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Review

Biomarkers for personalised primary or secondary prevention in cardiovascular diseases: a rapid scoping review

Chantal Babb de Villiers[1*], Elena Plans-Beriso[2,3], Chaitanya Erady[1], Laura Blackburn[1], Hayley Wilson[1], Heather Turner[1], Isla Kuhn[4], Cristina Barahona-López[2,3], Paul Diez-Echave[2,3], Orlando Hernández[2,3], Nerea Fernández de Larrea-Baz[2,3], Dafina Petrova[2,5,6,7], Ramon Cierco[8], Pablo Fernández-Navarro[2,3], Esther García García-Esquinas[2,3], Virginia Jiménez-Planet[9], Fernando Rodríguez-Artalejo[2,10], María José Sánchez[2,5,6], Víctor Moreno[2,11,12], Marina Pollán[2,3], Beatriz Perez-Gomez[2,3], and Mark Kroese[1]

[1] PHG Foundation, University of Cambridge, Cambridge, United Kingdom.
[2] CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain.
[3] Department of Epidemiology of Chronic Diseases, National Centre for Epidemiology, Instituto de Salud Carlos III, Madrid, Spain.
[4] Cambridge University Medical Library, Cambridge, United Kingdom.
[5] Instituto de Investigación Biosanitaria ibs. GRANADA, Granada, Spain.
[6] Escuela Andaluza de Salud Pública (EASP), Granada, Spain.
[7] University Hospital Virgen de las Nieves, Granada, Spain
[8] International Agency for Research on Cancer (IARC/WHO), Evidence Synthesis and Classification Branch, Lyon,France.
[9] National Library of Health Sciences, Instituto de Salud Carlos III, Madrid, Spain.
[10] Department of Preventive Medicine and Public Health, Universidad Autónoma de Madrid, Madrid, Spain; IMDEA23 Food Institute, CEI UAM+CSIC, Madrid, Spain.
[11] Oncology Data Analytics Program, Catalan Institute of Oncology (ICO), L'Hospitalet de Llobregat, Barcelona, Spain.
[12] Colorectal Cancer Group, ONCOBELL Program, Institut de Recerca Biomedica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain.
* Correspondence: Chantal.babbdevilliers@phgfoundation.org

Abstract

(1) Background: Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality globally. Early detection and personalised prevention strategies are crucial for reducing the burden of CVD. The use of biomarkers plays a pivotal role in identifying individuals at risk and facilitating timely interventions. This rapid scoping review aims to identify and evaluate current research on biomarkers used for primary and secondary personalised prevention of CVD, highlighting evidence gaps and the integration of digital technologies. (2) Methods: A comprehensive search was conducted in Medline and Embase databases from January 2020 to February 2023. Joanna Briggs Institute (JBI) Manual for Evidence Synthesis and PRISMA-ScR guidelines were followed. (3) Results: A total of 775 studies were included, with ischemic heart disease (IHD) and stroke being the most investigated CVD. Molecular, cellular, imaging, physiological, and anthropometric biomarkers were included. Molecular biomarkers, particularly genetic and biochemical, were the most researched. For secondary prevention there was considerable research using imaging biomarkers. (4) Conclusion: Genetic biomarker research was the most frequent category of biomarker identified, particularly using variant analysis and polygenic scores, followed by biochemical, imaging, and physiological biomarkers. There was also evidence of the integration of artificial intelligence to enhance the predictive capabilities of these biomarkers. Despite progress, research gaps were identified for less common CVDs such as aortic aneurysm and nonrheumatic valvular heart disease

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and limited research investigating other molecular biomarker types such as epigenetics and transcriptomics.

