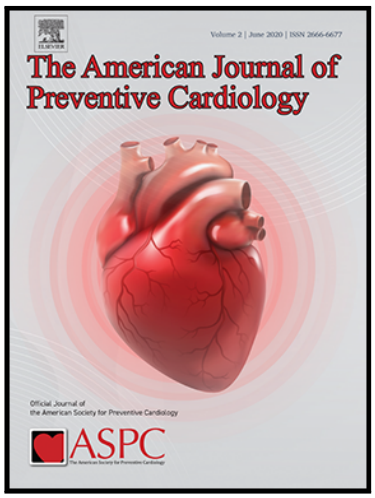
Journal Pre-proof



Estimating the Potential Cardiovascular Benefit of Lifestyle Risk Factors Using Causal Machine Learning: Insights from UK Biobank

Christophe A.T. Stevens , Julia Brandts , Amany Elshorbagy , Fotis Barkas , Didac Llop , Kanika I. Dharmayat , Irene Karungi , Sunganani Kwilasi , Alireza Mahani , Mansour T.A. Sharabiani , Antonio J. Vallejo-Vaz , Kausik K. Ray

PII: S2666-6677(26)01137-2
DOI: https://doi.org/10.1016/j.ajpc.2026.102563
Reference: AJPC 102563

To appear in: *American Journal of Preventive Cardiology*

Received date: 15 August 2026
Revised date: 29 September 2026
Accepted date: 8 October 2026

Please cite this article as: Christophe A.T. Stevens , Julia Brandts , Amany Elshorbagy , Fotis Barkas , Didac Llop , Kanika I. Dharmayat , Irene Karungi , Sunganani Kwilasi , Alireza Mahani , Mansour T.A. Sharabiani , Antonio J. Vallejo-Vaz , Kausik K. Ray , Estimating the Potential Cardiovascular Benefit of Lifestyle Risk Factors Using Causal Machine Learning: Insights from UK Biobank, *American Journal of Preventive Cardiology* (2026), doi: https://doi.org/10.1016/j.ajpc.2026.102563

This is a PDF of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability. This version will undergo additional copyediting, typesetting and review before it is published in its final form. As such, this version is no longer the Accepted Manuscript, but it is not yet the definitive Version of Record; we are providing this early version to give early visibility of the article. Please note that Elsevier's sharing policy for the Published Journal Article applies to this version, see: https://www.elsevier.com/about/policies-and-standards/sharing#4-published-journal-article. Please also note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2026 Published by Elsevier B.V.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Journal Pre-proof

Estimating the Potential Cardiovascular Benefit of Lifestyle Risk Factors Using Causal Machine Learning: Insights from UK Biobank

Christophe A.T. Stevens (PhD),[*a] Julia Brandts (MD),[a,b] Amany Elshorbagy(PhD),[a,d] Fotis Barkas (MD, PhD),[a,c] Didac Llop(PhD),[a] Kanika I. Dharmayat (PhD),[a] Irene Karungi (MBChB),[a] Sunganani Kwilasi (MSc),[a] Alireza Mahani (PhD),[e] Mansour T.A. Sharabiani (PhD)[‡a], Antonio J. Vallejo-Vaz (PhD), [‡a,f,g,h], Kausik K. Ray (FMedSci)[‡a]

[a] Department of Primary Care and Public Health, School of Public Health, Imperial College London, London, United Kingdom.

[b] Department of Medicine I, University Hospital Aachen, Aachen, Germany.

[c] Department of Internal Medicine, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece.

[d] Department of Physiology, Faculty of Medicine, University of Alexandria, Alexandria, Egypt

[e] Quantitative Research, Davidson Kempner Capital Management, New York, United States.

[f] Department of Medicine, Faculty of Medicine, Universidad de Sevilla, Sevilla, Spain.

[g] Clinical Epidemiology and Vascular Risk, Instituto de Biomedicina de Sevilla (IBiS), IBiS/Hospital Universitario Virgen del Rocío/Universidad de Sevilla/CSIC, Sevilla, Spain.

[h] Centro de Investigación Biomédica en Red (CIBER) de Epidemiología y Salud Pública, Instituto de Salud Carlos III, Spain.

[‡]Joint senior authors: Mansour T.A. Sharabiani, Antonio Vallejo-Vaz and Kausik K. Ray should be considered joint senior authors.

Corresponding author: Christophe A.T. Stevens, Department of Primary Care and Public Health, School of Public Health, Imperial College London, London, United Kingdom. School of Public Health Building, 90 Wood Lane, London W12 0BZ, United Kingdom

Word count (excluding abstract, references, tables, figures): 3998

Keywords : cardiovascular disease; lifestyle; primary prevention; causal inference; machine learning; UK Biobank

Journal Pre-proof

Journal Pre-proof

Abstract

Background: Increasingly recommendations for prevention focus on global risk assessment in lower risk individuals where sufficient lifestyle changes may reduce the need for pharmacotherapy; yet these benefits are hard to quantify, undermining adherence. We aimed to derive a tool that personalises the cardiovascular benefit associated with lifestyle risk factors.

Methods: Baseline exposures were linked to longitudinal outcomes in 371,102 UK Biobank participants without prior CVD. Causal effects were estimated using directed acyclic graphs with inverse propensity weighting (IPW), augmented IPW, generalised linear models, and causal machine learning for smoking (former/never vs current), obesity (BMI <30 vs ≥30 kg/m²), physical activity (≥600 vs <600 MET-minutes/week), and alcohol (less-than-daily vs daily). The outcome was a 10-year composite of cardiovascular death, non-fatal MI, or stroke.

Results: Median age was 58 years (IQR 50–63), 56% female; 15,752 CVD events occurred over ten years. The largest risk difference was for former/never versus current smoking (absolute risk difference [ARD] 3.2–3.8%), followed by BMI <30 versus ≥30 kg/m² (ARD 1.0–1.1%) and higher versus lower physical activity (ARD 0.2–0.4%); less-than-daily versus daily alcohol carried a small but higher risk. Differences were larger at higher baseline risk and with co-existing risk factors, increasing with pack-year for smoking (β=+0.23% per SD), and were slightly lower at higher BMI (β=−0.04%).

Conclusion: Among the lifestyle risk factors examined, smoking provided the largest risk difference, increasing with pack-years. Estimates for BMI were smaller and broadly consistent across the obesity range. Findings are accessible via a free tool (lifestyle-cvd.casefinding.com).

Journal Pre-proof

Journal Pre-proof

Introduction

Atherosclerotic cardiovascular disease (ASCVD), encompassing ischaemic heart disease, ischaemic stroke, and peripheral artery disease, remains a leading cause of death, accounting for approximately 19% of global mortality in 2019.[1] While most of the ASCVD burden is attributable to risk factors such as hypercholesterolaemia, diabetes, and hypertension, lifestyle risk factors also play an important role. Tobacco smoking, high body mass index (BMI) and low physical activity were estimated to contribute to 15%, 11% and 4% of all ischaemic heart disease deaths, and 10%, 5% and 4% of ischaemic stroke deaths, respectively, in 2021.[1, 2]

Although lifestyle modification accounts for a substantial proportion of preventable ASCVD risk, the clinically silent nature of atherosclerosis may undermine the perceived value of adherence to preventive measures among patients and clinicians.[3] Observational data suggests that combined optimal lifestyle adherence may be associated with a lower risk of CVD by over 50%,[4] but estimates of this kind are population averages. They describe what was observed in a cohort rather than what a particular person might expect and as such and are usually expressed in relative rather than absolute terms. Moreover, Randomised trials have produced mixed results in narrow populations, and hence most evidence arises from observational cohorts.[5-7] These are typically analysed in order to provide population-average associations rather than the individualised, absolute potential estimates which a clinician may need for shared decision making in a particular patient.

