scientific reports

Check for updates

OPEN

Understanding the role of metabolic syndrome in prostate cancer risk: A UK Biobank prospective cohort study

Shing Fung Lee[1,2], Maja Nikšić[3] & Miguel Angel Luque-Fernandez[4,5]✉

Predictive value of metabolic syndrome for prostate cancer risk is not clear. We aimed to assess the association between metabolic syndrome and its components with prostate cancer incidence. The primary outcome was prostate cancer incidence, i.e., incidence rate ratios and adjusted cumulative incidence curves derived from flexible parametric survival models. Adjusted cumulative incidence curves were derived using a flexible survival parametrical modeling framework. We analysed UK Biobank data including 242,349 adult males, recruited during 2006–2010 and followed up until 2021, during which 6,467 (2.7%) participants were diagnosed with prostate cancer. Our findings indicate that metabolic syndrome, as a whole, was not associated with prostate cancer risk (incidence rate ratios, 1.07; 95% confidence interval, 0.94–1.22). However, specific components such as hypertension and obesity increased the risk (incidence rate ratios, 1.22; 95% confidence interval, 1.03–1.44 and incidence rate ratios, 1.24; 95% confidence interval, 1.05–1.46, respectively). Other components, such as prediabetes/diabetes and low cholesterol, were associated with a reduced risk (incidence rate ratios, 0.80; 95% confidence interval, 0.67–0.94 and incidence rate ratios, 0.82; 95% confidence interval, 0.69–0.97, respectively), while hyperlipidaemia showed no significant effect (incidence rate ratios, 1.07; 95% confidence interval, 0.93–1.24). Further research is needed to understand the underlying mechanisms behind these relationships. Prostate cancer prevention strategies might benefit from targeting modifiable risk factors, particularly hypertension and obesity.

Keywords Prostate Cancer, Metabolic Syndrome, Risk Factors, Lifestyle, Diet, Exercise

Prostate cancer is the fourth most commonly diagnosed cancer worldwide and is the eighth leading cause of cancer-related deaths among men globally[1]. In the UK, the prostate cancer incidence rates have risen since the 1990s, increasing notably from around age 45 and peaking in the 75–79 age group[2]. During the last decade (between 2007–2009 and 2017–2019), age-standardised prostate cancer incidence rates increased by 9% in the UK[2]. This aligns with increasing trends observed in other high-income regions, including the US, Canada, Europe, and Australasia; with a steady rate of average increase of 2% per year globally, since 1990[3].

The rising incidence underscores the need to re-examine potential risk factors for prostate cancer and develop effective preventive strategies. Established non-modifiable risk factors include older age, ethnicity, Black race, family history of prostate cancer, and certain genetic polymorphisms[4,5]. Conversely, metabolic syndrome is considered a modifiable risk factor[6]. Although the extent to which it can be effectively managed or reversed depends on individual factors such as overall health and lifestyle changes.

Metabolic syndrome is a cluster of interconnected anthropometrical and biochemical risk factors and metabolic diseases, including hypertension, high triglyceride, central obesity, low high-density lipoprotein-cholesterol, and prediabetes/diabetes[7]. Given the current lifestyle trends leading to increasing obesity[8], hypertension[9], and prediabetes/diabetes[10], the prevalence of metabolic syndrome is projected to continue to rise, especially in most developed countries and some developing countries[11,12]. Previous studies often considered metabolic syndrome as a combined entity due to the frequent co-occurrence and interdependence of its individual components,

[1]Department of Radiation Oncology, National University Cancer Institute, National University Hospital, Singapore, Singapore. [2]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. [3]Centre for Health Services Studies, University of Kent, Canterbury, UK. [4]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK. [5]Department of Statistics and Operations Research, University of Granada, Granada, Spain. ✉email: Miguel-Angel.Luque@lshtm.ac.uk

and the resulting synergistic effect on health outcomes[13–18]. This approach, however, potentially overlooks the differential impact each component might have on the prostate cancer risk.

Findings about the role of metabolic syndrome in prostate cancer risk are limited and contradictory, with variations observed across different geographic regions, races/ethnicities, and definitions of metabolic syndrome[16–21]. Furthermore, the separate, additive, or non-linear associations of the individual metabolic components with prostate cancer risk have seldom been investigated in depth. For example, some studies have found diabetes to be associated with an increased incidence of prostate cancer[22] while others have found no significant association, or even a protective effect[21,23,24]. This discrepancy points to the importance of disentangling the influence of individual metabolic syndrome components on prostate cancer risk, which this study aimed to do. Therefore, our aim was to assess the association between metabolic syndrome and its components with prostate cancer incidence.

Methods and materials

Study population and case definition

We used the UK Biobank, a prospective biomedical cohort database containing deidentified, individual-level health information from about half a million UK participants aged 40–69 years when recruited to the study during 2006–2010. It combines extensive and precise baseline assessment of exposures with comprehensive follow-up and assessment of many different health-related outcomes[25]. Detailed information was gathered at baseline via a self-completed touch-screen questionnaire and computer-assisted interview, anthropometric and functional measures, and collection of blood and other biological samples as appropriate[25]. The inclusion criteria for our prospective study were adult (≥ 18 year old) men, without records of prostate cancer at baseline. Participants were excluded if they had any cancer diagnosis prior to recruitment, except for non-melanoma skin cancer (International Classification of Diseases Tenth edition [ICD-10]: C44) or had missing data on measures of all five components of metabolic syndrome. The cancer data were determined via record linkage to the NHS Digital for participants residing in England and Wales, until the administrative censor date July 31, 2019 respectively[26]. The UK Biobank study was approved by the Northwest Multi-Centre Research Ethics Committee (application number 48860); all participants have provided written informed consent for data collection, data analysis, and record linkage.

Ethical considerations

All analyses were performed in accordance with the relevant guidelines and regulations, including the Declaration of Helsinki. The study was approved by the Northwest Multi-Centre Research Ethics Committee (application number 48860).

Definition of exposure and covariables

Metabolic syndrome was defined following the modified National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III criteria[27]. The presence of any three of the five factors is required for a diagnosis of metabolic syndrome: (1) abdominal obesity (increased waist circumference ≥ 102 cm; (2) hypertriglyceridaemia (triglycerides ≥ 1.7 mmol/L); (3) low high-density lipoprotein cholesterol (≤ 1.03 mmol/L); (4) high blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or on antihypertensive medications); and/or (5) impaired fasting glucose (fasting plasma glucose ≥ 5.6 mmol/L). As most subjects in UK Biobank had non-fasting blood for glucose, we used a more stable measure of blood glucose level, the glycated haemoglobin (HbA1c), based on the World Health Organisation/International Diabetes Federation guidelines, with a clinical cut-off of ≥ 42 mmol/mol (≥ 6.0%) and ≥ 48 mmol/mol (≥ 6.5%) for the diagnosis of prediabetes and diabetes respectively[28]. We categorised the individual conditions as dichotomised variables with the clinical cut-off values according to the above criteria.