Keywords: Precision medicine; biomarker; cardiovascular disease; prevention; early detection

1. Introduction

Cardiovascular diseases (CVD) are a leading cause of morbidity and mortality worldwide. The development and progression of CVD are influenced by a complex interplay of genetic predispositions, environmental exposures, and lifestyle choices, with significant differences across demographic factors including age, sex, and gender. It is estimated that 80% of cardiac events and strokes are preventable, and 25% to 75% may be prevented through intervention and early detection [1]. Accurate, and cost-effective ways for cardiovascular risk discrimination would allow the deployment of more effective prevention treatment strategies but appropriate tools for detection have been lacking [2]. Identification of appropriate biomarkers to enhance risk prediction and reduce disease prevalence by facilitating earlier interventions should result in better health outcomes.

In recent years, innovative health research has moved rapidly towards a new paradigm of analysing, processing and combining unprecedented sources and quantities of data of various kinds e.g. environmental, clinical, socio-demographic, epidemiological and biological. This has created new opportunities to better understand the origin and evolution of chronic diseases and facilitates the design of new targeted strategies to prevent, detect or treat at an individual level, which is known as "personalised medicine".

According to the European Council Conclusion on personalised medicine for patients (2015/C421/03), the term “personalised medicine” defines a medical model which characterises the genotypes, phenotypes, lifestyle and environmental exposures of individuals. The goal is to tailor the right therapeutic strategy for the right person at the right time, and/or to determine disease predisposition and/or to provide timely and targeted prevention [3]. Personalised prevention, a subset of personalised medicine, is an important factor in terms of public health. Personalised prevention aims to prevent the onset, progression and recurrence of disease by adopting targeted interventions considering biological information, environmental and behavioural characteristics, socio-economic and cultural context of individuals [4]. These interventions should be timely, effective, and equitable to maintain the best possible balance in the lifetime health trajectory.

In this context, non-communicable chronic diseases (NCDs) need specific attention due to their rising incidence, mortality, and their impact in terms of disability-adjusted life years [5], [6], [7]. According to the World Health Organization [8], each year NCDs kill 41 million people, equivalent to 74% of all deaths globally. Within the EU, NCDs are estimated to account for 80% of the overall burden of disease and, in 2021, one third of EU adults were reported to be suffering from a chronic condition [9]. According to the World Health Organization (WHO) in 2019 circulatory diseases accounted for over 17.9 million deaths or 32% of all global deaths [10]. There is already a significant body of knowledge about primary and secondary prevention strategies for CVD and its associated risk factors [7], [11]. Given the above, in 2019, the PRECeDI (Personalised medicine for disease prevention) consortium recommended the identification of biomarkers for the prevention of chronic diseases to support stratification of populations by indicating individuals’ risk or resistance to disease and their possible response to drugs, guiding preventive interventions [12]. Current research focusses on the identification of biomarkers that will aid more precise identification of which individuals can benefit from specific preventive strategies

or to design and adapt therapies for specific patients or groups of patients [13]. The question is whether there is any biomarker or combination of biomarkers that can improve identification of subgroups of individuals with different risks of developing a particular disease. Specific preventive strategies and interventions for each subgroup could have an impact on their clinical outcomes.

The aims of this scoping review are to: showcase current research on biomarkers that can help improve primary or secondary CVD prevention strategies by better identifying subgroups of individuals at different risk(s); highlight evidence gaps in research on the use of biomarkers in personalised prevention; and examine their integration with digital technologies, such as the use of wearable devices for measuring physical and physiological functions and use of artificial intelligence (AI).

This research is part of the "PeRsOnalised Prevention roadmap for the future HEalThcare" (PROPHET) project, funded by the European Union's Horizon Europe research and innovation programme and UK Research and Innovation. It is linked to the International Consortium for Personalised Medicine (https://www.icpermed.eu/). The PROPHET project seeks to describe the current research and identify the gaps in personalised preventive approaches in order to inform the development of a Strategic Research and Innovation Agenda (SRIA) for the European Union.

2. Materials and Methods

A scoping review methodology was developed as part of a larger project that included three parallel reviews (for cardiovascular diseases, cancer, and neurodegenerative diseases); this paper presents the findings for the cardiovascular disease review [14]. An overview of the research landscape and identified gaps in the research literature on biomarkers for personalised primary and secondary prevention of CVD.

