.13\* [1.08, 1.18] | <0.0001 |
| High cholesterol | 0.95\* [0.93, 0.98] | <0.0001 |

**Table 3 footnote.** Results are from logistic regression models with diseases of interest set as the model outcome (response variable), native T1 is the exposure of interest, and there is adjustment for age, sex, and age x sex. The effect estimates as expressed as OR per 1 SD increase in T1 (i.e., change in odds of outcome per 1SD=35.7ms increment in native T1) with corresponding 95% CI and p-values. CI: confidence interval; OR: odds ratio; SD: standard deviation. T1 \*Indicates statistically significant result following multiple testing adjustment with a false discovery rate of 0.05.

**Table 4. Associations of myocardial native T1 with incident events**

|  |  |  |
| --- | --- | --- |
|  | **HR [95% CI]** | **p-value** |
| Incident CVD (any) | 1.11\* [1.05, 1.17] | 0.0005 |
| Incident atrial fibrillation | 1.25\* [1.10, 1.43] | 0.0009 |
| Incident stroke | 1.12 [0.97, 1.28] | 0.1191 |
| Incident ischaemic heart disease | 1.00 [0.92, 1.08] | 0.9368 |
| Incident myocardial infarction | 0.91 [0.80, 1.05] | 0.1871 |
| Incident heart failure | 1.47\* [1.31, 1.65] | <0.0001 |
| All-cause mortality | 1.24\* [1.12, 1.36] | <0.0001 |
| Cardiovascular disease mortality | 1.40\* [1.14, 1.73] | 0.0014 |
| Ischaemic heart disease mortality | 1.36\* [1.03, 1.80] | 0.0310 |

**Table 4 footnote.** Results are from Cox proportional hazard regression models with outcomes of interest set as the model outcome (response variable), native T1 is the exposure of interest, and there is adjustment for age, sex, and age x sex. The effect estimates as expressed as HR per 1 SD increase in T1 (i.e., change in hazard of outcome 1SD=35.7ms increase in native T1) with corresponding 95% CI and p-values. CI: confidence interval; HR: hazard ratio; SD: standard deviation. \*Indicates statistically significant result following multiple testing adjustment with a false discovery rate of 0.05.

**Figure 1. Median myocardial native T1 by age and sex in the healthy subset**

![Chart, line chart

Description automatically generated]()**Figure 1 footnote.** Shaded areas indicate middle 50% (25th percentile to 75thpercentile). The solid line is the median myocardial native T1 within two-year age groups stratified by sex. The dashed line shows the linear trend of T1 by age, stratified by sex. The median points at the left-most group reflect the median T1 among participants 44 – 48 years. The final median points at right-most group reflect the median T1 among participants 78 – 84 years.

**Central illustration. Associations of myocardial native T1 with prevalent and incident outcomes**

Graphical user interface, Word

Description automatically generated

**Central illustration footnote.** 2a) Results are odds ratios from logistic regression models. 2b) Results are hazard ratios from Cox hazard proportional regression models. The diseases listed are set as the model outcome (response variable) and native T1 is the exposure of interest. The “age and sex adjusted models” are adjusted for age, sex, and age x sex. The “confounder adjusted” models are adjusted for age, sex, age x sex, haematocrit, body mass index, and heart rate. Each bar corresponds to a separate model. The point estimate and 95% confidence interval are indicated by the point and bars, respectively. The greyed-out bars indicate statistically non-significant associations. CVD: cardiovascular disease; SD: standard deviation.

**SUPPLEMENTARY MATERIAL**

**Supplementary Figure 1. Summary of approach to selection of participants**

Native T1 available

n= 42,894

Excluded:

Dice score <0.7 (n= 586)

Excluded:

any CVD (n= 4,885)

any VRF (n=18,126)

Analysable native T1 n= 42,308

**Healthy subset**

n= 19,297

**Clinical associations**

n= 42,308

**Supplementary Figure 1 footnote.** VRF: vascular risk factors. CVD: cardiovascular disease. VRFs included: diabetes, hypertension, high cholesterol, or smoking.