Statistical analysis

Descriptive statistics for participants' sociodemographic, clinical, and behavioral characteristics and follow-up period were compared between the whole cohort of men and men who developed prostate cancer. The primary outcome was the incidence of prostate cancer, defined as the first diagnosed case of malignancy (excluding non-melanoma skin cancer [ICD-10: C44]) during the follow-up period. Person-years were calculated from the date of UK Biobank assessment to the date of cancer registration, death, or the administrative censoring date (July 31, 2019), whichever occurred first. Time since the patients' baseline UK Biobank measurements served as the time scale in all analyses.

As for the exposure model, the main exposure of interest was metabolic syndrome (yes/no). In univariate analysis, we fitted flexible parametric Piecewise Exponential models to derive unadjusted incidence rate ratios to assess the association of all the variables at baseline, including the metabolic syndrome, with the incidence of prostate cancer[29]. We selected the candidate variables in the analysis considering their statistical and clinical relevance: age, ethnicity, Townsend Deprivation index, cigarette smoking, processed meat intake[30], fruit intake[31], physical activity, body mass index, ever had a prostate-specific antigen test, family history of prostate cancer among first degree relative, C-reactive protein level, testosterone, and insulin-like growth factor-I[32]. A directed acyclic graph revealing the relationships between potential confounders is shown in Figure S1. We then derived adjusted incidence rate ratios for each of the individual components of metabolic syndrome on the risk of prostate cancer[33]. Furthermore, we also modelled each of the individual metabolic conditions as separate binary exposure variables: prediabetes/diabetes mellitus, hypertension, hyperlipidaemia, low HDL-C level, and obesity.

We used a flexible survival parametric modelling framework to study the associations between metabolic syndrome components and prostate cancer risk over time. They allow for more flexibility in modeling time-dependent effects[34]. Unlike the traditional Cox regression model, which assumes proportional hazards, flexible

parametric models can accommodate varying hazard rates, providing a more detailed understanding of the associations between metabolic syndrome components and prostate cancer risk over time[34].

Finally, we derived adjusted prostate cancer cumulative incidence curves by components of metabolic syndrome using the augmented inverse probability of treatment weights estimator. We used a flexible parametric survival modeling approach to compute the nuisance models. We plotted the prostate cancer cumulative incidence standardised to the distribution of confounders included in the analysis (using the Stata command *standsurv)*[35,36]. The standardisation was applied by obtaining the average of individual estimates across all study participants. The predictors were the same covariates described in our final multivariate survival model (Table S1). In sensitivity analysis we assessed for positivity violations via the overlap of the propensity score (i.e., positivity) for metabolic syndrome and all of its individual components[37].

Finally, we directly compared the age-specific incidence rates of prostate cancer within the UK Biobank to those reported by Cancer Research UK for the general UK population[2], allowing us to assess the generalisability of our results to the broader UK prostate cancer population.

We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist in the design, analysis, and reporting of this study.[38] The checklist guided our approach to describing the study population, statistical methods, and presentation of results, ensuring clarity, reproducibility, and completeness[38]. We used Stata v.18 (Stata Corp, College Station, TX, USA) for statistical analysis. All data analysis and results for reproducibility are available in a GitHub repository: https://github.com/migariane/Prostate_Cancer_UK-48860.

Results

Table 1 shows the socio-demographic, clinical and behavioral characteristics of the whole cohort of men (N = 242,349) and the cohort of men diagnosed with prostate cancer (N = 6,467). Most men were white (95.8% *vs.* 2.1% black), and mean age at diagnosis was 75 years (standard deviation, 5 years). As of July 31, 2019, the median follow-up time was 12.0 years (interquartile range, 11.3–12.7 years), providing 2,861,933 person-years of follow-up. The median interval to prostate cancer incidence from date of baseline assessment was 3.9 years (interquartile range, 2.0–5.5 years). The incidence rate of prostate cancer was 226 (95% confidence interval, 220–232) per 100,000 person-years.

In our univariate analysis utilising piecewise exponential regression to estimate the incidence rate ratios, we found that the relationship between the number of metabolic syndrome components and prostate cancer risk was non-linear (Table 2). While the incidence rate ratios initially increase with the number of components—from 1.39 (95% confidence interval, 1.22–1.57) for one component to 1.58 (95% confidence interval, 1.40–1.79) for three components—there is a decrease to 1.29 (95% confidence interval, 1.13–1.47) when four to five components are present.

Metabolic syndrome was not associated with the risk of prostate cancer in the final multivariate adjusted model (incidence rate ratio, 1.07; 95% confidence interval, 0.94–1.22), which was consistent across models. Table 3 shows prostate cancer incidence rate ratios in relation to individual metabolic syndrome components. Inverse associations with prostate cancer incidence were observed for prediabetes/diabetes (incidence rate ratio, 0.80; 95% confidence interval, 0.67–0.94) and low high-density lipoprotein-cholesterol (incidence rate ratio, 0.82; 95% CI, 0.69–0.97); while hypertension (incidence rate ratio, 1.22; 95% confidence interval, 1.03–1.44) and obesity (incidence rate ratio, 1.24; 95% confidence interval, 1.05–1.46) were positively associated with prostate cancer. There was no association between hyperlipidaemia and prostate cancer (incidence rate ratio, 1.07; 95% confidence interval, 0.93–1.24). Figure 1 illustrates the cumulative incidence curves for prostate cancer stratified by metabolic syndrome status, while Figures S2–S6 depict the cumulative incidences for prostate cancer corresponding to each individual component of metabolic syndrome. Table S2 presents Models 1–4 adjusted for the individual components of metabolic syndrome rather than metabolic syndrome as a whole components.

The comparison of age-specific incidence rates between the UK Biobank cohort and Cancer Research UK data revealed that, except for the 50–59 age group, the incidence of prostate cancer was consistently higher in the UK Biobank cohort (Table S3).

Discussion

Key results

We found no strong evidence of an association between the incidence of prostate cancer and metabolic syndrome taken as a full cluster. However, individual components of metabolic syndrome were associated with a higher (hypertension and obesity) or lower prostate cancer risk (prediabetes/diabetes and low HDL-C level). Most previous studies investigated the total effect of all metabolic syndromes, often finding a mixed results—either negative[16,17,21] or positive association[18–20].