2.1. Protocol

The review process followed the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards based on the Population, Concept and Context (PCC) framework [15]. Specifically, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR) checklist was followed. The full protocol has been published [14] and is available on Open Science Framework (OSF) with registration DOI: https://doi.org/10.17605/OSF.IO/7JRWD .

2.2. Data Sources and search strategy

To identify relevant studies for inclusion, the electronic databases Medline and Embase via Ovid were searched. The search was limited to the period 1st January 2020 until 21st February 2023. The Embase preprints via Ovid search was limited to January 2021 until 21st of February 2023. This timeframe for preprints was chosen since it is likely that any papers older than two years would have undergone peer review and been published, and therefore captured in the main search.

To optimise the search matrix and terms, freely accessible tools such as SR-Accelerator & Polyglot Search Translator [16], Citationchaser [17] and Yale Mesh Analyzer [18] were used. Key words and thesaurus terms were identified, and a pilot study was done to refine the search strategy and test the literature review management software Covidence [19]. An experienced librarian and content experts were consulted on the search strategy.

Population Concept and Context (PCC) Framework

For the scoping review a PCC framework was used to develop the search strategy matrix [14] (Supplementary 1) and was as follows:

Population: Papers with a focus on the general adult population and population subgroups that are at an elevated risk of CVD were considered. The elevated risk of CVD subgroup included populations who were smoking, consume alcohol, have a family history of CVD, diabetics, hypertension, cholesterol/dyslipidaemia, obesity, and kidney failure/chronic kidney disease [7], [11]. Some papers classified individuals as 'at risk' or 'high-risk' of CVD due to the presence of clinical features on the pathophysiological pathway to CVD which included atherosclerosis. Additional groupings in the literature included high CVD risk, those with a history of CVD, revascularization, or major cardiovascular events. For this review these populations were grouped and categorized as a 'high-risk CVD' population.

Concept

Biomarkers: For this review, a biomarker is defined as a substance, structure, characteristic or process that can be objectively measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure [20], [21]. Biomarkers were classified into molecular, cellular, imaging, physiological and anthropometric measures. Each biomarker class contained several subcategories which are detailed in Table 1. This scoping review maps the current research landscape for novel biomarkers, rather than analysing biomarkers already established in routine clinical practice.

Diseases: The cardiovascular diseases included in this scoping review are the main causes of CVD deaths globally and follow the global burden of disease categorisation: ischemic heart disease (IHD), stroke, cardiomyopathy and myocarditis, atrial fibrillation and atrial flutter (AF), aortic aneurysm, nonrheumatic valvular heart disease (NRVHD), and peripheral artery disease (PAD) [7]. Alternate names and subcategories of these disease groups were included. Rheumatic heart disease and endocarditis have not been considered because of their infectious aetiology. Another not considered is heart failure. Although heart failure is a significant burden in healthcare, it is not categorised in the global burden of disease as it is rather a syndrome that is a consequence of other cardiovascular issues. Therefore primary and secondary prevention of a CVD should prevent heart failure.

A composite endpoint of diseases was often classified under major adverse cardiac events (MACE), major adverse cardiac and cerebrovascular events (MACCE), or cardiovascular events (CVE), and frequently included CVD related deaths. Definition of these terms vary between researchers and for this review the term MACE has been used to cover all these categories. Papers that included MACE were only included when a CVD of interest was named, and the paper met the review criteria. The MACE disease group was challenging to capture as individual disease breakdown was not always available. Therefore, a MACE category was included in the data extraction form. If a disease breakdown for MACE was available, both the specific disease and MACE were captured.

Prevention: The scoping review focused on personalised primary and secondary prevention for CVD. Papers aimed at preventing or delaying the development of the disease were categorised as primary prevention, while those aimed at identifying patients in the early stages of the disease were categorised as secondary prevention. If the prevention pathway for the biomarker was not specified in the paper primary or secondary prevention was determined based on the patient's clinical status (no observable vs. observable clinical manifestations) or the biomarker's purpose (risk assessment or early detection/screening), respectively.