**Supplementary Table 1. Disease definitions**

|  |  |  |
| --- | --- | --- |
| **Source** | **UKB Field ID / Code** | **Description** |
| **Alzheimer’s / dementia** | | |
| Self-report | 20002 | dementia/Alzheimer’s/cognitive impairment |
| ICD9 | 290 | Senile and presenile organic psychotic conditions |
|  | 331 | Other cerebral degenerations |
| ICD10 | F00.0 | Dementia in Alzheimer's disease with early onset |
|  | F00.1 | Dementia in Alzheimer's disease with late onset |
|  | F00.2 | Dementia in Alzheimer's disease, atypical or mixed type |
|  | F00.9 | Dementia in Alzheimer's disease, unspecified |
|  | F01 | Vascular dementia |
|  | F02 | Dementia in other diseases classified elsewhere |
|  | F03 | Unspecified dementia |
|  | F05.1 | Delirium superimposed on dementia |
|  | G30.0 | Alzheimer's disease with early onset |
|  | G30.1 | Alzheimer's disease with late onset |
|  | G30.8 | Other Alzheimer's disease |
|  | G30.9 | Alzheimer's disease, unspecified |
|  | G31 | Other degenerative diseases of nervous system, not elsewhere classified |
|  | I67.3 | Progressive vascular leukoencephalopathy |
| First occurrences | 130836 | dementia in Alzheimer’s disease |
|  | 130838 | vascular dementia |
|  | 130840 | dementia in other diseases classified elsewhere |
|  | 130842 | unspecified dementia |
|  | 131036 | Alzheimer’s disease |
|  | 131038 | other degenerative diseases of nervous system, not elsewhere classified |
| Algorithm | 42022 | Date of vascular dementia report |
|  | 42018 | Date of all cause dementia report |
|  | 42024 | Date of frontotemporal dementia report |
|  | 42020 | Date of Alzheimer’s disease report |
| **Benign neoplasm of brain, meninges and other parts of the CNS** | | |
| Self-report | 20002 | benign neuroma |
|  | 20002 | meningioma / benign meningeal tumour |
| ICD10 | D32 | Benign neoplasm of meninges |
|  | D33 | Benign neoplasm of brain and other parts of central nervous system |
| Date of cancer | 40005 | Match to field 40006 |
| Cancer register | 40006: D32 | Benign neoplasm of meninges |
|  | 40006: D33 | Benign neoplasm of brain and other parts of central nervous system |
| **Brain abscess/intracranial abscess** | | |
| Self-report | 20002 | brain abscess/intracranial abscess |
|  | 20002 | spinal abscess |
| ICD10 | G06 | Intracranial and intraspinal abscess and granuloma |
|  | G07 | Intracranial and intraspinal abscess and granuloma in diseases classified elsewhere |
|  | G08 | Intracranial and intraspinal phlebitis and thrombophlebitis |
|  | G09 | Sequelae of inflammatory diseases of CNS |
| First occurrences | 131004 | intracranial and intraspinal abscess and granuloma |
|  | 131006 | intracranial and intraspinal abscess and granuloma in diseases classified elsewhere |
|  | 131008 | intracranial and intraspinal phlebitis and thrombophlebitis |
|  | 131010 | sequelae of inflammatory diseases of central nervous system |
| **Cerebral palsy** |  |  |
| Self-report | 20002 | cerebral palsy |
| ICD10 | G80 | Cerebral palsy |
| First occurrences | 131100 | cerebral palsy |
| **Cerebrovascular diseases** | | |
| ICD10 | I65 | Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction |
|  | I66 | Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarct |
|  | I67 | Other cerebrovascular diseases |
|  | I68 | Cerebrovascular disorders in diseases classified elsewhere |
| First occurrences | 131370 | Date I65 first reported (occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction) |
|  | 131372 | Date I66 first reported (occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction) |
|  | 131374 | Date I67 first reported (other cerebrovascular diseases) |
|  | 131376 | Date I68 first reported (cerebrovascular disorders in diseases classified elsewhere) |
| **Epilepsy** |  |  |
| Self-report | 20002 | epilepsy |
| ICD10 | G40 | Epilepsy |
|  | G41 | Status epilepticus |
| First occurrences | 131048 | Epilepsy |
|  | 131050 | Status epilepticus |
| **Inflammatory diseases of the CNS - Meningitis** | | |
| Self-report | 20002 | meningitis |
|  | 20002 | infection of nervous system |
| ICD10 | G00 | Bacterial meningitis, not elsewhere classified |
|  | G01 | Meningitis in bacterial diseases classified elsewhere |
|  | G03 | Meningitis due to other and unspecified causes |
| First occurrences | 130992 | bacterial meningitis, not elsewhere classified |
|  | 130994 | meningitis in bacterial diseases classified elsewhere |
|  | 130998 | meningitis due to other and unspecified causes |
| Self-report | 20002 | encephalitis |
| ICD10 | G04.0 | Acute disseminated encephalitis |
|  | G04.2 | Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified |
|  | G04.8 | Other encephalitis, myelitis and encephalomyelitis |
|  | G04.9 | Encephalitis, myelitis and encephalomyelitis, unspecified |
|  | G05 | Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere |
| First occurrences | 131000 | Encephalitis, myelitis and encephalomyelitis |
|  | 131002 | Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere |
| **Malignant neoplasm of brain** | | |
| Self-report | 20001 | Brain cancer / primary malignant brain tumour |
|  | 20001 | Spinal cord or cranial nerve cancer |
| ICD10 | C71.0 | Cerebrum, except lobes and ventricles |
|  | C71.1 | Frontal lobe |
|  | C71.2 | Temporal lobe |
|  | C71.3 | Parietal lobe |
|  | C71.4 | Occipital lobe |
|  | C71.5 | Cerebral ventricle |