For instance, Tande et al. (ARIC Study) and Blanc-Lapierre et al. (Montreal Case–Control Study) reported an inverse association between metabolic syndrome and prostate cancer risk[16,17]. Tande et al. hypothesised that reduced prostate cancer risk might be linked to lower bioavailable testosterone levels among men with metabolic syndrome particularly diabetes[17]. Similarly, Blanc-Lapierre et al. found a significant protective effect of metabolic syndrome (odds ratio, 0.70; 95% confidence interval, 0.60–0.82), with a decreased risk observed with the number of metabolic syndrome components[16]. Contrastingly, the Uppsala Study, which focused on competing risks and conditional probabilities, found a modestly higher cumulative incidence of prostate cancer among men with metabolic syndrome, with abdominal obesity showing a nonsignificant trend toward increased risk[19]. Similarly, the Kailuan Study reported a significant association between metabolic syndrome and prostate cancer risk (hazard ratio, 1.47; 95% confidence interval, 1.04–2.07), with central obesity also being significantly associated with an increased risk of prostate cancer (hazard ratio, 1.68; 95% CI, 1.18–2.40)[20].

Characteristics	Whole cohort (N = 242,349)	Men with prostate cancer (n = 6,467)	Men with metabolic syndrome (n = 89,961)	Men without metabolic syndrome (n = 152,388)
Metabolic Syndrome, n (%)	89,961 (37.1)	2464 (38.1)	-	-
Hypertension, n (%)	195,022 (80.5)	5,423 (83.9)	84,185 (93.6)	110,837 (72.7)
Hyperlipidemia, n (%)	157,381 (64.9)	4,349 (67.3)	85,307 (94.8)	72,074 (47.3)
Reduced HDL-C, n (%)	46,131 (19.0)	1,136 (17.6)	38,271 (42.5)	7,860 (5.2)
Prediabetes/diabetes, n (%)	47,578 (19.6)	1,230 (19.0)	39,498 (43.9)	8,080 (5.3)
Obesity/overweight, n (%)	79,004 (32.6)	2,102 (32.5)	63,601 (70.7)	15,403 (10.1)
Number of metabolic syndrome components*				
0, n (%)	15,706 (6.5)	294 (4.6)	0	15,706 (10.3)
1, n (%)	59,110 (24.4)	1,527 (23.6)	0	59,110 (38.8)
2, n (%)	77,572 (32.0)	2,182 (33.7)	0	77,572 (50.9)
3, n (%)	55, 780 (23.0)	1,641 (25.4)	55,780 (62.0)	0
4–5, n (%)	34,181 (14.1)	823 (12.7)	34,181 (38.0)	0
Key demographic				
Age at recruitment (years), mean (SD)	70 (8)	75 (5)	71 (8)	69 (8)
Body mass index (kg/m2), mean (SD)	28.0 (4.4)	27.7 (4.0)	30.9 (4.6)	26.3 (3.3)
Waist circumference (cm), mean (SD)	97.5 (11.8)	97.6 (10.9)	106.1 (11.4)	92.5 (8.7)
Have a wife or partner, n (%)	180,630 (74.5)	5,071 (78.4)	65,198 (72.5)	115,432 (75.8)
Black ethnicity, n (%)	3,537 (1.5)	135 (2.1)	1,270 (1.4)	2,267 (1.5)
Townsend Deprivation Index in quintiles				
1st quintile (most affluent)	48,354 (20.0)	1,4130 (21.9)	16,139 (17.9)	32,215 (21.1)
2nd quintile	48,535 (20.0)	1,451 (22.4)	16,797 (18.7)	31,738 (20.8)
3rd quintile	48,451 (20.0)	1,432 (22.1)	17,656 (19.6)	30,795 (20.2)
4th quintile	48,451 (20.0)	1,191 (18.4)	18,667 (20.8)	29,784 (19.5)
5th quintile (most deprived)	48,241 (20.0)	977 (15.1)	20,576 (22.9)	27,665 (18.2)
Cigarette smoke, n (%)				
Current smoker	33,335 (13.8)	639 (9.9)	12,991 (14.4)	20,344 (13.4)
Ex-smoker	94,067 (38.8)	2,892 (44.7)	40,128 (44.6)	53,939 (35.4)
Never	113,321 (46.8)	2,894 (44.8)	35,964 (40.0)	77,357 (50.8)
Lifestyle and physical activities Processed meat intake, n (%)**				
Low	63,552 (26.2)	1,732 (26.8)	21,001 (23.3)	42,551 (27.9)
Moderate	161,327 (66.6)	4,298 (66.5)	61,900 (68.8)	99,427 (65.3)
High	16,194 (6.7)	414 (6.4)	6,396 (7.1)	9,798 (6.4)
Portions of fruit, n (%)				
< 5 portions per day	223,760 (92.3)	5,973 (92.4)	82,018 (91.2)	141,742 (93.0)
≥ 5 portions per day	16,494 (6.8)	449 (6.9)	6,902 (7.7)	9,592 (6.3)
Level of physical activity, n (%)				
Low	40,176 (16.6)	950 (14.7)	18,903 (21.0)	21,273 (14.0)
Moderate	77,165 (31.9)	2,179 (33.7)	28,390 (31.6)	48,775 (32.0)
High	84,008 (34.6)	2,234 (34.5)	24,710 (27.5)	59,298 (38.9)
Prostate specific factors prior to recruitment				
Ever had a PSA test, n (%)	66,837 (27.6)	2,754 (42.8)	25,224 (28.0)	41,613 (27.3)
Father had prostate cancer, n (%)	15,412 (6.4)	636 (9.8)	5,225 (5.8)	10,187 (6.7)
Siblings had prostate cancer, n (%)	2,940 (1.2)	224 (3.5)	1,208 (1.3)	1,732 (1.1)
Increased C-reactive protein (≥ 1.00 mg/dL), n (%)	137,562 (56.8)	3,721 (57.5)	60,822 (67.6)	76,740 (50.4)
Testosterone (above mean of 12.0 nmol/L), n (%)	120,426 (49.7)	3,171 (49.0)	33,987 (37.8)	86,439 (56.7)
Insulin-like growth factor-I (above mean of > 21.7 nmol/L), n (%)	127,993 (52.7)	3,269 (50.6)	44,232 (49.2)	83,761 (55.0)
Missing or prefer not to answer, n (%)				
Cigarette smoke	1,626 (0.7)	42 (0.7)	878 (1.0)	748 (0.5)
Portions of fruit	2,095 (0.9)	45 (0.7)	1,041 (1.2)	1,054 (0.7)
Level of physical activity	41,000 (16.9)	1,104 (17.1)	17,958 (20.0)	23,042 (15.1)
Townsend Deprivation Index	317 (0.1)	3 (0.1)	126 (0.1)	191 (0.1)
Continued				