Recent advances in causal machine learning may address this gap. A technique called “double machine learning” with causal forests, for example, can estimate how treatment effects vary across individuals and exposure levels, capturing complex non-linear relationships and effect heterogeneity beyond the reach of traditional propensity score methods used in prior studies,[9, 10] whilst accounting for measured confounding in observational cohorts.[7, 8]

Thus, we aimed to estimate the difference in 10-year risk of incident ASCVD associated with four modifiable lifestyle risk factors: former or never versus current smoking, BMI <30 versus ≥30 kg/m², physical activity ≥600 versus <600 MET-minutes/week, and less-than-daily versus daily alcohol consumption. These are counterfactual contrasts between exposure states at baseline, not observed effects due to behavioural change. The four exposures were selected as the most reliably measured and believed to carry the highest attributable-burden of modifiable lifestyle factors capture in UK Biobank. Alcohol was included as a modifiable behaviour which has been the subject of considerable clinical and patient interest, although it does not feature in

Journal Pre-proof

established CVD risk calculators.[11, 12] Because counterfactual outcomes are never observed, our estimates cannot be validated in the conventional sense. We therefore benchmarked our causal estimates against published cohort findings and against the smoking-attributable risk encoded in SCORE2/SCORE2-DM as a consistency check. Personalised quantification of lifestyle benefits may may support lifestyle counselling and inform the development of digital decision-support.[13, 14]

Methods

An overview of the analytical workflow is provided in **Figure 1**.

Study Population

We analysed data from UK Biobank (application 67789), a prospective cohort recruiting 502,000 participants aged 40–69 years (baseline 2006–2010).[15] Individuals with prior cardiovascular events at recruitment were excluded. Continuous variables were retained on their original clinical scales; repeated measurements were averaged. Variables with >20% missing data were excluded; remaining variables (≤20% missing) were imputed through multiple imputation via chained equations (MICE; 40 imputed datasets, 10 iterations, 20 CPU cores) with convergence confirmed across all variables. Recalibration parameters were pooled across all 40 imputations using Rubin's rules, whereas causal estimates used five imputations, having confirmed stability across the full set.[16]

Outcome and Exposure Definition

The primary outcome was a binary composite of cardiovascular death, non-fatal MI, or non-fatal stroke occurring within 10 years of recruitment (ICD-10 codes for non-fatal MI: I21–I23; non-fatal stroke: I61, I63–I69; cardiovascular death: I10–I73, R96.0–R96.1), ascertained through linkage to Hospital Episode Statistics and national death registries. ICD-10 codes were aligned with the SCORE2 and SCORE2-DM outcome definitions,[11, 12] so that estimated treatment effects are expressed on the same risk scale as these validated algorithms, facilitating direct clinical interpretation.

Journal Pre-proof

Journal Pre-proof

Four binary contrasts between lifestyle behaviours at recruitment were defined: smoking, former/never vs current smoker; obesity, BMI <30 vs BMI ≥30 kg/m²; physical activity, International Physical Activity Questionnaire (IPAQ) category moderate/high vs low, corresponding to a threshold of ≥600 Metabolic Equivalent of Task-minute (MET) minutes/week, consistent with WHO recommendations (>150 minutes of moderate or >75 minutes of vigorous activity per week);[17, 18] and alcohol consumption, less-than-daily vs daily. The alcohol contrast is presented as exploratory, given the limited characterisation of the exposure and because alcohol is not an established risk factor for the composite outcome used here. Intermediary risk factors such as blood pressure and HbA1c were not considered as exposures, as they lie on the causal pathway between lifestyle and ASCVD, and their inclusion would introduce mediation bias.

Effect measures were absolute risk difference (ARD), predicted relative risk difference (RRD; calculated as ARD divided by SCORE2-predicted baseline risk; see Cardiovascular Risk Prediction Model Calibration below), and predicted number needed to treat (NNT) or harm (NNH). These terms are used in their conventional sense and denote differences in risk between exposure states at baseline, not the effect of a change in exposure. Heterogeneity in these effects was assessed by baseline SCORE2 risk category and by co-existing cardiovascular risk factors.

Causal Inference Framework

To estimate the potential cardiovascular benefit associated with each lifestyle risk factor from observational data, we used causal inference methods to adjust for baseline differences between groups. These rely on three assumptions: that the adjustment set captures all common causes of exposure and outcome; that both exposure states are possible for every participant; and that the exposure is consistently defined. None can be verified from the data alone.

For each exposure, a directed acyclic graph (DAG) was constructed to encode the assumed causal relationships between the exposure, outcome, and potential confounders (**Supplementary Figures 1–4**). Adjustment sets were specified separately for each exposure and are given in full in Supplementary Table 1. Each analysis also adjusted for the three lifestyle factors not under study, isolating the effect of each exposure independently. Adjustment sets were revised where robustness checks indicated inadequate adjustment, with candidates restricted to those consistent with existing knowledge of the causal structure and selection guided by the diagnostics rather than the estimates. The graphs presented are the final specifications.

Journal Pre-proof

Journal Pre-proof

Four estimation methods were applied: inverse propensity weighting (IPW), generalised linear models (GLM), augmented IPW (AIPW),[19] and double machine learning with causal forests (Supplementary Methods).[20] The latter additionally provided individualised treatment effect estimates, enabling identification of in whom the estimated differences are largest. Robustness was assessed with four checks (**Supplementary Methods**). A placebo (negative-control) test re-estimated the effect on an outcome that should be unaffected by the exposure; a non-zero estimate (the "residual effect") indicates residual confounding or model misspecification. Simulated confounding introduced an unmeasured confounder of known strength to quantify how much the estimate would shift. Subsampling re-estimated effects across random partitions of the data to assess stability. Standard regression sensitivity analyses examined dependence on model specification. Causal analyses were conducted in Python 3.8,[21] with data preparation and heterogeneity analyses performed in R 4.3.1.[22]

Cardiovascular Risk Prediction Model Calibration

We expressed the estimated differences as a percentage of the 10-year ASCVD risk predicted by SCORE2, contingent on its satisfactory calibration in UK Biobank. To evaluate SCORE2 performance in UK Biobank, 10-year risk was calculated using SCORE2 (individuals without diabetes) and SCORE2-DM (individuals with diabetes),[11, 12] and discrimination and calibration assessed using standard metrics. Where miscalibration was identified, logistic recalibration was applied (**Supplementary Methods**). Recalibrated predictions were used for European Society of Cardiology (ESC) risk category classification at baseline and in subsequent analyses. As the four-level ESC risk classification is defined on fatal rather than total (fatal and non-fatal) cardiovascular risk, recalibrated estimates using fatal and non-fatal events in those with or without diabetes were converted to a single fatal scale, analogous to the SCORE measure used in the 2019 guidance, before categories were assigned at baseline (**Supplementary Methods**). To benchmark the smoking effect, we recomputed each participant's SCORE2/SCORE2-DM risk with and without current-smoker status, holding all other covariates constant, and took the median difference as the algorithm-implied smoking-attributable risk.

Journal Pre-proof

Journal Pre-proof

Results

Participant Characteristics

Among the 371,102 UK Biobank participants included in the analysis, median age was 58 years (interquartile range 50–63), with 56% female and 96% of white ethnicity. The prevalence of modifiable lifestyle risk factors was: 10.6% current smokers, 24.6% with obesity (BMI ≥30 kg/m²), 20.3% consuming alcohol daily, and 15.1% with low physical activity levels (<600 MET-minutes/week). There were additionally 6.7% identified as having hypertension and 1.8% with diabetes. Lipid-lowering and blood-pressure-lowering therapy were received by 17.9% and 5.7% of participants. According to ESC risk stratification tool SCORE2,[11, 12] 83.2% were classified as low risk, 4.9% as moderate risk, 11.7% as high risk, and 0.1% as very high risk at baseline (**Table 1**).