|  | C71.6 | Cerebellum |
|  | C71.7 | Brain stem |
|  | C71.8 | Overlapping lesion of brain |
|  | C71.9 | Brain, unspecified |
|  | C72.0 | Spinal cord |
| Date of cancer | 40005 | Match to field 40006 |
| Cancer register | 40006: C71 | Malignant neoplasm of brain |
|  | 40006: C72.0 | Spinal cord |
| **Motor neuron disease (and other spinal muscular atrophies)** | | |
| Self-report | 20002 | Motor neurone disease |
| ICD10 | G12 | Motor neuron disease and other spinal muscular atrophies |
| First occurrences | 131016 | Spinal muscular atrophy and related syndromes |
| Algorithm | 42028 | Date of motor neurone disease report |
| **Multiple Sclerosis** |  |  |
| Self-report | 20002 | Multiple sclerosis |
| ICD10 | G35 | Multiple sclerosis |
| First occurrences | 131042 | Multiple sclerosis |
| **Myasthenia gravis and other myoneural disorders** | | |
| Self-report | 20002 | Myasthenia gravis |
| ICD10 | G70 | Myasthenia gravis and other myoneural disorders |
| First occurrences | 131092 | Myasthenia gravis and other myoneural disorders |
| **Neurological injury/trauma** | | |
| Self-report | 20002 | Neurological injury/trauma |
| ICD10 | S06 | Intracranial injury |
| **Organic, including symptomatic, mental disorders** | | |
| ICD10 | F06 | Other mental disorders due to brain damage and dysfunction and to physical disease |
|  | F07 | Personality and behavioural disorders due to brain disease, damage and dysfunction |
|  | F09 | Unspecified organic or symptomatic mental disorder |
|  | F70 | Mild mental retardation |
|  | F71 | Moderate mental retardation |
|  | F72 | Severe mental retardation |
|  | F73 | Profound mental retardation |
|  | F78 | Other mental retardation |
|  | F79 | Unspecified mental retardation |
| First occurrences | 130848 | Other mental disorders due to brain damage and dysfunction and to physical disease |
|  | 130850 | Personality and behavioural disorders due to brain disease, damage and dysfunction |
|  | 130852 | Unspecified organic or symptomatic mental disorder |
|  | 130950 | Mild mental retardation |
|  | 130952 | Moderate mental retardation |
|  | 130954 | Severe mental retardation |
|  | 130958 | Other mental retardation |
|  | 130960 | Unspecified mental retardation |
| **Other degenerative diseases of the nervous system** | | |
| Self-report | 20002 | Chronic/degenerative neurological problem |
| ICD10 | F04 | Organic amnesic syndrome, not induced by alcohol and other psychoactive substances |
|  | G23 | Other degenerative diseases of basal ganglia |
|  | G24.0 | Drug-induced dystonia |
|  | G24.1 | Idiopathic familial dystonia |
|  | G24.2 | Idiopathic nonfamilial dystonia |
|  | G24.8 | Other dystonia |
|  | G24.9 | Dystonia, unspecified |
|  | G25.3 | Myoclonus |
|  | G25.4 | Drug-induced chorea |
|  | G25.5 | Other chorea |
|  | G25.8 | Other specified extrapyramidal and movement disorders |
|  | G25.9 | Extrapyramidal and movement disorder, unspecified |
|  | G32 | Other degenerative disorders of nervous system in diseases classified elsewhere |
| First occurrences | 130844 | Organic amnesic syndrome, not induced by alcohol and other psychoactive substances |
|  | 131028 | Other degenerative diseases of basal ganglia |
|  | 131040 | Other degenerative disorders of nervous system in diseases classified elsewhere |
| Algorithm | 42034 | Date of progressive supranuclear palsy report |
|  | 42036 | Date of multiple system atrophy report |
| **Other demyelinating diseases of CNS** | | |
| Self-report | 20002 | Other demyelinating disease (not multiple sclerosis) |
| ICD10 | G36 | Other acute disseminated demyelination |
|  | G37 | Other demyelinating diseases of central nervous system |
| First occurrences | 131044 | Other acute disseminated demyelination |
|  | 131046 | Other demyelinating diseases of central nervous system |
| **Other disorders of the nervous system** | | |
| Self-report | 20002 | Spina bifida |
|  | 20002 | Spinal cord disorder |
| ICD10 | Q00 | Anencephaly and similar malformations |
|  | Q01 | Encephalocele |
|  | Q02 | Microcephaly |
|  | Q03 | Congenital hydrocephalus |
|  | Q04 | Other congenital malformations of brain |
|  | Q05 | Spina bifida |
|  | Q06 | Other congenital malformations of spinal cord |
|  | Q07 | Other congenital malformations of nervous system |
|  | G91 | Hydrocephalus |
|  | G92 | Toxic encephalopathy |
|  | G93.1 | Anoxic brain damage, not elsewhere classified |
|  | G93.2 | Benign intracranial hypertension |
|  | G93.4 | Encephalopathy, unspecified |
|  | G93.5 | Compression of brain |
|  | G93.6 | Cerebral oedema |
|  | G94 | Other disorders of brain in diseases classified elsewhere |
|  | G95 | Other diseases of spinal cord |
| First occurrences | 132432 | Anencephaly and similar malformations |
|  | 132434 | Encephalocele |
|  | 132436 | Microcephaly |
|  | 132438 | Congenital hydrocephalus |
|  | 132440 | Other congenital malformations of brain |
|  | 132442 | Spina bifida |
|  | 132444 | Other congenital malformations of spinal cord |
|  | 132446 | Other congenital malformations of nervous system |
|  | 131110 | Hydrocephalus |
|  | 131112 | Toxic encephalopathy |
|  | 131114 | Other disorders of brain |
|  | 131116 | Other disorders of brain in diseases classified elsewhere |
|  | 131118 | Other diseases of spinal cord |
| **Other mental and behavioural disorders** | | |