For the purposes of this scoping review, papers needed to include the potential use of the biomarker for personalised prevention. In the literature, there is ambiguity and variability in the definition of personalisation [22], [23]. As such, if not specified in the paper we used a broad definition of personalised prevention to cover the research landscape of both primary and secondary prevention. Where biomarkers were assessed as part of a model that would subgroup variables or stratified analyses, these were included in the review. A paper was considered to cover personalised prevention if it attempted to define different disease risk levels and grouped individuals based on the biomarker.

This combination of definitions for personalised and prevention may have overestimated the number of biomarkers through inclusion of papers, but avoided the loss of potentially useful papers.

Context

This review included papers evaluated within a clinical or public health setting, conducted in any geographical location, and published between January 2020 and mid-February 2023. Only papers published in English were considered.

2.3. Eligibility Criteria

This review included papers evaluated within a clinical or public health setting, conducted in any geographical location, and published between January 2020 and mid-February 2023. Studies involving laboratory research in animals, human tissues, and cell lines were excluded. Only papers published in English were considered.

Inclusion criteria: Umbrella reviews, systematic reviews, meta-analyses with systematic reviews, scoping reviews, randomised controlled trials, non-randomised controlled trials, cohort studies, case-control studies, and analytical/descriptive cross-sectional studies. English language publications.

Exclusion criteria: Editorials, narrative reviews, protocols, qualitative Delphi studies, case reports, guidelines, and conference abstracts. The purpose of this scoping review is the identification of novel biomarkers and therefor well-established CVD biomarkers were excluded (details in Supplementary 2). These biomarkers were only included when analysed in combination with novel biomarkers. Known monogenic disorders with increased risk for CVD were excluded. Papers that sought to classify patients with the disease according to their possible prognosis (tertiary prevention) were outside the scope of this review. More detail in Supplementary 2.

2.4. Screening process

The screening criteria were established a priori and calibrated through a series of pilot tests [14]. Screening started with dual review and after >90 % agreement was observed (achieved when 28% of papers were reviewed). Search results were then screened independently, and discrepancies or challenging papers were resolved through discussion. All screening and data extraction was done using Covidence.

2.5. Data extraction

A data extraction form (Supplementary 3) was developed and calibrated using 10% of a random sample of studies.

The Covidence data extraction form captured citation details, study design, disease group, biomarker information, technology used, disease type, prevention type, and at-risk population groups. For primary prevention papers, it included risk factors like smoking, exercise, diet, alcohol consumption, air pollution, obesity, family history, and preventive drug use. Information on technologies, including artificial intelligence (AI), was also captured (Supplementary 3). Data extraction was done by two reviewers, with

discrepancies resolved through discussion based on the defined definitions and criteria established for primary and secondary prevention as well as biomarker classification and population groups.

2.6. Data analysis

Results of the data extraction process were exported from Covidence and analysed using R programming language [24]. Tables summarising the data were created using R package 'reactable (v0.4.4)' [25], and bubble plots were created using R package 'ggplot2 (v3.4.4)' [14]. The R codes are accessible via https://github.com/phg-foundation/PROPHET. Interactive mosaic plots or evidence gap maps (EGMs) [4] available at http://hdl.handle.net/20.500.12105/19630 were created using Python [26] and the EPPI-Mapper tool [27] (Supplementary 4). It should be noted that most research papers discuss multiple diseases or biomarkers. Therefore, one paper does not necessarily correspond to one disease or one biomarker.

3. Results

From the search, a total of 5,321 papers were identified, of which 871 were duplicates based on title, author and year of publication. Of the 4,450 papers screened for suitability based on their title and abstract, 1,053 papers were retained for full-text review. A further 278 papers were excluded based on full-text review, leaving 775 papers for this review. Ultimately 376 focused on primary prevention, 353 on secondary prevention, and 46 on both (Figure 1).