Participants with the modifiable lifestyle risk factors of interest demonstrated distinct clinical profiles. Current smokers and, more markedly, individuals with obesity showed adverse cardiometabolic profiles: higher triglycerides, C-reactive protein, blood pressure and HbA1c, lower HDL-cholesterol, and higher prevalence of diabetes, hypertension and lipid-lowering medication use (Table 1). This higher baseline risk burden justifies confounder adjustment.

Ten-year cumulative incidence of cardiovascular disease varied substantially by lifestyle risk factor: 7.1% amongst current smokers against 3.9% in former or never smokers, 5.2% in individuals with obesity against 3.9% below a body mass index of 30 kg/m², 4.7% with low physical activity against 4.2% in the moderate or high categories, and 4.6% in daily alcohol consumers, against 4.2% with less-than-daily consumption.

Robustness and Sensitivity Analyses

For smoking and obesity contrasts, GLM passed all four robustness checks (**Table 2)**; IPW showed a small residual effect in the placebo test (0.33% and 0.30% respectively), suggesting minor sensitivity to model specification. Physical activity estimates remained stable but showed greater sensitivity to unmeasured confounding. Alcohol consumption showed the most complex pattern: IPW failed the placebo test (residual effect 0.82%), whilst GLM performed acceptably across all tests. The direction and magnitude of the alcohol estimate persisted when participants in poor baseline health, defined as renal impairment, underweight or type 1 diabetes, were excluded as a test of reverse causation (**Supplementary Table 2**).

Journal Pre-proof

Journal Pre-proof

Cardiovascular Risk Prediction Model Performance

To stratify participants by baseline cardiovascular risk and generate individualised risk trajectories, we validated SCORE2 and SCORE2-DM in our cohort. Both models demonstrated acceptable discrimination (C-statistics: SCORE2 0.716; SCORE2-DM 0.661). However, calibration assessment revealed systematic miscalibration: SCORE2 overpredicted risk by 10% (E/O 1.104) whilst SCORE2-DM underpredicted by 30% (E/O 0.704). Following logistic recalibration against the observed composite outcome, calibration in this cohort was by construction close to ideal (E/O 0.979 and 0.989 respectively; **Supplementary Figures 6–7).** Recalibrated predictions were used for individualised trajectory projections, and, after conversion to fatal scale, for ESC risk category classification.

Estimated Risk Differences

Table 2 presents estimated risk differences across four causal inference methods. The largest risk difference was for former or never versus current smoking (ARD 3.2–3.8%, RRD ~50%, NNT 26–31), followed by BMI <30 vs ≥30 kg/m^2 (ARD 1.0–1.1%, RRD ~20%, NNT 91–101). The risk difference between ≥600 and <600 MET-minutes/week was modest but consistent (ARD 0.2–0.4%, NNT 244–417). Less-than-daily vs daily alcohol consumption was associated with a small increase in cardiovascular risk (absolute risk increase 0.3–0.4%, NNH 227–303). Estimates were consistent in direction and magnitude across all four methods; wider confidence intervals for AIPW and double machine learning reflect their reliance on fewer modelling assumptions. As a benchmark, predicted smoking-attributable risk derived from SCORE2 and SCORE2-DM (median 2.2% and 4.7% respectively) bracketed our estimates (ARD 3.2–3.8%), consistent with the mixed diabetes status of the cohort. Confidence in these estimates differs. The smoking contrast was the largest, was consistent across methods, and agreed with external benchmarks; the obesity and physical activity contrasts were smaller but similarly consistent. The alcohol contrast was the only one in the opposite direction and showed the largest residual effect in the placebo test.

Heterogeneity by Cardiovascular Risk Profile

Across all contrasts, ARDs increased with baseline cardiovascular risk category, whilst RRDs showed the opposite pattern, reflecting the mathematical relationship between absolute and relative effects at differing baseline risks (**Figure 2**). The smoking contrast showed the steepest absolute gradient (3.10% ARD in low-risk to 3.81% ARD in very-high-risk individuals) and the sharpest fall in RRD across increasing ESC risk categories (60% to 17%), consistent with a fixed potential additive benefit applied to an increasingly high baseline. Estimates in the very-high-risk category rest on small numbers, between 27 and 147

Journal Pre-proof

participants depending on the contrast, and should be interpreted with caution. The other three contrasts showed more attenuated gradients across risk strata.

Absolute risk differences also increased with the number of co-existing lifestyle risk factors (smoking, obesity, low physical activity, and alcohol consumption) for most contrasts (**Figure 3**). The smoking ARD rose from 3.25% with no co-existing factors to 4.03% with three or more. Physical activity ARD nearly doubled with increasing risk factor burden (0.38% to 0.72%). The obesity contrast showed a modest inverse pattern (1.13% to 0.99%), and the small increase in risk associated with less-than-daily alcohol consumption was fairly consistent across strata.

Stratification by prevalent clinical conditions **(Supplementary Figure 5**) showed modestly higher absolute difference in participants with diabetes or hypertension, with effect estimates otherwise consistent across subgroups including familial hypercholesterolaemia.

Effect Modification by Exposure Intensity

Figure 4A shows the estimated risk difference for the smoking contrast increasing with cumulative pack-years. **Figure 4B** shows the estimated risk difference for the BMI contrast which declines slightly across the range of baseline BMI. To quantify these relationships, predicted ARD was regressed on standardised continuous pack-years and BMI respectively; neither variable was included in the respective causal forest models. Each 1 SD increase in pack-years was associated with a 0.234 percentage point greater predicted ARD for the smoking contrast ($p<0.001$; $R^2=0.04$). Each 1 SD increase in BMI was associated with a 0.035 percentage point reduction in predicted ARD for the BMI contrast ($p<0.001$; $R^2=0.005$).

Individualised Risk Trajectories

Figure 5 presents 30-year cardiovascular risk trajectories under alternative lifestyle risk factor scenarios for two illustrative participants representing high-risk (SCORE2-DM 12%) and lower-risk (SCORE2 6%) profiles.

The high-risk participant had a baseline 10-year risk of 12%, projected to rise to 22% at 20 years. Had the same participant not been a smoker, the projected 20-year risk would have been 13%; had he not been obese, 21%; and had he been physically active, 21.8%. The lower-risk participant had a baseline 10-year risk of 6%, projected to rise to 11% at 20 years, with corresponding counterfactual projected 20-year risks of 6.5%, 9% and 10%.

Journal Pre-proof

Journal Pre-proof

Discussion

This study employed causal machine learning to estimate individualised risk CVD differences for four lifestyle risk factors amongst 371,102 UK Biobank participants. Using exposure-specific directed acyclic graphs and four complementary causal inference methods, the largest estimated difference was for former or never versus current smoking (ARD 3.2–3.8%), followed by BMI <30 versus ≥30 kg/m² (ARD 1.0–1.1%) and moderate or high versus low physical activity (ARD 0.2–0.4%). By contrast, less-than-daily alcohol consumption was associated with a small increase in risk (absolute risk increase 0.4%). Estimated risk differences were larger at higher baseline cardiovascular risk and with a greater number of co-existing lifestyle risk factors. The consistency of estimates across methods, combined with individualised risk estimation, may inform the development of lifestyle counselling tools to guide shared clinical decision-making. The difference associated with former or never smoking increased with baseline pack-years, whereas the difference for the BMI contrast varied little across the range of baseline BMI.

Our smoking estimates align with established observational cohort studies. The Framingham Heart Study and Nurses' Health Study demonstrated that smoking cessation was associated with approximately 50% lower cardiovascular mortality within years of quitting, with sustained benefits over decades.[23-25] Our estimated relative risk difference of approximately 50% is consistent with these findings, albeit across a broader composite outcome including non-fatal myocardial infarction and stroke, and our contrast compares smoking status at baseline rather than observed cessation, with a comparator that pools former with never-smokers who differ in residual risk. Our ARD estimates of 3.2–3.8% align with the smoking-attributable risk encoded in SCORE2 and SCORE2-DM (median 2.2% and 4.7% respectively),[11, 12] which bracketed our estimates, consistent with the cohort's mixed diabetes status.