| Self-report | 20002 | Schizophrenia |
|  | 20002 | Mania/bipolar disorder/manic depression |
|  | 20002 | Obsessive compulsive disorder (OCD) |
|  | 20002 | Anorexia/bulimia/other eating disorder |
| ICD10 | F20 | Schizophrenia |
|  | F21 | Schizotypal disorder |
|  | F30 | Manic episode |
|  | F31 | Bipolar affective disorder |
|  | F42 | Obsessive-compulsive disorder |
|  | F50 | Eating disorders |
| First occurrences | 130874 | Schizophrenia |
|  | 130876 | Schizotypal disorder |
|  | 130890 | Manic episode |
|  | 130892 | Bipolar affective disorder |
|  | 130908 | Obsessive-compulsive disorder |
|  | 130918 | Eating disorders |
| **Parkinson’s disease** | |  |
| Self-report | 20002 | Parkinson’s disease |
| ICD9 | 332 | Parkinson's disease |
| ICD10 | G22 | Parkinsonism in diseases classified elsewhere |
|  | G20 | Parkinson’s disease |
|  | G21 | Secondary Parkinsonism |
| First occurrences | 131022 | Parkinson’s disease |
|  | 131024 | Secondary parkinsonism |
|  | 131026 | Parkinsonism in diseases classified elsewhere |
| Algorithm | 42030 | Date of all cause parkinsonism report |
|  | 42032 | Date of Parkinson’s disease report |
| **Subarachnoid haemorrhage** | | |
| Self-report | 20002 | Subarachnoid haemorrhage |
| ICD9 | 430 | Subarachnoid haemorrhage |
| ICD10 | I60 | Subarachnoid haemorrhage |
| First occurrences | 131360 | Subarachnoid haemorrhage |
| Algorithm | 42012 | Date of subarachnoid haemorrhage (should be covered by 42006) |
| **Systemic atrophies primarily affecting the CNS** | | |
| ICD10 | G10 | Huntington's disease |
|  | G11 | Hereditary ataxia |
|  | G13 | Systemic atrophies primarily affecting central nervous system in diseases Classified elsewhere |
| First occurrences | 131012 | Huntington’s disease |
|  | 131014 | Hereditary ataxia |
|  | 131018 | Systemic atrophies primarily affecting central nervous system in diseases classified elsewhere |
| **Transient ischaemic attack (TIA)** | | |
| Self-report | 20002 | Transient ischaemic attack (TIA) |
| ICD9 | 435 | Transient cerebral ischaemia |
| ICD10 | G45 | Transient cerebral ischaemic attacks and related syndromes |
| First occurrences | 131056 | Transient cerebral ischaemic attacks and related syndromes |
| **Stroke** |  |  |
| Self-report | 20002 | Stroke |
|  | 20002 | Ischaemic stroke |
|  | 20002 | Brain haemorrhage |
| ICD9 | 431 | Intracerebral haemorrhage |
|  | 432 | Other and unspecified intracranial haemorrhage |
| ICD10 | I64 | Stroke, not specified as haemorrhage or infarction |
|  | I63 | Cerebral infarction |
|  | I61 | Intracerebral haemorrhage |
|  | I62 | Other nontraumatic intracranial haemorrhage |
| First occurrences | 131368 | Date I64 first reported (stroke, not specified as haemorrhage or infarction) |
|  | 131366 | Cerebral infarction |
|  | 131362 | Intracerebral haemorrhage |
|  | 131364 | other nontraumatic intracranial haemorrhage |
| Diagnosed by doctor | 4056 | Age stroke diagnosed |
|  | 6150: 3 | Stroke |
| Algorithm | 42006 | Date of stroke |
|  | 42008 | Date of ischaemic stroke |
|  | 42010 | Date of intracerebral haemorrhage |
| **Cardiac arrhythmia** | | |
| Self-report | 20002 | Sick sinus syndrome |
|  | 20002 | SVT / supraventricular tachycardia |
|  | 20002 | Atrial flutter |
|  | 20002 | Heart arrhythmia |
|  | 20002 | Irregular heart beat |
| ICD10 | I44.1 | Atrioventricular block, second degree |
|  | I44.2 | Atrioventricular block, complete |
|  | I45.3 | Trifascicular block |
|  | I45.6 | Preexcitation syndrome |
|  | I46.0 | Cardiac arrest with successful resuscitation |
|  | I46.1 | Sudden cardiac death, so described |
|  | I46.9 | Cardiac arrest, unspecified |
|  | I47.0 | Re-entry ventricular arrhythmia |
|  | I47.1 | Supraventricular tachycardia |
|  | I47.2 | Ventricular tachycardia |
|  | I47.9 | Paroxysmal tachycardia, unspecified |
|  | I48.3 | Typical atrial flutter |
|  | I48.4 | Atypical atrial flutter |
|  | I49.0 | Ventricular fibrillation and flutter |
|  | I49.5 | Sick sinus syndrome |
| First occurrences | 131346 | Cardiac arrest |
|  | 131348 | Paroxysmal tachycardia |
|  | 131350 | Atrial fibrillation and flutter |
| **Cardiac arrhythmia (Atrial fibrillation)** | | |
| Self-report | 20002 | Atrial fibrillation |
| ICD10 | I48.0 | Paroxysmal atrial fibrillation |
|  | I48.1 | Persistent atrial fibrillation |
|  | I48.2 | Chronic atrial fibrillation |
|  | I48.9 | Atrial fibrillation and atrial flutter, unspecified |
| **Heart failure (unspecified aetiology)** | | |
| Self-report | 20002 | Heart failure/pulmonary oedema |
| ICD10 | I50.0 | Congestive heart failure |
|  | I50.1 | Left ventricular failure |
|  | I50.9 | Heart failure, unspecified |
| First occurrences | 131354 | Heart failure |
| **Ischaemic heart disease** | | |
| Self-report | 20002 | Angina |
| ICD10 | I20 | Angina pectoris |
|  | I24 | Other acute ischaemic heart diseases |
|  | I25 | Chronic ischaemic heart disease |
| First occurrences | 131296 | Angina pectoris |
|  | 131304 | Other acute ischaemic heart diseases |
|  | 131306 | Chronic ischaemic heart disease |
| Diagnosed by doctor | 3627 | Age angina diagnosed |
|  | 6150: 2 | Angina |
| **Ischaemic heart disease (Myocardial infarction)** | | |
| Self-report | 20002 | Heart attack/myocardial infarction |
| ICD9 | 410 | Acute myocardial infarction |
|  | 411 | Other acute and subacute forms of ischaemic heart disease |