Characteristics	Whole cohort (N = 242,349)	Men with prostate cancer (n = 6,467)	Men with metabolic syndrome (n = 89,961)	Men without metabolic syndrome (n = 152,388)
Processed meat	1,276 (0.5)	3 (0.4)	664 (0.7)	612 (0.4)
Ever had a PSA test	14,327 (5.9)	325 (5.0)	6,478 (7.2)	7,849 (5.2)
C-reactive protein	16,205 (6.7)	452 (7.0)	8,728 (9.7)	7,477 (4.9)
Testosterone	17,582 (7.3)	494 (7.6)	9,197 (10.2)	8,385 (5.5)
Insulin-like growth factor-I	16,723 (6.9)	459 (7.1)	8,833 (9.8)	7,890 (5.2)

Table 1. Baseline characteristics of men in the UK Biobank Cohort (N = 242,349) stratified by metabolic syndrome status, recruited during 2006–2010, followed up until 2019. *HDL-C* high-density lipoprotein-cholesterol, *PSA* prostate-specific antigen, *SD* standard deviation. *Metabolic comorbid conditions included obesity/ overweight, hypertension, reduced HDL-C, hyperlipidemia, and prediabetes/diabetes. **Low intake: never or less than once a week; moderate intake: once a week or 2–4 times a week; high intake: 5–6 times a week or once or more daily.

Variables	N	Person-time at risk	Incidence rate*	Incidence rate ratios	P-value
Metabolic syndrome					
No	4,002	1,796,128	222.8 (216.0–229.8)	1 (ref)	
Yes	2,464	1,065,805	231.2 (222.2–240.5)	1.04 (0.99–1.10)	0.095
Prediabetes/diabetes mellitus					
No	5,236	2,297,328	227.9 (221.8–234.2)	1 (ref)	
Yes	1,230	564,605	217.9 (206.0–230.4)	0.96 (0.90–1.02)	0.211
Hypertension					
No	1,044	557,999	187.1 (176.1–198.8)	1 (ref)	
Yes	5,422	2,303,934	235.3 (229.2–241.7)	1.26 (1.18–1.35)	<0.001
Hyperlipidemia					
No	2,118	10,020,801	211.2 (202.4–220.4)	1 (ref)	
Yes	4,348	1,859,131	233.9 (227.0–240.9)	1.11 (1.05–1.17)	<0.001
Low high-density lipoprotein-cholesterol level					
No	5,330	2,314,922	230.2 (224.1–236.5)	1 (ref)	
Yes	1,136	547,011	207.7 (195.9–220.1)	0.91 (0.85–0.97)	0.002
Obesity					
No	4,364	1,928,359	226.3 (219.7–233.1)	1 (ref)	
Yes	2,102	933,574	225.2 (215.7–235.0)	1.00 (0.95–1.05)	0.870
Metabolic syndrome components**					
0	294	185,554	158.4 (141.3–177.6)	1 (ref)	
1	1,527	697,457	218.9 (208.2–230.2)	1.39 (1.22–1.57)	<0.001
2	2,181	913,117	238.9 (229.0–249.1)	1.51 (1.34–1.71)	<0.001
3	1,641	659,460	248.8 (237.1–261.2)	1.58 (1.40–1.79)	<0.001
4–5	823	406,345	202.5 (189.2–216.9)	1.29 (1.13–1.47)	<0.001

Table 2. Prostate cancer incidence rate ratios by metabolic syndrome and individual components in the UK Biobank cohort (N = 242,349), recruited during 2006–2010 with follow up to 2021. *Per 100,000 person-year. **Metabolic comorbid conditions included obesity/ overweight, hypertension, reduced HDL-C, hyperlipidemia, and prediabetes/type 2 diabetes.

These results suggest that while the overall metabolic syndrome may not be predictive of prostate cancer, specific components of this syndrome play a critical role. Our results highlight the need for more granular, component-based considerations when investigating the role of metabolic syndrome in prostate cancer risk. We advise against using a metabolic syndrome as a full cluster in prediction of prostate cancer risk.

Interpretations

The association of hypertension and increased incidence risk of prostate cancer is controversial[39,40] People with hypertension may have a heightened activity of the sympathetic nervous system that can lead to androgen-mediated stimulation of prostate cancer cell growth[41]. Furthermore, abdominal obesity may be associated with hyperinsulinaemia[42], leading to raised circulating levels of insulin-like growth factor-I, increasing the risk of prostate cancer[43].