Findings for the BMI contrast require careful contextualisation. The Look AHEAD trial of intensive lifestyle intervention in type 2 diabetes showed no significant reduction in the primary cardiovascular endpoint despite meaningful weight loss.[5] A post-hoc per-protocol analysis, however, showed that participants who actually achieved ≥10% weight loss had a 21% lower cardiovascular risk (HR 0.79), suggesting the intention-to-treat null result reflects insufficient sustained weight reduction rather than the absence of a biological effect.[26] Emerging evidence suggests substantial cardiovascular benefits from pharmacologically induced weight loss. In SELECT, semaglutide (median 9.4% weight loss) reduced major adverse cardiovascular events by 20% in established cardiovascular disease and obesity.[27] The Swedish Obese Subjects (SOS) study of bariatric surgery showed substantial cardiovascular benefits following

Journal Pre-proof

major weight reduction, with hazard ratios ranging from 0.50 to 0.70.[28] Our estimates of 1.0–1.1% absolute risk difference (19% RRD) are consistent in direction with these trials, but concerns obesity status at baseline rather than the magnitude of weight change.

Physical activity is associated with lower cardiovascular risk across cohort studies and meta-analyses: a meta-analysis of 33 cohort studies reported 35% lower cardiovascular mortality,[29] and a 19% lower CVD incidence with leisure-time activity across 103 cohorts.[30] Our estimated 8.5% relative risk difference is more modest. Our exposure, self-reported and derived from the IPAQ questionnaire, captures overall activity status at baseline (<600 vs ≥600 MET-minutes weekly) without distinguishing leisure from occupational domains, and we cannot examine whether the physical activity paradox, in which leisure-time activity lowers cardiovascular risk whilst occupational activity does not,[30, 31] or the attenuation of benefit reported at very high exercise volumes (≥3,000 MET-minutes/week),[32] contributes to this difference.

The alcohol findings should be regarded as exploratory. Less-than-daily compared with daily consumption was associated with a small increase in cardiovascular risk, a direction consistent with the J-shaped curve observed in epidemiological studies,[33, 34] but not with recent Mendelian randomisation evidence.[35] Our exposure captures frequency alone, not quantity consumed per occasion and therefore does not capture “binge drinking”, nor beverage type. We defined the exposure this way because drinking frequency is a behaviour individuals can recognise and modify without measurement, and because it is more reliably self-reported than volume. Reverse causation and differential non-cardiovascular mortality are each plausible contributors, and neither could be excluded with the present data.

Exposure intensity modified the estimated risk differences in opposite directions for the two dominant factors. For smoking, the estimated risk difference rose with cumulative exposure before plateauing and remained substantial even among those with the heaviest exposure. For BMI, the difference was slightly smaller at higher baseline BMI, though the gradient was small and based on few participants at the highest values. Cumulative tobacco exposure explained considerably more between-individual variation in the estimates than baseline BMI (R^2=0.04 vs 0.005), and it is there that meaningful heterogeneity lies.

The 2021 ESC Guidelines on cardiovascular disease prevention emphasise lifestyle modification as the cornerstone of prevention, assigning Class I recommendations to smoking cessation, weight management, and physical activity.[38] Our findings provide quantitative support for these recommendations

Journal Pre-proof

whilst highlighting important nuances. Relative differences declined across ascending risk strata, so lifestyle factors account for proportionally more of the risk in those at lower baseline risk and lesser atherosclerotic burden, whereas higher-risk individuals may additionally require pharmacotherapy. Effect modifiers help identify in whom the estimated difference in risk are the largest, supporting targeted resource allocation.

In prior work, Naito and colleagues performed a related analysis in UK Biobank, asking whether the magnitude of the association between lifestyle exposures and disease varies by genetic risk, and concluding that in large part it does not.[39] Our aim is different: we estimate the individual risk difference itself, conditioned on characteristics routinely available in clinical practice rather than on genotype. Our outcome is a composite of incident cardiovascular death, non-fatal myocardial infarction and non-fatal stroke within ten years of baseline, whereas that analysis used disease-specific endpoints and combined prevalent with incident cases.

Strengths and Limitations

Strengths include a large sample with extended follow-up, enabling examination of treatment-effect heterogeneity across subgroups. The causal inference framework incorporates four complementary methods—inverse propensity weighting, generalised linear models, augmented inverse propensity weighting, and double machine learning with causal forests—extending beyond traditional propensity score approaches. This multi-method approach with convergent estimates across different causal identification strategies strengthens confidence that findings are not artefacts of particular modelling assumptions. The double machine learning framework enabled individualised treatment effect estimation and assessment of effect modification by continuous exposure variables (pack-years, body mass index), capabilities beyond standard propensity score methods. Important limitations warrant consideration. These data are observational and cannot fully eliminate unmeasured confounding despite comprehensive adjustment. Causal machine learning permits estimation of heterogeneous effects but does not address unmeasured confounding, and our estimates remain conditional on the available measured adjustment data. Unlike supervised machine learning, causal inference estimates scenarios that were not observed; one cannot know whether our estimate of what would have happened had a smoker never smoked is accurate, as this counterfactual was never realised. The robustness checks, likewise, test sensitivity to specified violations, and agreement between methods cannot establish whether the heterogeneity we report is real. This also limits formal external validation of our

Journal Pre-proof

Journal Pre-proof

tool beyond assessing calibration of baseline risk predictions in independent populations. Our intent, however, is not to develop a predictive model but a decision support tool that quantifies counterfactual treatment effects to inform shared clinical decision-making rather than predict individual outcomes.

Cross-sectional exposure definitions preclude distinction between intentional and incidental lifestyle differences; for weight in particular,[40] those classified as non-obese may include individuals who never had obesity, alongside those at lower weight following intentional or unintentional weight loss. Unintentional weight loss may be caused by disease that puts patients at higher baseline risk, diluting our estimate. Confidence intervals for stratum-specific estimates narrow with increasing stratum size, as they reflect the distribution of individual treatment effects rather than model uncertainty, and should be interpreted accordingly. Unmeasured confounders, including socioeconomic factors, dietary patterns, psychological characteristics, and healthcare access may bias estimates in unpredictable directions. UK Biobank represents a healthier, more educated and predominantly White subset of the general population, and is not representative of the UK population,[41] particularly those at highest cardiometabolic risk, which may yield underestimated estimates of potential effect sizes. Our outcome was a binary indicator of a cardiovascular death, non-fatal myocardial infarction or non-fatal stroke within ten years rather than a time-to-event endpoint, so censoring was not performed: participants who died of non-cardiovascular causes were coded identically to those who remained event-free. Binary exposure definitions may not capture dose-response relationships optimally, and we cannot assess how long any exposure state had been held. For BMI specifically, dichotomisation may mask heterogeneity in body adiposity and its distribution, as individuals with the same body mass index may differ in lean mass and in central adiposity, affecting the accuracy of our estimates. Combined effects were not estimated; individual effects presented separately represent a conservative lower bound on the total difference in risk associated with differences in more than one exposure. The 10-year follow-up window may not capture full risk difference across the lifetime, particularly for exposure initiated at younger ages. Direct cross-cohort replication is constrained by the limited availability of comparable cohorts. Future replication will be required, and especially so in non-European ancestry populations who may have different baseline risk profiles and lifestyle patterns.

Conclusion

In this causal machine learning analysis of a large prospective cohort, former or never smoking, a body mass index below 30 kg/m², and moderate or high physical activity were each associated with meaningful differences in cardiovascular risk. These findings provide additional evidence to support individualised

Journal Pre-proof

estimates to help dialogue during shared decision-making in cardiovascular disease prevention. Findings are accessible via a free tool (lifestyle-cvd.casefinding.com).

Acknowledgements and Funding

This research was conducted using the UK Biobank Resource (application number 67789). Access to the UK Biobank data was funded by the EAS Familial Hypercholesterolemia Studies Collaboration.