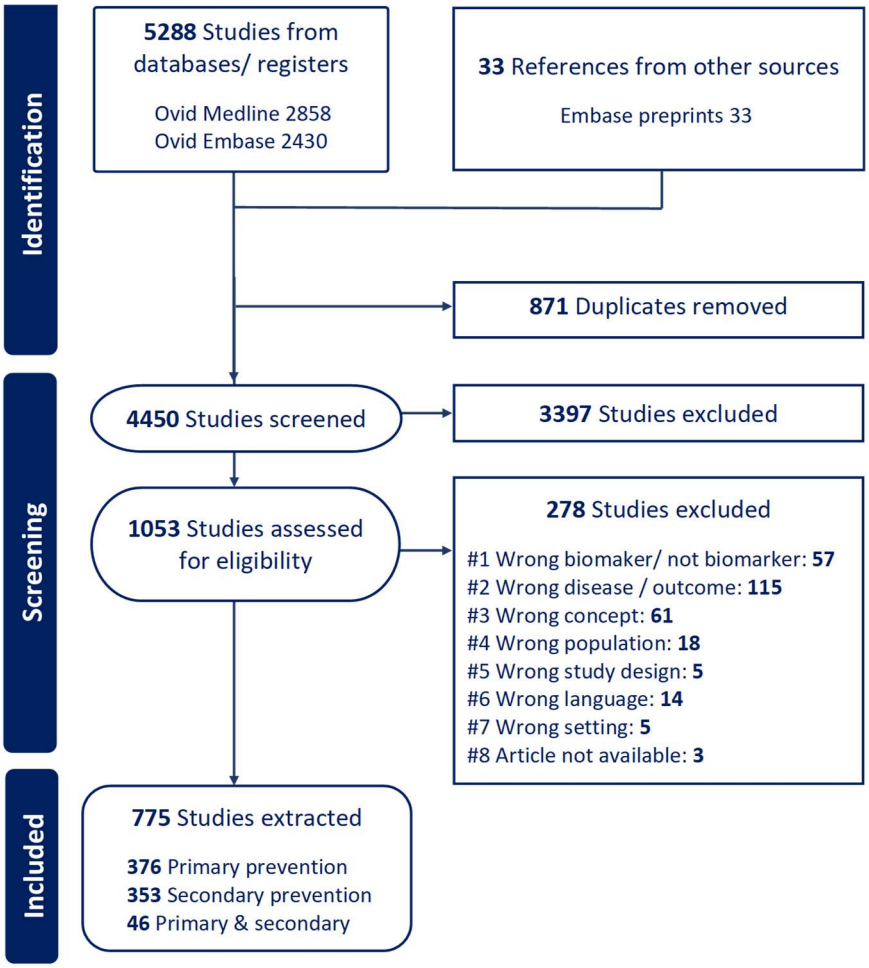

Figure 1. Cardiovascular diseases scoping review PRISMA flowchart.

Biomarker Research Landscape

Of the CVDs included, the majority (77%, 597/775) of papers investigated IHD (50%, 391/775) and stroke (44%, 338/775), followed by AF (11%, 83/775 papers) across primary and secondary prevention (Table 1). This was consistent across all biomarker groups, therefore unless otherwise mentioned the most commonly investigated disease will be IHD and stroke followed by AF. The molecular (74%, 575/775) and imaging (23%, 179/775) biomarker categories were the most frequently investigated. For molecular biomarkers, the genetics subcategory (56%, 238/422) was the most commonly investigated in primary prevention and second for secondary prevention of CVD, after the biochemical subcategory (Table 1).