Variables	Unadjusted IRR (95% CI)	Model 1: Adjusted IRR (95% CI)	Model 2: Adjusted IRR (95% CI)	Model 3: Adjusted IRR (95% CI)	Model 4: Adjusted IRR (95% CI)	Model 5: Adjusted IRR (95% CI)	Model 6: Adjusted IRR (95% CI)
Metabolic syndrome (yes vs. no)	1.90 (1.19–3.04)	1.21 (0.88–1.66)	1.14 (0.85–1.51)	1.02 (0.90–1.16)	1.04 (0.92–1.18)	1.07 (0.94–1.22)	-
Prediabetes/ diabetes mellitus (yes vs. no)	1.38 (0.92–2.07)	–	–	–	–	–	0.80 (0.67–0.94)
Hypertension (yes vs. no)	1.41 (0.94–2.12)	–	–	–	–	–	1.22 (1.03–1.44)
Hyperlipidemia (yes vs. no)	2.11 (1.14–3.91)	–	–	–	–	–	1.07 (0.93–1.24)
Low HDL-C level (yes vs. no)	1.47 (1.00–2.16)	–	–	–	–	–	0.82 (0.69–0.97)
Obesity (yes vs. no)	0.46 (0.26–0.80)	–	–	–	–	–	1.24 (1.05–1.46)
Age at recruitment, year							
81 to 90 vs. 50 to 65	8.08 (5.69–11.48)	8.78 (6.29–12.24)	8.45 (6.03–11.84)	6.25 (4.44–8.79)	5.13 (3.59–7.33)	6.73 (4.59–9.88)	6.27 (4.24–9.27)
76 to 80 vs. 50 to 65	9.14 (5.80–14.40)	10.21 (6.71–15.55)	10.65 (7.24–15.66)	9.87 (7.03–13.84)	7.74 (5.44–11.02)	9.60 (6.56–14.05)	9.02 (6.14–13.26)
71 to 75 vs. 50 to 65	8.26 (5.23–13.05)	8.94 (5.69–14.06)	8.91 (5.73–13.86)	7.60 (4.75–12.16)	6.42 (4.14–9.95)	7.85 (5.01–12.30)	7.42 (4.72–11.65)
66 to 70 vs. 50 to 65	0.88 (0.40–1.96)	1.04 (0.48–2.24)	1.13 (0.57–2.26)	1.58 (0.69–3.61)	1.51 (0.70–3.25)	1.97 (0.91–4.28)	1.94 (0.91–4.12)
Ethnicity							
Black vs. white	2.61 (1.53–4.44)	4.04 (2.75–5.93)	3.95 (2.60–6.00)	4.06 (2.63–6.27)	3.88 (2.54–5.91)	3.45 (2.19–5.45)	3.74 (2.36–5.92)
Asians including Chinese vs. white	0.88 (0.53–1.47)	0.86 (0.60–1.24)	0.84 (0.58–1.21)	0.71 (0.46–1.09)	0.72 (0.44–1.16)	0.81 (0.48–1.37)	0.92 (0.54–1.54)
Mixed/ other vs. white	2.58 (1.02–6.54)	3.64 (1.53–8.64)	3.51 (1.47–8.36)	3.27 (1.31–8.12)	3.63 (1.47–8.98)	3.40 (1.29–8.93)	3.66 (1.37–9.72)
Townsend Deprivation index in quintiles							
1st (most deprived) vs. 5th quintile (least deprived)	0.67 (0.32–1.37)		1.56 (0.91–2.69)	1.22 (0.78–1.89)	1.22 (0.76–1.94)	1.32 (0.82–2.14)	1.33 (0.82–2.16)
2nd vs. 5th quintile (least deprived)	0.42 (0.19–0.94)		1.18 (0.75–1.84)	0.98 (0.69–1.37)	1.03 (0.75–1.42)	0.99 (0.72–1.37)	1.00 (0.72–1.38)
3rd vs. 5th quintile (least deprived)	2.13 (1.32–3.47)		2.81 (1.64–4.83)	2.19 (1.45–3.30)	2.02 (1.39–2.94)	1.75 (1.16–2.64)	1.74 (1.16–2.61)
4th vs. 5th quintile (least deprived)	1.34 (0.96–1.88)		1.77 (1.19–2.62)	1.36 (1.11–1.67)	1.37 (1.11–1.69)	1.34 (1.09–1.64)	1.33 (1.09–1.63)
Smoking							
Current smoker vs. non-smoker	2.10 (1.20–3.68)			1.02 (0.77–1.34)	0.98 (0.75–1.29)	1.03 (0.77–1.37)	1.04 (0.78–1.39)
Ex-smoker vs. non-smoker	2.03 (1.14–3.61)			1.08 (0.80–1.46)	1.03 (0.76–1.39)	1.00 (0.73–1.37)	1.00 (0.73–1.36)
Processed meat intake							
High vs. low	0.82 (0.60–1.14)			1.03 (0.35–3.06)	1.17 (0.41–3.37)	1.26 (0.43–3.67)	1.27 (0.44–3.64)
Moderate vs. low	0.31 (0.07–1.45)			0.96 (0.81–1.15)	0.94 (0.78–1.13)	0.90 (0.75–1.08)	0.91 (0.76–1.09)
Fruit (≥ 5 vs. < 5 portions per day)	0.60 (0.31– 1.14)			0.47 (0.26–0.84)	0.48 (0.28–0.84)	0.46 (0.25–0.85)	0.48 (0.26–0.88)
Body mass index, per 1 kg/m^2 increase	0.94 (0.91–0.97)			0.96 (0.93–1.00)	0.95 (0.92–0.99)	0.96 (0.92–1.00)	0.95 (0.91–0.99)
Level of physical activity							
High vs. low	2.38 (1.04– 5.47)			1.35 (0.71–2.58)	1.24 (0.68–2.26)	1.31 (0.70–2.48)	1.33 (0.71–2.49)
Moderate vs. low	2.02 (0.84– 4.88)			1.42 (0.86–2.36)	1.29 (0.84–2.00)	1.25 (0.79–1.95)	1.26 (0.81–1.95)
Medication use							
Cholesterol lowering medication vs no	2.34 (1.73–3.15)			1.14 (0.97–1.34)	1.19 (1.02–1.40)	1.24 (1.02–1.49)	1.30 (1.07–1.58)
Blood pressure medication vs no	1.14 (0.43–3.01)			2.01 (1.45–2.78)	1.96 (1.46–2.62)	1.95 (1.45–2.62)	1.89 (1.41–2.53)
Insulin vs no	1.30 (0.52–3.27)			1.06 (0.42–2.67)	1.35 (0.54–3.41)	1.41 (0.56–3.57)	1.69 (0.67–4.30)
Ever had an PSA test (yes vs. no)	3.20 (1.940–5.28)				1.54 (1.16–2.06)	1.41 (1.05–1.90)	1.40 (1.04–1.88)
Continued							

Variables	Unadjusted IRR (95% CI)	Model 1: Adjusted IRR (95% CI)	Model 2: Adjusted IRR (95% CI)	Model 3: Adjusted IRR (95% CI)	Model 4: Adjusted IRR (95% CI)	Model 5: Adjusted IRR (95% CI)	Model 6: Adjusted IRR (95% CI)
Father had prostate cancer (yes vs. no)	0.82 (0.29– 2.29)				1.82 (1.29–2.58)	1.76 (1.21–2.56)	1.76 (1.22–2.56)
Sibling had prostate cancer (yes vs. no)	8.26 (4.45–15.34)				3.09 (2.09–4.55)	2.85 (1.92–4.23)	2.78 (1.87–4.11)
C-reactive protein level (> 1 mg/L vs. < 1 mg/L)	0.59 (0.39– 0.91)					1.03 (0.88–1.21)	1.02 (0.87–1.19)
Testosterone, per 1 nmol/L increase	1.05 (0.99–1.11)					1.01 (0.98–1.04)	1.01 (0.98–1.04)
Insulin-like growth factor-I, per 1 nmol/L increase	1.06 (1.05–1.08)					1.04 (1.03–1.05)	1.04 (1.03–1.05)

Table 3. Prostate cancer specific risk by metabolic syndrome and its components in the UK Biobank cohort (N = 242,349), recruited during 2006–2010 with follow up to 2021. HDL-C, high-density lipoprotein-cholesterol; PSA, prostate-specific antigen; RR, relative risk. Model 1: metabolic syndrome + age + ethnicity. Model 2: model 1 + deprivation index. Model 3: model 2 + smoking + alcohol intake + fruit intake + processed meat intake + body mass index + medications + exercise level. Model 4: model 3 + ever had prostate-specific antigen test + father had prostate cancer + sibling had prostate cancer. Model 5: model 4 + C-reactive protein level + testosterone + Insulin-like growth factor-I. Model 6: model 5 but individual metabolic syndrome components instead of metabolic syndrome.