KID acknowledges support for a PhD Studentship from the National Institute for Health and Care Research (NIHR) Applied Research Collaboration Northwest London. The views expressed in this publication are those of the authors and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

AJVV acknowledges support from the Programme "Beatriz Galindo" from the Ministry of Universities, Spain, and University of Seville, Spain.

KKR acknowledges support from the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre, UK; his institution (Imperial College London) also receives support from the NIHR Applied Research Collaboration Northwest London.

Contributions

CATS: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Visualization, Project administration; Funding acquisition; **JB, AE**: Methodology, Formal analysis, Investigation, Writing - Review & Editing; **KID, IK, DL**: Writing - Review & Editing; **FB**: Data Curation, Investigation, Writing - Review & Editing; **SK**: Formal analysis, Data Curation; **AM, MTAS**: Methodology, Investigation, Writing - Review & Editing**; AJVV**: Conceptualization, Methodology, Investigation, Data Curation, Writing - Review & Editing, Supervision; **KKR**: Conceptualization, Methodology, Investigation, Writing - Review & Editing, Supervision, Funding acquisition;

Journal Pre-proof

Journal Pre-proof

Disclosures of Interest

CATS reports past or current participation in research grants to Imperial College London from Pfizer, Amgen, Merck Sharp & Dohme, Novartis, Sanofi-Aventis, Daiichi Sankyo, Ultragenyx, and Regeneron. **JB** received speaker honoraria from Amgen, Daiichi Sankyo, Novartis, Novo Nordisk, Sanofi and research grant support from AstraZeneca, outside the submitted work. **AE** reports past or current participation in research grants to Imperial College London from Daiichi Sankyo, Merck Sharp & Dohme, and Regeneron. **FB** reports personal fees and research grants from Novartis, Amgen, Novo Nordisk, Chiesi, Eli Lilly, and honoraria from Novartis, Viatris and Sanofi. **KID** reports past or current participation in research grants to Imperial College London from Pfizer, Amgen, Merck Sharp & Dohme, Sanofi-Aventis, Daiichi Sankyo, and Regeneron, outside the submitted work; and personal fees for consulting from Bayer and Regeneron, all outside the submitted work. **IK** reports past or current participation in research grants to Imperial College London from Ultragenyx. **SK** reports past or current participation in research grants to Imperial College London from Daiichi Sankyo, Merck Sharp & Dohme. **DL** reports past or current participation in research grants to Imperial College London from Daiichi Sankyo. **AJVV** reports past or current participation in research grants to Imperial College London from Pfizer, Amgen, Merck Sharp & Dohme, Sanofi-Aventis, Daiichi Sankyo, and Regeneron, outside the submitted work; and personal fees for consulting from Bayer and Regeneron outside the submitted work. **KKR** reports receiving lecture fees from Aegerion Pharmaceuticals, Kowa, Cipla, Algorithm, and Zuelling Pharma; grant support paid to his institution; lecture fees and advisory board fees from Amgen, Regeneron Pharmaceuticals/Sanofi, and Pfizer; lecture fees and fees for serving on steering committees for trials from AstraZeneca and Eli Lilly; fees for serving on steering committees for trials from Cerenis Therapeutics, The Medicines Company, and Esperion; advisory board fees from Akcea Therapeutics, Novartis, Silence Therapeutics, Bayer, and Daiichi Sankyo; lecture fees and advisory board fees from Takeda, Boehringer Ingelheim, and Dr Reddy's Laboratories; grant support and advisory board fees from Merck Sharp & Dohme; fees for serving on a clinical events adjudication committee from AbbVie; and fees for serving as principal investigator for a trial from Resverlogix. **MTAS** and **AM** do not have conflict of interest to disclose.

Journal Pre-proof

Journal Pre-proof

Data availability statement

The data used in this study is available from the UK Biobank, but restrictions apply to the availability of these data, and so are not publicly available. Researchers will need to apply to access the UK Biobank database at www.ukbiobank.ac.uk. The underlying source code is not publicly available owing to intellectual-property considerations; the tool is freely accessible at lifestyle-cvd.casefinding.com.

References

1. Institute for Health Metrics and Evaluation. Global Burden of Disease Results 2019 [1 Dec 2024]. Available from: https://vizhub.healthdata.org/gbd-results/.
2. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-88.
3. Andersson EM, Lindvall K, Wennberg P, Johansson H, Nordin S. From risk communication about asymptomatic atherosclerosis to cognitive and emotional reactions and lifestyle modification. BMC Psychol. 2024;12(1):47.
4. Sebastian SA, Shah Y, Paul H, Arsene C. Life's Essential 8 and the risk of cardiovascular disease: a systematic review and meta-analysis. Eur J Prev Cardiol. 2025;32(5):358-73.
5. The Look AHEAD Research Group. Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes. N Engl J Med. 2013;369(2):145-54.
6. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11):e596-e646.
7. Shi J, Norgeot B. Learning Causal Effects From Observational Data in Healthcare: A Review and Summary. Front Med (Lausanne). 2022;9:864882.
8. Feuerriegel S, Frauen D, Melnychuk V, Schweisthal J, Hess K, Curth A, et al. Causal machine learning for predicting treatment outcomes. Nat Med. 2024;30(4):958-68.
9. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424.
10. Austin PC. A Tutorial and Case Study in Propensity Score Analysis: An Application to Estimating the Effect of In-Hospital Smoking Cessation Counseling on Mortality. Multivariate Behav Res. 2011;46(1):119-51.
11. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439-54.
12. SCORE2-Diabetes Working Group and the ESC Cardiovascular Risk collaboration. SCORE2-Diabetes: 10-year cardiovascular risk estimation in type 2 diabetes in Europe. Eur Heart J. 2023;44(28):2544-56.

Journal Pre-proof

Journal Pre-proof

13. Komuro K, Kaneko H, Komuro J, Suzuki Y, Okada A, Mizuno A, et al. Differences in the association of lifestyle-related modifiable risk factors with incident cardiovascular disease between individuals with and without diabetes. Eur J Prev Cardiol. 2025;32(5):376-83.
14. Walli-Attaei M, Aboyans V. The capital importance of lifestyle and diet in cardiovascular disease prevention. Eur J Prev Cardiol. 2025;32(5):355-7.
15. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562(7726):203-9.
16. Van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw. 2011;45(3):1 - 67.
17. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35(8):1381-95.
18. World Health Organization. WHO Guidelines on Physical Activity and Sedentary Behaviour. Geneva: World Health Organization; 2020.
19. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70(1):41-55.
20. Chernozhukov V, Chetverikov D, Demirer M, Duflo E, Hansen C, Newey W, et al. Double/debiased machine learning for treatment and structural parameters. Econom J. 2018;21(1):C1-C68.
21. Python Software Foundation. Python Language Reference, version 3.8. Python Software Foundation; 2019.
22. R Core Team. R: A Language and Environment for Statistical Computing. 2021.
23. Sytkowski PA, Kannel WB, D'Agostino RB. Changes in Risk Factors and the Decline in Mortality from Cardiovascular Disease. N Engl J Med. 1990;322(23):1635-41.
24. Duncan MS, Freiberg MS, Greevy RA, Jr, Kundu S, Vasan RS, Tindle HA. Association of Smoking Cessation With Subsequent Risk of Cardiovascular Disease. JAMA. 2019;322(7):642-50.
25. Kenfield SA, Stampfer MJ, Rosner BA, Colditz GA. Smoking and smoking cessation in relation to mortality in women. JAMA. 2008;299(17):2037-47.
26. The Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol. 2016;4(11):913-21.
27. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023;389(24):2221-32.
28. Sjöström L, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H, et al. Bariatric surgery and long-term cardiovascular events. JAMA. 2012;307(1):56-65.
29. Nocon M, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008;15(3):239-46.
30. Kazemi A, Soltani S, Aune D, Hosseini E, Mokhtari Z, Hassanzadeh Z, et al. Leisure-time and occupational physical activity and risk of cardiovascular disease incidence: a systematic review and dose-response meta-analysis of prospective cohort studies. Int J Behav Nutr Phys Act. 2024;21(1):45.
31. Holtermann A, Schnohr P, Nordestgaard BG, Marott JL. The physical activity paradox in cardiovascular disease and all-cause mortality: the contemporary Copenhagen General Population Study with 104 046 adults. Eur Heart J. 2021;42(15):1499-511.