|  | 412 | Old myocardial infarction |
| ICD10 | I21 | Acute myocardial infarction |
|  | I22 | Subsequent myocardial infarction |
|  | I23 | Certain current complications following acute myocardial infarction |
| First occurrences | 131298 | Acute myocardial infarction |
|  | 131300 | Subsequent myocardial infarction |
|  | 131302 | Certain current complications following acute myocardial infarction |
| Diagnosed by doctor | 3894 | Age heart attack diagnosed |
|  | 6150: 1 | Heart attack |
| Algorithm | 42000 | Date of myocardial infarction |
| **Non-ischaemic cardiomyopathies** | | |
| Self-report | 20002 | Cardiomyopathy |
|  | 20002 | Hypertrophic cardiomyopathy (HCM / HOCM) |
| ICD10 | I42 | Cardiomyopathy |
|  | I43 | Cardiomyopathy in diseases classified elsewhere |
|  | I11 | Hypertensive heart disease |
|  | I13 | Hypertensive heart and renal disease |
| First occurrences | 131338 | Cardiomyopathy |
|  | 131340 | Cardiomyopathy in diseases classified elsewhere |
|  | 131288 | Hypertensive heart disease |
|  | 131292 | Hypertensive heart and renal disease |
| **Valvular heart disease** | | |
| Self-report | 20002 | Mitral stenosis |
|  | 20002 | Mitral valve disease |
|  | 20002 | Heart valve problem/heart murmur |
|  | 20002 | Mitral regurgitation / incompetence |
|  | 20002 | Aortic valve disease |
|  | 20002 | Aortic stenosis |
|  | 20002 | Aortic regurgitation / incompetence |
| ICD10 | I34.0 | Mitral (valve) insufficiency |
|  | I34.2 | Non-rheumatic mitral (valve) stenosis |
|  | I34.8 | Other nonrheumatic mitral valve disorders |
|  | I34.9 | Non-rheumatic mitral valve disorder, unspecified |
|  | I35 | Non-rheumatic aortic valve disorders |
|  | I36 | Non-rheumatic tricuspid valve disorders |
|  | I37 | Pulmonary valve disorders |
|  | I38 | Endocarditis, valve unspecified |
|  | I39.0 | Mitral valve disorders in diseases classified elsewhere |
|  | I39.1 | Aortic valve disorders in diseases classified elsewhere |
|  | I39.3 | Pulmonary valve disorders in diseases classified elsewhere |
|  | I39.4 | Multiple valve disorders in diseases classified elsewhere |
|  | I39.8 | Endocarditis, valve unspecified, in diseases classified elsewhere |
|  | I05 | Rheumatic mitral valve diseases |
|  | I06 | Rheumatic aortic valve diseases |
|  | I07 | Rheumatic tricuspid valve diseases |
|  | I08 | Multiple valve diseases |
| First occurrences | 131322 | Non-rheumatic mitral valve disorders |
|  | 131324 | Non-rheumatic aortic valve disorders |
|  | 131326 | Non-rheumatic tricuspid valve disorders |
|  | 131328 | Pulmonary valve disorders |
|  | 131330 | Endocarditis, valve unspecified |
|  | 131332 | Endocarditis and heart valve disorders in diseases classified elsewhere |
|  | 131276 | Rheumatic mitral valve diseases |
|  | 131278 | Rheumatic aortic valve diseases |
|  | 131280 | Rheumatic tricuspid valve diseases |
|  | 131282 | Multiple valve diseases |
| **Diabetes** |  |  |
| Self-report | 20002 | Diabetes |
|  | 20002 | Type 1 diabetes |
|  | 20002 | Type 2 diabetes |
| Medications | 6177, 6153: 3 | Insulin |
| ICD9 | 250 | Diabetes mellitus |
| ICD10 | E10 | Type 1 diabetes mellitus |
|  | E11 | Type 2 diabetes mellitus |
|  | E13 | Other specified diabetes mellitus |
|  | E14 | Unspecified diabetes mellitus |
|  | G590 | Diabetic mononeuropathy |
|  | G632 | Diabetic polyneuropathy |
|  | H280 | Diabetic cataract |
|  | H360 | Diabetic retinopathy |
|  | M142 | Diabetic arthropathy |
|  | N083 | Glomerular disorders in diabetes mellitus |
|  | O240 | Diabetes mellitus in pregnancy: Pre-existing type 1 diabetes mellitus |
|  | O241 | Diabetes mellitus in pregnancy: Pre-existing type 2 diabetes mellitus |
|  | O243 | Diabetes mellitus in pregnancy: Pre-existing diabetes mellitus, unspecified |
|  | O244 | Diabetes mellitus arising in pregnancy |
|  | O249 | Diabetes mellitus in pregnancy, unspecified |
|  | Y423 | Insulin and oral hypoglycaemic [antidiabetic] drugs |
| First occurrences | 130706 | Date E10 first reported (insulin-dependent diabetes mellitus) |
|  | 130708 | Date E11 first reported (non-insulin-dependent diabetes mellitus) |
|  | 130712 | Date E13 first reported (other specified diabetes mellitus) |
|  | 130714 | Date E14 first reported (unspecified diabetes mellitus) |
| Diagnosed by doctor | 2443 | Diabetes diagnosed by doctor |
|  | 2976 | Age diabetes diagnosed by doctor |
| Biochemistry | 30750 | Glycated haemoglobin (HbA1c) >48 mmol/L |
| **High cholesterol** |  |  |
| Self-report | 20002 | High cholesterol |
| Medications | 6177, 6153: 1 | Cholesterol lowering medication |
| ICD10 | E780 | Pure hypercholesterolaemia |
|  | E782 | Mixed hyperlipidaemia |
|  | E783 | Hyperchylomicronaemia |
|  | E784 | Other hyperlipidaemia |
|  | E785 | Hyperlipidaemia, unspecified |
| First occurrences | 130814 | Date E78 first reported (disorders of lipoprotein metabolism and other lipidaemias) |
| Biochemistry | 30690 | Cholesterol >7mmol/L |
| **Hypertension** |  |  |
| Self-report | 20002 | Essential hypertension |
|  | 20002 | Hypertension |
| Medications | 6177, 6153: 2 | Blood pressure medication |
| ICD10 | I10 | Essential (primary) hypertension |
| First occurrences | 131286 | Date I10 first reported (essential (primary) hypertension) |
| Diagnosed by doctor | 2966 | Age high blood pressure diagnosed |
|  | 6150: 4 | High blood pressure |