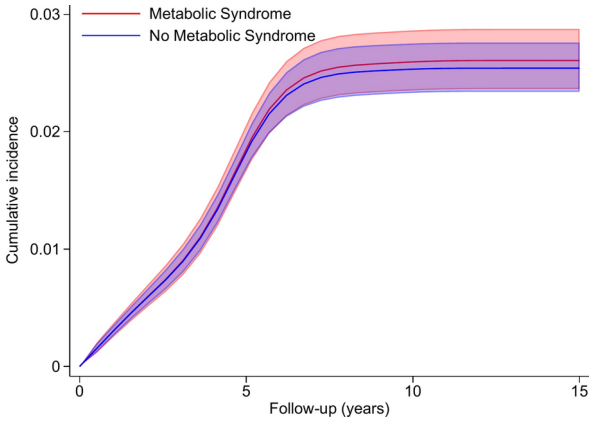

Fig. 1. Cumulative incidence curves for prostate cancer stratified by metabolic syndrome status. UK Biobank (N = 6,467). The bands represent the 95% confidence intervals.

The relationship between HDL-C levels and the risk of prostate cancer remains contradictory[44,45]. HDL-C has known anti-inflammatory and anti-proliferative properties[46]. The reason why low HDL-C level (as one of the criteria of metabolic syndrome) was associated with a decreased risk of prostate cancer in the present study is not clear. Further research is required to explore this, and to determine whether HDL-C is a therapeutic target to modify prostate cancer risk.

The reduced prostate cancer risk among diabetic participants corroborates findings from other cohort studies[47,48]. There could also be potential anti-carcinogenic properties of the anti-diabetic medications[49]. Our analysis carefully adjusted for the baseline circulating insulin-like growth factor-I and testosterone, which were linked with prostate cancer risk[50–52].

Metabolic syndrome, largely influenced by lifestyle factors, is a modifiable condition, highlighting its relevance to prostate cancer from a public health perspective[53]. Preventative interventions may range from lifestyle modifications to specific medical treatments, depending on individual metabolic conditions[53]. For instance, interventions for patients with hypertension may include dietary adjustments to decrease salt consumption, alcohol and caffeine intake, stress reduction programs such as meditation[54], complemented by medications, where needed, to manage blood pressure. Obese patients might benefit from healthier diet and increased physical activity levels[55,56].

Our results confirm an increased prostate cancer risk with advancing age, particularly for individuals over 75, and significant ethnic disparities, with Black patients facing over three times the risk compared to Whites. We found a complex relationship between socio-economic status and prostate cancer risk, with middle quintiles showing particularly increased risk. Future interventions may benefit from targeting the elderly and ethnic minority groups; thereby, prioritising high-risk demographics.

To our knowledge, our study is the most comprehensive UK cohort study on prostate cancer and metabolic syndrome. Using generalised standardisation, we adjusted CI and RRs for confounding and to avoid paradoxical

findings. Many key metrics, like blood pressure or blood tests, were assessed by specialised clinics or certified labs, solidifying data quality.

Generalisability

Prostate cancer incidence in the UK Biobank cohort was found to be higher than national statistics reported by Cancer Research UK across most age groups. This discrepancy may reflect differences in diagnostic practices, such as a higher likelihood of prostate-specific antigen testing among UK Biobank participants, leading to earlier and more frequent diagnoses rather than a "healthy volunteer effect". Participants in the UK Biobank cohort may represent a more health-conscious population, with greater access to healthcare and higher engagement with cancer screening programs, potentially leading to increased prostate cancer detection rates. These findings underscore the importance of considering cohort-specific diagnostic practices when interpreting incidence data[57,58].

Our sample is broadly representative of the UK population, although certain characteristics within the sample may not fully reflect the population distribution[2]. For example, lower socioeconomic status is underrepresented (16% sample *vs.* 33% the UK population)[58]. However, the cohort includes a sufficient number of individuals to allow robust investigations of socio-economic deprivation and disease risk of bias with high internal validity. Cancer incidence rates in the UK Biobank are generally lower than those in the broader UK population, although this varies by cancer type[58]. Consequently, the UK Biobank should not be used to estimate cancer prevalence or incidence rates for the population at large, but it is suitable for assessing etiological associations between exposures and cancer outcomes.

Increased prostate-specific antigen testing has led to higher detection rates of prostate cancer, including cases of early-stage and less aggressive forms that might otherwise remain undiagnosed[59,60]. Variations in prostate-specific antigen screening practices over time could contribute to case-mix variations observed in our study.

We presented prostate cancer incidence and prevalence rates in our study to facilitate comparisons between our less socio-economically deprived population sub-group and the general population. These targeted insights may help inform cancer policy and practice, identifying specific needs of different population sub-groups.

Limitations

Possible limitations of our study include unmeasured confounders, such as intricate dietary patterns, a family history of all cancers, environmental exposure data including environmental toxins and occupational exposure. Some data, such as physical activity levels, had missing values that could potentially bias interpretations. Information on tumour stage and grade was not available. Therefore, we are unable to provide a complete assessment of the links between metabolic syndrome and cancer severity. We could not factor in the potential escalating risk of prostate cancer with increasing metabolic syndrome components or their specific combinations. Furthermore, we evaluated metabolic syndrome at a single point, overlooking the potential relevance of disease duration or progression over time. Since disease progression is inherently a time-varying process, the duration for which an individual has had a particular condition, or the changes in the conditions over time, may be crucial. Finally, given prostate cancer's slow progression, our follow-up period may not have been ideal. Future studies with extended follow-ups or dynamic metabolic syndrome assessments might warrant a better understanding of how metabolic conditions influence prostate cancer risk over time.

Conclusions

The relationship between metabolic syndrome and prostate cancer is intricate, with our evidence indicating that specific components, such as obesity and hypertension, potentially play significant roles in the onset and progression of prostate cancer. The precise mechanisms underlying these associations remain elusive, highlighting a critical gap in our current understanding that necessitates further exploration.

Our findings underscore that metabolic syndrome, as a single entity, is not associated with prostate cancer risk, and should not be used as a prognostic marker. The distinct impact of metabolic syndrome's individual components on prostate cancer underscores the importance of dissecting these relationships more finely in future research. This approach is vital, not only for elucidating the pathophysiological mechanisms at play but also for refining risk stratification, and developing screening protocol and targeted interventions, ultimately improving patient outcomes and public health.

Data availability

Data analysis and results for reproducibility are shared in a GitHub repository available at: https://github.com/migariane/Prostate_Cancer_UK-48860.