Journal Pre-proof

32. Berry JD, Zabad N, Kyrouac D, Leonard D, Barlow CE, Pavlovic A, et al. High-Volume Physical Activity and Clinical Coronary Artery Disease Outcomes: Findings From the Cooper Center Longitudinal Study. Circulation. 2025;151(18):1299-308.
33. O'Keefe JH, Bhatti SK, Bajwa A, DiNicolantonio JJ, Lavie CJ. Alcohol and Cardiovascular Health: The Dose Makes the Poison…or the Remedy. Mayo Clin Proc. 2014;89(3):382-93.
34. Roerecke M, Rehm J. The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. Addiction. 2012;107(7):1246-60.
35. Carr S, Bryazka D, McLaughlin SA, Zheng P, Bahadursingh S, Aravkin AY, et al. A burden of proof study on alcohol consumption and ischemic heart disease. Nat Commun. 2024;15(1):4082.
36. Ananda RA, Solomon B, Nicholls SJ, Ray KK. Obesity, metabolic health status, and adverse outcomes in men and women. Am J Prev Cardiol. 2026;28:101556.
37. Ananda RA, Solomon B, Ray KK. Individual and joint associations of obesity and metabolic health parameters on arterial stiffness: Evidence from the UK Biobank. Diabetes Obes Metab. 2025;27(2):899-910.
38. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). Eur Heart J. 2021;42(34):3227-337.
39. Naito T, Inoue K, Namba S, Sonehara K, Suzuki K, Matsuda K, et al. Machine learning reveals heterogeneous associations between environmental factors and cardiometabolic diseases across polygenic risk scores. Communications Medicine. 2024;4(1):181.
40. Pack QR, Rodriguez-Escudero JP, Thomas RJ, Ades PA, West CP, Somers VK, et al. The prognostic importance of weight loss in coronary artery disease: a systematic review and meta-analysis. Mayo Clin Proc. 2014;89(10):1368-77.
41. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. Am J Epidemiol. 2017;186(9):1026-34.

Table 1 Participants summary characteristics by lifestyle modifiable risk factor

Characteristics	Study Population (N=371,102)	Current Smoker (N=39,472)	Obese (N=91,454)	Daily alcohol user (N=75,266)	Low Physical Activity (N=56,150)
Age (years)[1]	58 (50,63)	55 (48,61)	58 (51,63)	60 (53,64)	57 (50,62)
Gender[2]					
Male	162,968 (43.91)	20,724 (52.50)	41,473 (45.35)	41,962 (55.75)	25,833 (46.01)
Female	208,134 (56.09)	18,748 (47.50)	49,981 (54.65)	33,304 (44.25)	30,317 (53.99)

Journal Pre-proof

Journal Pre-proof

Characteristics	Study Population (N=371,102)	Current Smoker (N=39,472)	Obese (N=91,454)	Daily alcohol user (N=75,266)	Low Physical Activity (N=56,150)
Ethnicity[2]					
White	355,640 (95.83)	37,672 (95.44)	87,091 (95.23)	74,100 (98.45)	53,387 (95.08)
Asian	6992 (1.88)	685 (1.74)	1563 (1.71)	479 (0.64)	1367 (2.43)
Black	5919 (1.59)	778 (1.97)	2346 (2.57)	385 (0.51)	963 (1.72)
Chinese	1119 (0.30)	70 (0.18)	71 (0.08)	78 (0.10)	196 (0.35)
Mixed	1432 (0.39)	267 (0.68)	383 (0.42)	224 (0.30)	237 (0.42)
BMI Weight Categories[2]					
Underweight <18.5	1845 (0.50)	429 (1.09)	NA	420 (0.56)	255 (0.45)
Normal: 18.5-25	120,141 (32.37)	13,834 (35.05)	NA	27,151 (36.07)	14,423 (25.69)
Overweight: - 25-30	157,662 (42.48)	16,295 (41.28)	NA	33,658 (44.72)	23,011 (40.98)
Obese >=30	91,454 (24.64)	8914 (22.58)	91,454 (100.00)	14,037 (18.65)	18,461 (32.88)
Smoking[2]					
No or ex	331,630 (89.4)	NA	82,540 (90.3)	65,057 (86.4)	49,333 (87.9)
Yes	39,472 (10.6)	39,472 (100.0)	8914 (9.7)	10,209 (13.6)	6817 (12.1)
Alcohol[2]					
Never	29,736 (8.0)	3124 (7.9)	9254 (10.1)	NA	5063 (9.0)
Special occasion	43,489 (11.7)	5234 (13.3)	14,604 (16.0)	NA	7000 (12.5)
1x to 3x a month	41,846 (11.3)	4437 (11.2)	12,441 (13.6)	NA	6714 (12.0)
1x or 2x a week	95,614 (25.8)	8990 (22.8)	23,749 (26.0)	NA	14,155 (25.2)
3x or 4x a week	84,758 (22.8)	7430 (18.8)	17,227 (18.8)	NA	11,778 (21.0)
Daily or almost daily	75,266 (20.3)	10,209 (25.9)	14,037 (15.3)	75,266 (100.0)	11,440 (20.4)
Physical Activity (IPAQ)[2]					
Missing	72,242 (19.5)	8649 (21.9)	20,706 (22.6)	11,894 (15.8)	0 (0%)
Low	56,150 (15.1)	6817 (17.3)	18,461 (20.2)	11,440 (15.2)	56,150 (100.0)
Moderate	121,245 (32.7)	11,856 (30.0)	28,323 (31.0)	26,310 (35.0)	NA
High	121,465 (32.7)	12,150 (30.8)	23,964 (26.2)	25,622 (34.0)	NA
Systolic blood pressure (mmHg)[1]	136.5 (125.0,149.5)	134.0 (122.5,147.0)	140.0 (129.0,152.5)	139.0 (127.0,152.5)	136.0 (124.0,148.5)
Diastolic blood pressure (mmHg)[1]	82.0 (75.0,89.0)	81.5 (74.5,88.5)	86.0 (79.0,92.0)	83.5 (76.5,90.0)	82.5 (75.5,89.5)

Journal Pre-proof

Characteristics	Study Population (N=371,102)	Current Smoker (N=39,472)	Obese (N=91,454)	Daily alcohol user (N=75,266)	Low Physical Activity (N=56,150)
Low-density lipoprotein cholesterol (mmol/L)[1]	3.56 (3.00,4.13)	3.57 (3.00,4.18)	3.57 (2.98,4.17)	3.56 (3.02,4.14)	3.56 (2.99,4.15)
High-density lipoprotein cholesterol (mmol/L)[1]	1.45 (1.21,1.71)	1.38 (1.14,1.65)	1.30 (1.10,1.57)	1.57 (1.31,1.83)	1.40 (1.15,1.67)
HbA1c (mmol/mol)[1]	35.3 (32.8,38.0)	36.2 (33.7,39.0)	36.6 (33.9,39.6)	34.9 (32.5,37.4)	35.4 (32.8,38.3)
Diabetes[2]	6767 (1.8)	773 (2.0)	3567 (3.9)	921 (1.2)	1474 (2.6)
Hypertension[2]	24,896 (6.7)	2185 (5.5)	11,068 (12.1)	4674 (6.2)	4443 (7.9)
Lipid lowering medication[2]	66,349 (17.9)	6729 (17.0)	23,220 (25.4)	14,037 (18.6)	10,953 (19.5)
ESC Risk Category[2]					
Low	308,937 (83.2)	28,704 (72.7)	72,838 (79.6)	61,244 (81.4)	46,457 (82.7)
Moderate	18,310 (4.9)	6091 (15.4)	5217 (5.7)	5148 (6.8)	2718 (4.8)
High	43,484 (11.7)	4650 (11.8)	13,252 (14.5)	8828 (11.7)	6872 (12.2)
Very-high	371 (0.1)	27 (0.1)	147 (0.2)	46 (0.1)	103 (0.2)
Incident CVD (10-years)[2]	15,752 (4.2)	2809 (7.1)	4783 (5.2)	3462 (4.6)	2639 (4.7)

[1] Median (IQR)
[2] N (%)
Abbreviations: BMI, body mass index; IPAQ, International Physical Activity Questionnaire; FH, familial hypercholesterolaemia; HbA1c, glycated haemoglobin; ESC, European Society of Cardiology; CVD, cardiovascular disease; IQR, interquartile range; NA, not applicable.