**Supplementary Table 1 footnote.** Where a 3-digit ICD10 code is given, this includes all subsections (e.g. I21 includes I21.0, I21.1 etc.)

**Supplementary Table 2. The association of age with myocardial native T1 in healthy men and women**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Sample | Standardised beta | 95% CI | p-value | N |
| Women | -0.33\* | [-0.41, -0.24] | <0.0001 | 11,479 |
| Men | 0.48\* | [0.39, 0.57] | <0.0001 | 7,818 |

**Supplementary Table 2 footnote:** Linear regression models with myocardial native T1 set as the outcome (response variable) and age as the exposure of interest, separately in men and women. Results are standard deviation change in myocardial native T1 per 1 standard deviation increase in age (7.7 years) in the healthy cohort.

**Supplementary Table 3. Associations of myocardial native T1 with potential confounders**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes/ confounders** | **Beta** | **95% CI** | **p-value** | **n** |
| Heart rate | 0.17\* | [0.16, 0.18] | <0.0001 | 37,175 |
| BMI (kg/m2) | -0.13\* | [-0.14, -0.12] | <0.0001 | 42,307 |
| Haematocrit percentage (baseline) | -0.06\* | [-0.07, -0.05] | <0.0001 | 40,314 |

**Supplementary Table 3 footnote.** Results are from linear regression models with confounders of interest set as the model outcome and native T1 as the exposure of interest; models are adjusted for age, sex, and age x sex. The effect estimates as expressed as standardised beta coefficients with corresponding standardised 95% CI and p-values. CI: confidence interval