Within the genetics subcategory, single nucleotide polymorphism (SNP) genotyping association studies were the most common study type identified. These studies aim to identify genetic variants associated with disease that could be used to predict disease risk in individuals. These studies investigated single or multiple variants in a single gene or variants across multiple genes. The majority of genes were unique to the papers found, with a small number (n=<10) repeated across the papers in the review. The genes that appeared in multiple papers included the methylenetetrahydrofolate reductase (MTHFR) gene and the matrix metalloproteinase-9 (MMP-9) gene. A small number of papers focused on long non-coding RNAs (lncRNAs) or mitochondrial DNA (mtDNA). There were 6 papers that reported whole exome or genome wide association studies (GWAS), which provide broad SNP coverage of the entire genome. The genetic biomarker subcategory included papers looking at mendelian randomisation (MR) studies. MR uses genetic markers as surrogate measures of features (biochemical biomarkers, protein levels, clinical features such as obesity, hand grip strength, height, lifestyle factors such as smoking, or sleeping habits) to investigate possible causal links with disease [28].

The most investigated molecular subcategory in secondary prevention of CVD was biochemical (40%, 159/399), and this was the second most common molecular subcategory for primary prevention (Table 1). Many biochemical markers were serum markers detectable by standard clinical blood sampling tests such as high sensitivity C-reactive protein (hs-CRP), cortisol levels, N-terminal brain natriuretic pro-peptide (NT-proBNP), lipid panels or uric acid. Refinement in the measurements, measuring derivatives, calculations of ratios, combinations with other clinical features or biomarkers as well as their potential use in predicting other diseases were investigated.

For imaging biomarkers in primary prevention 13% (56/422) of papers investigated the subcategories of ultrasound (5%, 22 papers), CT scan (3%, 14) and MRI (3%, 12). In 134 imaging biomarker papers investigating secondary prevention the most common subcategories were MRI (11%, 44/399), CT Scan (11%, 45/399), ultrasound (10%, 39/399) and PET/SPECT (4%, 16/399) (Table 1). We identified that for the early detection of stroke there was research activity with the use of MRI followed by CT scans.

The physiological, anthropometric and cellular biomarker groups were the least frequently researched (Table 1). Physiological biomarkers had some activity in primary prevention (9%, 38/422), with more activity in secondary prevention (15%, 60/399), particularly with the use of ECG. This was followed by anthropometric biomarkers (primary 6%, 24/422; secondary 1%, 5/399). Across both primary and secondary prevention there was limited research being done on cellular biomarkers (primary 1%, 3/422, secondary 2%, 7/399).

Table 1. Number of papers found for primary and secondary prevention by biomarker categories and cardiovascular disease.