Characteristics of the study population are presented as an overall description; the exposure groups are subsets of this population and are not mutually exclusive, so differences between an exposure column and the study population column should not be interpreted as between-group contrasts. Four separate 'unexposed' columns are not shown as participants may belong to multiple exposure categories simultaneously and given the low prevalence of individual risk factors (10–25%), unexposed subgroups largely approximate the overall cohort characteristics.

Table 2: Average predicted treatment effect of lifestyle modifiable risk factors with four methods and robustness checks

Lifestyle Contrasts and Causal Analysis Methods	ARD % (95% CI)	Predicted RRD % (95% CI)	Predicted NNT / NNH (95% CI)	Sensitivity (robustness) Tests			
				Placebo[1]	Random Cause[2]	Subset Refuter[3]	Unobserved cause[4]
Smoking							

Journal Pre-proof

between patients: former/never vs current smoker at baseline							
IPW	3.67 (3.38, 3.95)	51.60 (47.57, 55.63)	27 (25,30)	✗(e=0.33%)	✓ (Δ=0%)	✓(Δ=0.01%)	✓ (Δ=0.82%)
GLM	3.83 (3.58, 4.07)	53.86 (50.44, 57.29)	26 (25,28)	✓(e=0.00%)	✓ (Δ=0%)	✓(Δ=0.03%)	✓ (Δ=0.84%)
AIPW[5]	3.23 (2.33, 4.13)	45.47 (32.74, 58.19)	31 (24,47)	-			
DML[5]	3.50 (2.20,4.80)	49.27 (31.01, 67.53)	29 (21,45)	-			
Obesity							
between patients: <30 vs ≥30 kg/m² at baseline							
IPW	1.00 (0.84, 1.17)	19.18 (15.96, 22.40)	100 (85,119)	✗(e=0.30%)	✓ (Δ=0%)	✓(Δ=0.08%)	✓(Δ=0.20%)
GLM	1.09 (0.93, 1.25)	20.83 (17.82, 23.83)	92 (80,108)	✓(e=0.01%)	✓ (Δ=0%)	✓(Δ=0.01%)	✓(Δ=0.19%)
AIPW[5]	0.99 (0.53, 1.44)	18.86 (10.20, 27.53)	101 (69,189)	-			
DML[5]	1.10 (0.32, 1.88)	21.00 (6.03, 35.96)	91 (53,312)	-			
Physical Activity							
between patients: moderate/high (≥600 MET-minutes/week) vs low (<600 MET-minutes/week) IPAQ category at baseline							
IPW	0.40 (0.21, 0.59)	8.51 (4.52, 12.51)	250 (169,476)	✓(e=0.07%)	✓ (Δ=0%)	✓(Δ=0.00%)	⚠ (Δ=0.22%)
GLM	0.41 (0.26, 0.55)	8.63 (5.47, 11.78)	244 (182,384)	✓(e=0.01%)	✓ (Δ=0%)	✓(Δ=0.03%)	⚠ (Δ=0.35%)
AIPW[5]	0.24 (-0.21, 0.69)	5.04 (-4.57, 14.66)	NNT 417 (145, NNH 476)	-			
DML[5]	0.40 (-0.38, 1.18)	8.51 (-8.17, 25.19)	NNT 250 (87, NNH 263)	-			
Alcohol Consumption							
between patients: less-than-daily vs daily alcohol consumption at baseline							
IPW	-0.40 (-0.52, -0.29)	-8.75 (-11.29, -6.22)	NNH 250 (192, 345)	✗(e=0.82%)	✓ (Δ=0%)	✓(Δ=0.01%)	⚠ (Δ=0.28%)
GLM	-0.44 (-0.55, -0.33)	-9.49 (-11.88, -7.09)	NNH 227 (182, 303)	✓(e=0.01%)	✓ (Δ=0%)	✓(Δ=0.01%)	✓ (Δ=0.21%)
AIPW[5]	-0.33 (-0.78, 0.13)	-7.16 (-17.04, 2.72)	NNH 303 (128, NNT 769)	-			
DML[5]	-0.40 (-0.99, 0.19)	-8.70 (-21.50, 4.09)	NNH 250 (101, NNT 526)	-			

[1] Placebo: Treatment assignments were randomly permuted; e = residual effect. ✓ p>0.05 (effect not distinguishable from chance); ✗ p≤0.05 (residual effect detected).

[2] Random Cause: A simulated common confounder was introduced; Δ = absolute change in ARD. ✓ <20% relative change in estimate; ✗ ≥20% relative change.

[3] Subset Refuter: Estimate stability was assessed across ten random 80% subsamples; Δ = absolute change in ARD. ✓ p>0.05 or <30% relative change; ✗ otherwise.

[4] Unobserved Cause: A hypothetical unmeasured confounder was introduced (effect on treatment: binary flip probability 0.01; effect on outcome: linear effect 0.02); Δ = absolute change in ARD. ✓ <50% relative change; ⚠ ≥50% relative change.

[5] Sensitivity tests were not applied to AIPW and DML as they were not available for these estimators in the software used.

Journal Pre-proof

Journal Pre-proof

Predicted number needed to treat and number needed to harm are the reciprocals of a modelled counterfactual risk difference between groups defined at baseline. They are not equivalent to values derived from randomised trials, in which a treatment strategy is assigned, and should not be read as the number of individuals who must change a behaviour in order to prevent one event.

Abbreviations: ARD: absolute risk difference; RRD: relative risk difference; NNT: number needed to treat; NNH: number needed to harm; CI: confidence interval; IPW: inverse propensity weighting; GLM: generalised linear model; AIPW: augmented inverse propensity weighting; DML: double machine learning; IPAQ: International Physical Activity Questionnaire.

Journal Pre-proof

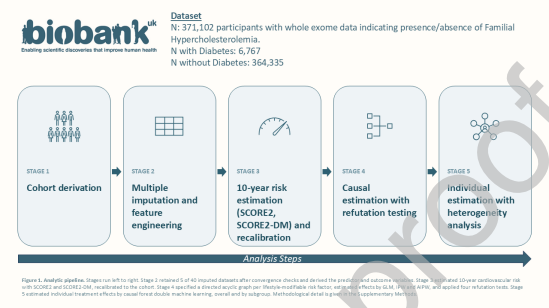


Figure 1: Overview of the analytical workflow

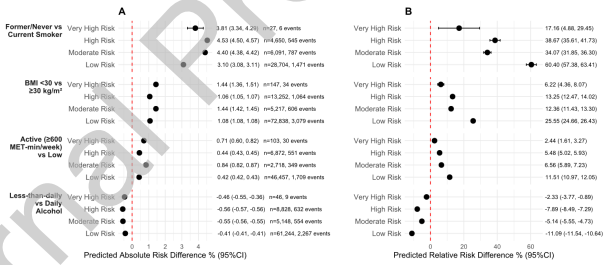


Figure 2: Absolute (A) and relative (B) risk difference associated with each lifestyle contrast, stratified by ESC cardiovascular risk category (low, moderate, high, very high) at baseline. Points represent mean treatment effects estimated using double machine learning causal forests; horizontal bars represent 95% confidence intervals.