**Supplementary Table 4. Associations of myocardial native T1 with prevalent disease and incident outcomes with additional adjustment for potential measurement confounders**

|  |  |  |  |
| --- | --- | --- | --- |
| **Prevalent outcomes** | **OR [95% CI]** | **p-value** | **Cases / N** |
| Any cardiovascular disease | 1.11\* [1.07, 1.15] | <0.0001 | (3,939 / 35,361) |
| Any brain disease | 1.12\* [1.08, 1.18] | <0.0001 | (2,461 / 35,361) |
| Valvular heart disease | 1.12\* [1.02, 1.21] | 0.0108 | (641 / 35,361) |
| Heart failure | 1.47\* [1.29, 1.66] | <0.0001 | (217 / 35,361) |
| Non-ischaemic cardiomyopathies | 1.46\* [1.18, 1.77] | 0.0003 | (81 / 35,361) |
| Cardiac arrhythmias | 1.19\* [1.13, 1.25] | <0.0001 | (1,828 / 35,361) |
| Atrial fibrillation | 1.25\* [1.15, 1.36] | <0.0001 | (594 / 35,361) |
| Myocardial infarction | 1.18\* [1.09, 1.27] | <0.0001 | (850 / 35,361) |
| Ischaemic heart disease | 1.07\* [1.02, 1.12] | 0.0105 | (2,086 / 35,361) |
| Stroke | 1.15\* [1.06, 1.24] | 0.0007 | (692 / 35,361) |
| Hypertension | 0.91\* [0.89, 0.94] | <0.0001 | (11,542 / 35,361) |
| Diabetes | 1.11\* [1.06, 1.17] | <0.0001 | (2,026 / 35,361) |
| High cholesterol | 0.99 [0.96, 1.01] | 0.3098 | (12,320 / 35,361) |
| **Incident outcomes** | **HR [95% CI]** | **p-value** | **Cases / N** |
| Incident CVD (any) | 1.11\* [1.05, 1.19] | <0.0001 | (3,939 / 35,361) |
| Incident atrial fibrillation | 1.25\* [1.09, 1.45] | 0.0019 | (196 / 34,767) |
| Incident stroke | 1.12 [0.97, 1.30] | 0.1219 | (197 / 34,669) |
| Incident ischaemic heart disease | 1.01 [0.92, 1.10] | 0.8162 | (580 / 33,275) |
| Incident myocardial infarction | 0.97 [0.84, 1.13] | 0.700 | (212 / 34,511) |
| Incident heart failure | 1.45\* [1.28, 1.65] | <0.0001 | (208 / 35,144) |
| All-cause mortality | 1.22\* [1.09, 1.35] | 0.0003 | (351 / 35,361) |
| Cardiovascular disease mortality | 1.47\* [1.17, 1.84] | 0.0009 | (64 / 35,361) |

**Supplementary Table 4 footnote.** Results are from logistic regression models for prevalent disease outcomes and Cox proportional hazard regression models for incident event outcomes. The effect estimates as expressed as HR and OR with corresponding 95% CI and p-values. The outcomes of interest are set as the model outcome, native T1 is the exposure of interest, and there is adjustment for age, sex, age\*sex, body mass index, haematocrit, and average heart rate. The effect estimates as expressed as HR with corresponding 95% CI and p-values. HR: hazard ratio; CI: confidence interval. \*Indicates statistically significant result following multiple testing adjustment with a false discovery rate of 0.05.

**Supplementary Table 5. Assessment of significant interaction of age and sex with T1 in the relationships with incident events**

|  |  |  |
| --- | --- | --- |
|  | T1 x age | T1 x sex |
| Incident cardiovascular disease (any) | 0.0334 | 0.7244 |
| Incident atrial fibrillation | 0.3551 | 0.7699 |
| Incident heart failure | 0.7385 | 0.1438 |
| Incident stroke | 0.3062 | 0.4400 |
| Incident myocardial infarction | 0.0413 | 0.9447 |
| Incident ischaemic heart disease | 0.4759 | 0.3203 |
| All-cause mortality | **0.0026** | 0.0894 |
| Cardiovascular disease mortality | **2.04x10-4** | 0.1506 |
| Ischaemic heart disease mortality | **2.41x10-5** | 0.9055 |

**Supplementary Table 5 footnote**. Results are p-values corresponding to the interaction terms T1x age and T1x sex- when added to our main models with incident disease and mortality events as the outcome.

**Supplementary Table 6. The associations of native T1 with mortality outcomes stratified by median age**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | ≤65 years-old | > 65 years-old |
| All-cause mortality | HR (95% CI) | 0.98 [0.82, 1.17] | 1.40 [1.25, 1.57] |
|  | p-value | 0.8111 | 3.77x10-9 |
|  | Events/N | (128 / 22,886) | (274 / 19,422) |
| CVD mortality | HR (95% CI) | 0.80 [0.52, 1.25] | 1.73 [1.38, 2.17] |
|  | p-value | 0.3336 | 2.18x10-6 |
|  | Events/N | (23 / 22,886) | (53 / 19,422) |
| IHD mortality | HR (95% CI) | 0.72 [0.43, 1.20] | 1.88 [1.39, 2.54] |
|  | p-value | 0.2097 | 4.45x10-5 |
|  | Events/N | (17 / 22,886) | (27 / 19,422) |

**Supplementary Table 6 footnote.** Results are from Cox proportional hazard regression models with outcomes of interest set as the model outcome (response variable), native T1 is the exposure of interest, and there is adjustment for age, sex, and age x sex. The effect estimates as expressed as HR per 1 SD increase in T1 (i.e., change in hazard of outcome 1SD=35.7ms increase in native T1) with corresponding 95% CI and p-values. CI: confidence interval; HR: hazard ratio; SD: standard deviation; CVD: cardiovascular disease.