Received: 23 May 2024; Accepted: 3 January 2025
Published online: 17 January 2025

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 74(3):229–263. https://doi.org/10.3322/caac.21834, (2024).
2. Cancer Research UK. Prostate cancer incidence statistics. Accessed July 13, 2024, https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/incidence
3. Bleyer, A., Spreafico, F. & Barr, R. Prostate cancer in young men: An emerging young adult and older adolescent challenge. *Cancer* **126**(1), 46–57. https://doi.org/10.1002/cncr.32498 (2020).
4. Cuzick, J. et al. Prevention and early detection of prostate cancer. *Lancet Oncol.* **15**(11), e484–e492. https://doi.org/10.1016/s1470-2045(14)70211-6 (2014).

5. Zhou, C. K. et al. Prostate cancer incidence in 43 populations worldwide: An analysis of time trends overall and by age group. *Int. J. Cancer.* **138**(6), 1388–1400. https://doi.org/10.1002/ijc.29894 (2016).
6. Esposito, K. et al. Effect of metabolic syndrome and its components on prostate cancer risk: meta-analysis. *J. Endocrinol. Invest.* **36**(2), 132–139. https://doi.org/10.1007/bf03346748 (2013).
7. Alberti, K. G. M. M. et al. Harmonizing the Metabolic Syndrome. *Circulation* **120**(16), 1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644 (2009).
8. Phillips, C. M. et al. Defining metabolically healthy obesity: role of dietary and lifestyle factors. *PLoS One* https://doi.org/10.1371/journal.pone.0076188 (2013).
9. Egan, B. M., Zhao, Y. & Axon, R. N. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *Jama* **303**(20), 2043–2050. https://doi.org/10.1001/jama.2010.650 (2010).
10. Lascar, N. et al. Type 2 diabetes in adolescents and young adults. *Lancet Diabetes Endocrinol.* **6**(1), 69–80. https://doi.org/10.1016/s2213-8587(17)30186-9 (2018).
11. Saklayen, M. G. The Global Epidemic of the Metabolic Syndrome. *Curr. Hypertens. Rep.* https://doi.org/10.1007/s11906-018-0812-z (2018).
12. Chew, N. W. S. et al. The global burden of metabolic disease: Data from 2000 to 2019. *Cell. Metab.* **35**(3), 414-428.e3. https://doi.org/10.1016/j.cmet.2023.02.003 (2023).
13. Braun, S., Bitton-Worms, K. & LeRoith, D. The Link between the Metabolic Syndrome and Cancer. *Rev. Int. J. Biol. Sci.* **7**(7), 1003–1015. https://doi.org/10.7150/ijbs.7.1003 (2011).
14. Uzunlulu, M., Telci Caklili, O. & Oguz, A. Association between Metabolic Syndrome and Cancer. *Annals Nutr. Metabol.* **68**(3), 173–179. https://doi.org/10.1159/000443743 (2016).
15. Gacci, M. et al. Meta-analysis of metabolic syndrome and prostate cancer. *Prostate Cancer Prostatic Dis.* **20**(2), 146–155. https://doi.org/10.1038/pcan.2017.1 (2017).
16. Blanc-Lapierre, A. et al. Metabolic syndrome and prostate cancer risk in a population-based case-control study in Montreal Canada. *BMC Public Health* **22**, 44. https://doi.org/10.1186/s12889-015-2260-x (2015).
17. Tande, A. J., Platz, E. A. & Folsom, A. R. The metabolic syndrome is associated with reduced risk of prostate cancer. *Am. J. Epidemiol.* **164**(11), 1094–1102. https://doi.org/10.1093/aje/kwj320 (2006).
18. Bhindi, B. et al. Dissecting the association between metabolic syndrome and prostate cancer risk: analysis of a large clinical cohort. *Eur Urol.* **67**(1), 64–70. https://doi.org/10.1016/j.eururo.2014.01.040 (2015).
19. Grundmark, B. et al. The metabolic syndrome and the risk of prostate cancer under competing risks of death from other causes. *Cancer Epidemiol. Biomarkers Prev.* **19**(8), 2088–2096. https://doi.org/10.1158/1055-9965.Epi-10-0112 (2010).
20. Jiang, R. et al. Association of metabolic syndrome and its components with the risk of urologic cancers: a prospective cohort study. *BMC Urol* https://doi.org/10.1186/s12894-023-01324-4 (2023).
21. Häggström, C. et al. Prostate cancer, prostate cancer death, and death from other causes, among men with metabolic aberrations. *Epidemiology* **25**(6), 823–828. https://doi.org/10.1097/ede.0000000000000174 (2014).
22. Kim, J. W. et al. Incidence of Prostate Cancer according to Metabolic Health Status: a Nationwide Cohort Study. *J. Korean Med. Sci.* https://doi.org/10.3346/jkms.2019.34.e49 (2019).
23. Dankner, R. et al. A historical cohort study on glycemic-control and cancer-risk among patients with diabetes. *Cancer Epidemiol.* **57**, 104–109. https://doi.org/10.1016/j.canep.2018.10.010 (2018).
24. Perez-Cornago, A. et al. Examination of potential novel biochemical factors in relation to prostate cancer incidence and mortality in UK Biobank. *Br. J. Cancer.* https://doi.org/10.1038/s41416-020-01081-3 (2020).
25. Sudlow, C. et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLOS Med.* https://doi.org/10.1371/journal.pmed.1001779 (2015).
26. UK Biobank Data providers and dates of data availability. Accessed Accessed on 31 October 2021, https://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=Data_providers_and_dates
27. Grundy, S. M. et al. Diagnosis and Management of the Metabolic Syndrome. *Circulation.* **112**(17), 2735–2752. https://doi.org/10.1161/CIRCULATIONAHA.105.169404 (2005).
28. Florkowski, C. HbA1c as a Diagnostic Test for Diabetes Mellitus - Reviewing the Evidence. *Clin. Biochem. Rev.* **34**(2), 75–83 (2013).
29. Luque-Fernandez, M. A. et al. Adjusting for overdispersion in piecewise exponential regression models to estimate excess mortality rate in population-based research. *BMC Med. Res. Methodol.* https://doi.org/10.1186/s12874-016-0234-z (2016).
30. Michaud, D. S. et al. A prospective study on intake of animal products and risk of prostate cancer. *Cancer Causes Control.* **12**(6), 557–567. https://doi.org/10.1023/a:1011256201044 (2001).
31. Kirsh, V. A. et al. Prospective study of fruit and vegetable intake and risk of prostate cancer. *J. Natl. Cancer Inst.* **99**(15), 1200–1209. https://doi.org/10.1093/jnci/djm065 (2007).
32. Watts, E. L. et al. Circulating insulin-like growth factor-I, total and free testosterone concentrations and prostate cancer risk in 200 000 men in UK Biobank. *Int. J. Cancer* **148**(9), 2274–2288. https://doi.org/10.1002/ijc.33416 (2021).
33. Gichangi A, Vach W. The analysis of competing risks data: A guided tour. 2005;
34. Royston, P. Flexible Parametric Alternatives to the Cox Model, and more. *Stata J.* **1**(1), 1–28. https://doi.org/10.1177/1536867x0100100101 (2001).
35. Kipourou, D. K., Charvat, H., Rachet, B. & Belot, A. Estimation of the adjusted cause-specific cumulative probability using flexible regression models for the cause-specific hazards. *Stat Med.* **38**(20), 3896–3910. https://doi.org/10.1002/sim.8209 (2019).
36. Lambert P. Standardized cumulative incidence functions. Accessed https://pclambert.net/software/standsurv/standardized_cif/, (2020).
37. Petersen, M. L., Porter, K. E., Gruber, S., Wang, Y. & van der Laan, M. J. Diagnosing and responding to violations in the positivity assumption. *Stat. Methods Med. Res.* **21**(1), 31–54. https://doi.org/10.1177/0962280210386207 (2012).
38. von Elm, E. et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J. Clin. Epidemiol.* **61**(4), 344–349. https://doi.org/10.1016/j.jclinepi.2007.11.008 (2008).
39. Jochems, S. H. J., Häggström, C., Stattin, P., Järvholm, B. & Stocks, T. Association of Blood Pressure with Prostate Cancer Risk by Disease Severity and Prostate Cancer Death: A Pooled Cohort Study. *Cancer Epidemiol. Biomarkers Prev.* **31**(7), 1483–1491. https://doi.org/10.1158/1055-9965.Epi-22-0159 (2022).
40. Häggström, C. et al. Prospective study on metabolic factors and risk of prostate cancer. *Cancer* **118**(24), 6199–6206. https://doi.org/10.1002/cncr.27677 (2012).
41. Gann, P. H., Daviglus, M. L., Dyer, A. R. & Stamler, J. Heart rate and prostate cancer mortality: results of a prospective analysis. *Cancer Epidemiol. Biomarkers Prev.* **4**(6), 611–616 (1995).
42. Moyad, M. A. Is obesity a risk factor for prostate cancer, and does it even matter? A hypothesis and different perspective. *Urology* **59**(4 Suppl 1), 41–50. https://doi.org/10.1016/s0090-4295(01)01175-x (2002).
43. Wolk, A. et al. Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study. *J. Natl. Cancer Inst.* **90**(12), 911–915. https://doi.org/10.1093/jnci/90.12.911 (1998).
44. Mondul, A. M., Weinstein, S. J., Virtamo, J. & Albanes, D. Serum total and HDL cholesterol and risk of prostate cancer. *Cancer Causes Control.* **22**(11), 1545–1552. https://doi.org/10.1007/s10552-011-9831-7 (2011).
45. YuPeng, L. et al. Cholesterol Levels in Blood and the Risk of Prostate Cancer: A Meta-analysis of 14 Prospective Studies. *Cancer Epidemiol. Biomarkers Prev.* **24**(7), 1086–1093. https://doi.org/10.1158/1055-9965.Epi-14-1329 (2015).