Journal Pre-proof

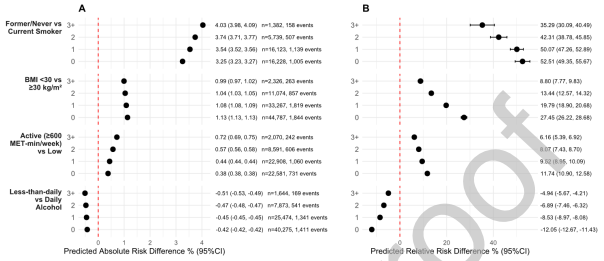


Figure 3: Absolute (A) and relative (B) risk difference associated with each lifestyle contrast, stratified by number of co-existing lifestyle risk factors (0, 1, 2, ≥3) at baseline, excluding the lifestyle factor under study. Points represent mean treatment effects estimated using double machine learning causal forests; horizontal bars represent 95% confidence intervals. Co-existing lifestyle risk factors comprised current smoking, obesity (BMI ≥30 kg/m²), low physical activity (<600 MET-minutes/week), and daily alcohol consumption.

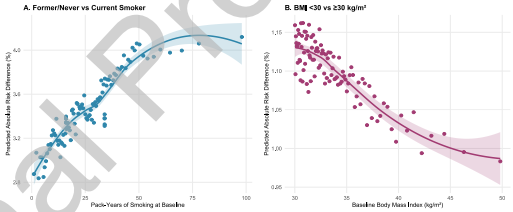


Figure 4: Absolute risk difference associated with (A) smoking status (former/never vs current) by cumulative pack-year exposure, and with (B) BMI category (<30 vs ≥30 kg/m²) by baseline BMI; both estimated using double machine learning causal forests adjusted for all covariates in their respective directed acyclic graphs. Note the differing vertical scales.

Predicted absolute risk difference was regressed on standardised pack-years and standardised baseline BMI respectively; neither variable was included in the corresponding causal forest. Panel A conditions on cumulative pack-years within the pooled comparator and does not distinguish former from never smokers. The gradient across baseline BMI in panel B is small and rests on few participants at the highest values.

Journal Pre-proof

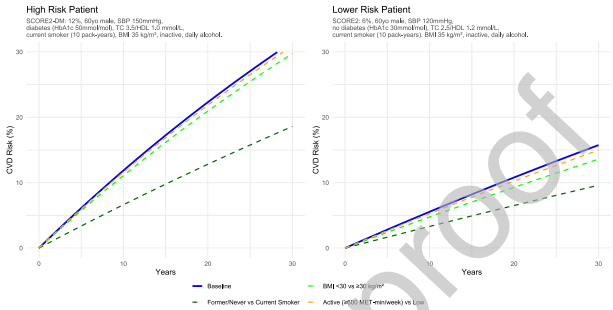


Figure 5 (Central Illustration): Projected 30-year cardiovascular disease risk trajectories for a high-risk (SCORE2-DM 12%) and lower-risk (SCORE2 6%) patient, under alternative lifestyle risk factor profile.

Trajectories assume proportional hazards, with individual treatment effects estimated using double machine learning causal forests. Dashed lines represent the projected risk had the same participant been in the alternative exposure category for each lifestyle contrast at recruitment; they do not represent the consequence of a change in behaviour. Note: less-than-daily vs daily alcohol consumption is associated with increased cardiovascular risk and is not shown. Abbreviations: SCORE2, Systematic COronary Risk Evaluation 2; SCORE2-DM, SCORE2 for patients with diabetes mellitus; SBP, systolic blood pressure; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; HbA1c, glycated haemoglobin; BMI, body mass index; MET, metabolic equivalent of task; CVD, cardiovascular disease.

AuthorAgreement

- The work described has not been published previously except in the form of an abstract, as part of an academic thesis.
- The article is not under consideration for publication elsewhere.
- The article's publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out.
- If accepted, the article will not be published elsewhere in the same form, in English or in any other language, including electronically, without the written consent of the copyright-holder.

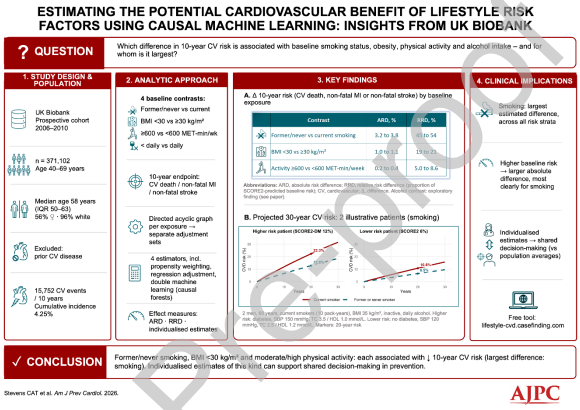
Submitted by the corresponding author on behalf of all authors.

Journal Pre-proof

Journal Pre-proof

Christophe Stevens

Central Illustration



Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Christophe A.T. Stevens reports past or current participation in research grants to Imperial College London from Pfizer, Amgen, Merck Sharp & Dohme, Novartis, Sanofi-Aventis, Daiichi Sankyo, Ultragenyx, and Regeneron. Julia Brandts received speaker honoraria from Amgen, Daiichi Sankyo, Novartis, Novo Nordisk, Sanofi and research grant support from AstraZeneca, outside the submitted work. Amany Elshorbagy reports past or current participation in research grants to Imperial College London from Daiichi Sankyo, Merck Sharp & Dohme, and Regeneron. Fotis Barkas reports personal fees and research grants from Novartis, Amgen, Novo Nordisk, Chiesi, Eli Lilly, and honoraria from Novartis, Viatris and Sanofi. Kanika I. Dharmayat reports past or current participation in research grants to Imperial College London from Pfizer, Amgen, Merck Sharp & Dohme, Sanofi-Aventis, Daiichi Sankyo, and Regeneron, outside the submitted work; and personal fees for consulting from Bayer and Regeneron, all outside the submitted work. Irene Karungi

Journal Pre-proof

reports past or current participation in research grants to Imperial College London from Ultragenyx. Sunganani Kwilasi reports past or current participation in research grants to Imperial College London from Daiichi Sankyo, Merck Sharp & Dohme. Didac Llop reports past or current participation in research grants to Imperial College London from Daiichi Sankyo. Antonio J. Vallejo-Vaz reports past or current participation in research grants to Imperial College London from Pfizer, Amgen, Merck Sharp & Dohme, Sanofi-Aventis, Daiichi Sankyo, and Regeneron, outside the submitted work; and personal fees for consulting from Bayer and Regeneron outside the submitted work. Kausik K. Ray reports receiving lecture fees from Aegerion Pharmaceuticals, Kowa, Cipla, Algorithm, and Zuelling Pharma; grant support paid to his institution; lecture fees and advisory board fees from Amgen, Regeneron Pharmaceuticals/Sanofi, and Pfizer; lecture fees and fees for serving on steering committees for trials from AstraZeneca and Eli Lilly; fees for serving on steering committees for trials from Cerenis Therapeutics, The Medicines Company, and Esperion; advisory board fees from Akcea Therapeutics, Novartis, Silence Therapeutics, Bayer, and Daiichi Sankyo; lecture fees and advisory board fees from Takeda, Boehringer Ingelheim, and Dr Reddy's Laboratories; grant support and advisory board fees from Merck Sharp & Dohme; fees for serving on a clinical events adjudication committee from AbbVie; and fees for serving as principal investigator for a trial from Resverlogix. Mansour T.A. Sharabiani and Alireza Mahani do not have conflict of interest to disclose.

Journal Pre-proof