**Supplementary Table 7. The associations of native T1 with incident outcomes stratified by median T1**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **T1 <median** | **T1 ≥Median** |
| Incident CVD (any) | HR [95% CI] | 1.01 [0.89, 1.15] | 1.20 [1.09, 1.33] |
|  | p-value | 0.8683 | 3.15x10-4 |
|  | Events/N | (655 / 18,577) | (601 / 18,846) |
| Incident atrial fibrillation | HR [95% CI] | 1.38 [0.97, 1.96] | 1.55 [1.28, 1.88] |
|  | p-value | 0.0695 | 8.55x10-6 |
|  | Events/N | (118 / 20,782) | (97 / 20,773) |
| Incident heart failure | HR [95% CI] | 1.17 [0.82, 1.66] | 1.55 [1.32, 1.83] |
|  | p-value | 0.3868 | 1.32x10-7 |
|  | Events/N | (103 / 21,027) | (140 / 21,003) |
| Incident stroke | HR [95% CI] | 1.07 [0.77, 1.48] | 1.12 [0.87, 1.44] |
|  | p-value | 0.6976 | 0.3735 |
|  | Events/N | (108 / 20,716) | (107 / 20,740) |
| Incident ischaemic heart disease | HR [95% CI] | 0.98 [0.82, 1.15] | 1.17 [1.01, 1.37] |
|  | p-value | 0.7698 | 0.0382 |
|  | Events/N | (378 / 19,679) | (271 / 20,025) |
| Incident myocardial infarction | HR [95% CI] | 0.94 [0.72, 1.21] | 1.11 [0.84, 1.46] |
|  | p-value | 0.6229 | 0.4706 |
|  | Events/N | (152 / 20,543) | (89 / 20,704) |
| All-cause mortality | HR [95% CI] | 0.97 [0.77, 1.24] | 1.21 [1.03, 1.42] |
|  | p-value | 0.8268 | 0.0236 |
|  | Events/N | (180 / 21,154) | (222 / 21,154) |
| Cardiovascular disease mortality | HR [95% CI] | 1.10 [0.59, 2.04] | 1.19 [0.82, 1.72] |
|  | p-value | 0.7731 | 0.3509 |
|  | Events/N | (30 / 21,154) | (46 / 21,154) |
| Ischaemic heart disease mortality | HR [95% CI] | 0.80 [0.41, 1.54] | 1.32 [0.84, 2.09] |
|  | p-value | 0.4988 | 0.2295 |
|  | Events/N | (19 / 21,154) | (25 / 21,154) |

**Supplementary Table 7 footnote.** Results are from Cox proportional hazard regression models with outcomes of interest set as the model outcome (response variable), native T1 is the exposure of interest, and there is adjustment for age, sex, and age x sex. The effect estimates as expressed as HR per 1 SD increase in T1 (i.e., change in hazard of outcome 1SD=35.7ms increase in native T1) with corresponding 95% CI and p-values. CI: confidence interval; HR: hazard ratio; SD: standard deviation.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

|  |  |  |  |
| --- | --- | --- | --- |
|  | Item No | Recommendation | Section addressed |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | Title |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Abstract |
| Introduction | | |  |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Introduction |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Introduction, Methods |
| Methods | | |  |
| Study design | 4 | Present key elements of study design early in the paper | Title, Methods |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Methods |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | Methods |
| (*b*)For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Methods |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Methods |
| Bias | 9 | Describe any efforts to address potential sources of bias | Methods |
| Study size | 10 | Explain how the study size was arrived at | Methods, Suppl. Figure 1 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Methods |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Methods |
| (*b*) Describe any methods used to examine subgroups and interactions | Methods |
| (*c*) Explain how missing data were addressed | Methods |
| (*d*) If applicable, explain how loss to follow-up was addressed | Methods |
| (*e*) Describe any sensitivity analyses | Methods |
| Results | | |  |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Suppl. Figure 1 |
| (b) Give reasons for non-participation at each stage | Suppl. Figure 1 |
| (c) Consider use of a flow diagram | Suppl. Figure 1 |
| Descriptive data | 14\* | (a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders | Results, Table 1 |
| (b) Indicate number of participants with missing data for each variable of interest | Suppl. Figure 1, Table 1 |
| (c) Summarise follow-up time (e.g., average and total amount) | Results |
| Outcome data | 15\* | Report numbers of outcome events or summary measures over time | Table 1 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 3, Table 4 |
| (*b*) Report category boundaries when continuous variables were categorized | Table 2 |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| Other analyses | 17 | Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses | Suppl. Table 2-4 |
| Discussion | | |  |
| Key results | 18 | Summarise key results with reference to study objectives | Discussion |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Discussion |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Discussion |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Discussion |
| Other information | | |  |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Acknowledgements, Role of funders |

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.