46. Toth,. High-density lipoprotein as a therapeutic target: clinical evidence and treatment strategies. *Am J Cardiol* https://doi.org/10.1016/j.amjcard.2005.08.008 (2005).
47. Perez-Cornago, A. et al. Prospective investigation of risk factors for prostate cancer in the UK Biobank cohort study. *Br. J. Cancer.* **117**(10), 1562–1571. https://doi.org/10.1038/bjc.2017.312 (2017).
48. Monroy-Iglesias, M. J. et al. Metabolic syndrome biomarkers and prostate cancer risk in the UK Biobank. *Int. J. Cancer* **148**(4), 825–834. https://doi.org/10.1002/ijc.33255 (2021).
49. Liu YC, Nguyen PA, Humayun A, et al. Does long-term use of antidiabetic drugs changes cancer risk? *Medicine (Baltimore)*. https://doi.org/10.1097/md.0000000000017461, (2019).
50. Teppala S, Shankar A. Association between serum IGF-1 and diabetes among U.S. Adults. *Diabetes Care*. https://doi.org/10.2337/dc10-0770, (2010).
51. Renehan, A. G. et al. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* **363**(9418), 1346–1353. https://doi.org/10.1016/s0140-6736(04)16044-3 (2004).
52. Grossmann, M. Low testosterone in men with type 2 diabetes: significance and treatment. *J. Clin. Endocrinol. Metab.* **96**(8), 2341–2353. https://doi.org/10.1210/jc.2011-0118 (2011).
53. van Namen, M., Prendergast, L. & Peiris, C. Supervised lifestyle intervention for people with metabolic syndrome improves outcomes and reduces individual risk factors of metabolic syndrome: A systematic review and meta-analysis. *Metabolism* https://doi.org/10.1016/j.metabol.2019.153988 (2019).
54. Rainforth, M. V. et al. Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis. *Curr. Hypertens. Rep.* **9**(6), 520–528. https://doi.org/10.1007/s11906-007-0094-3 (2007).
55. Allott, E. H., Masko, E. M. & Freedland, S. J. Obesity and Prostate Cancer: Weighing the Evidence. *Eur. Urol.* https://doi.org/10.1016/j.eururo.2012.11.013 (2013).
56. Bhindi, B. et al. Obesity Is Associated with Risk of Progression for Low-risk Prostate Cancers Managed Expectantly. *Eur. Urol.* https://doi.org/10.1016/j.eururo.2014.06.005 (2014).
57. Conroy, M. C. et al. UK Biobank: a globally important resource for cancer research. *Br. J. Cancer* **128**(4), 519–527. https://doi.org/10.1038/s41416-022-02053-5 (2023).
58. Fry, A. et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *Am. J. Epidemiol.* **186**(9), 1026–1034. https://doi.org/10.1093/aje/kwx246 (2017).
59. Welch, H. G. & Black, W. C. Overdiagnosis in cancer. *J. Natl. Cancer Inst.* **102**(9), 605–613. https://doi.org/10.1093/jnci/djq099 (2010).
60. Stamey, T. A. et al. The prostate specific antigen era in the United States is over for prostate cancer: what happened in the last 20 years?. *J. Urol.* **172**(4 Pt 1), 1297–1301. https://doi.org/10.1097/01.ju.0000139993.51181.5d (2004).

Acknowledgements

We thank Prof. Bernard Rachet, London School of Hygiene and Tropical Medicine for his valuable comments on the manuscript.

Author contributions

SFL conceptualised the study, designed the methodology, and led the writing of the original draft. MN was responsible for data curation and formal analysis, and she contributed significantly to the review and editing of the manuscript. MALF developed and validated the statistical software used for data analysis and also contributed to the manuscript's review and editing.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-85501-5.

Correspondence and requests for materials should be addressed to M.A.L.-F.