	Primary prevention										Secondary prevention									
Biomarker	**Total**	**IHD**	**Stroke**	**Cardio-myopathy myocarditis**	**AF**	**AA**	**NRV HD**	**PAD**	**Hyper-tensive CVD**	**MACE**	**Total**	**IHD**	**Stroke**	**Cardio-myopathy myocarditis**	**AF**	**AA**	**NRV HD**	**PAD**	**Hyper-tensive CVD**	**MACE**
Total	**422**	**227**	**198**	**11**	**67**	**19**	**7**	**20**	**21**	**21**	**399**	**191**	**157**	**24**	**43**	**20**	**2**	**22**	**12**	**45**
Molecular	361	190	172	10	55	17	6	17	20	17	247	135	96	10	22	12	0	13	6	33
Genetics	238	120	117	9	38	35	6	9	16	7	39	20	14	2	2	3	0	2	0	3
Epigenetics	7	3	6	0	0	0	0	0	0	0	4	1	2	1	0	0	0	0	0	0
Transcriptomics	26	9	13	0	3	1	1	0	2	0	31	14	10	2	4	3	0	0	1	1
Metabolomics	8	4	5	0	1	0	0	1	1	0	18	11	9	2	0	1	0	0	1	2
Proteomics	10	5	3	0	2	1	1	0	0	0	23	11	7	1	1	2	0	3	1	1
Microbiomics	1	1	0	0	1	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0
Biochemical	119	72	52	1	17	4	0	8	4	11	163	88	69	5	18	7	0	8	4	27
Other	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cellular	3	3	1	0	0	0	0	0	0	0	7	2	3	1	0	1	0	0	0	0
Histology	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0
Cytology	1	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
Other	2	2	1	0	0	0	0	0	0	0	5	1	3	1	0	0	0	0	0	0
Imaging	56	31	24	3	8	3	1	2	2	4	134	48	60	13	13	6	2	6	6	9
X rays	2	1	0	1	0	0	0	0	0	0	7	3	1	1	0	0	1	2	0	1
Ultrasound	22	8	8	2	5	1	0	2	1	1	39	10	12	6	5	4	1	3	1	1
CT scan	14	13	5	0	1	0	0	0	0	1	45	18	24	1	5	3	0	0	1	4
PET/ SPECT	5	4	1	0	0	0	0	0	0	1	16	11	2	2	1	1	0	0	0	1
Spectrometry	0	0	0	0	0	0	0	0	0	0	2	0	1	1	0	0	0	0	0	0
MRI	12	1	6	3	3	1	1	0	1	0	44	6	29	7	6	1	0	1	4	2
Scintigraphy (Gamma)	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0
Mammography	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
Other	7	5	4	0	1	1	0	0	0	1	0	2	2	0	0	0	0	1	0	0
Physiology	38	15	14	2	15	1	1	3	1	1	60	21	19	10	13	2	0	7	1	8
Blood pressure	16	6	7	0	7	1	0	1	0	1	16	4	7	2	2	1	0	1	0	2
Ankle-brachial index	2	1	1	0	0	0	0	1	0	0	4	1	1	0	0	0	0	0	0	1
ECG	14	3	2	2	9	0	1	0	0	0	30	10	4	8	11	1	0	0	1	2
EEG	1	0	1	0	0	0	0	0	0		1	0	1	0	0	0	0	0	0	0
Electromyography	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other	11	5	5	0	2	0	0	2	1	0	11	9	8	2	0	1	0	4	0	4
Anthropometric	24	12	11	0	8	1	0	2	0	1	5	2	1	0	1	1	0	0	0	0
BMI	13	7	6	0	5	0	0	1	0	1	3	2	1	0	0	0	0	0	0	0
Body perimeters	8	5	4	0	2	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Other	9	4	4	0	2	1	0	0	0	1	1	0	0	0	1	1	0	0	0	0

AF Atrial fibrillation and atrial flutter; AA Aortic aneurysm; IHD Ischemic heart disease; NRVHD nonrheumatic valvular heart disease; PAD peripheral artery disease; MACE major acute cardiac event; CT computed tomography; PET Positron emission tomography; SPECT single-photon emission computerized tomography; MRI Magnetic resonance imaging; ECG electrocardiogram; EEG electroencephalogram; BMI body mass index. Numbers can not be added up to give totals as some papers would look at more than one CVD or more than one type of biomarker.

The 'other' biomarkers category presents findings not captured in the listed categories (Table 1). These included; novel use of retinal-based imaging biomarkers [29], [30], [31], [32], [33], [34], [35] for secondary prevention of CVD and a mammography-based study for IHD [36]. Flow cytometry-based papers were also identified which evaluated cell count data [37], [38], [39]. Several new detection methods for physiological biomarkers are also being researched, for example algorithms that evaluate a range of physical and physiological parameters in the context of CVD [40], [41].

Novel technological modalities for biomarker identification (infrared cameras, innovative mass spectrometry techniques, and wearable monitors) that could improve CVD prediction and early detection were found. This included portable imaging devices, which are used to assist ambulance personnel during emergency assessment of risk of stroke outside of the hospital setting [42]. An implantable loop recorder to monitor heart rhythm [43], a seven-day ECG monitor [44], [45] and a wrist worn accelerometer [46] were being used for prediction and early detection of AF. One paper used infrared cameras for early detection of stroke [42]. The use of innovative mass spectrometry technologies [47], [48], [49], [50], [51], [52], [53] and a range of wearable monitors to track cardiac and other physiological parameters were also found [40], [44], [45], [54].

It was observed that some biomarkers used for one specific CVD were being repurposed and evaluated for use in other CVDs. For example, physiological measurement of ankle-brachial index is commonly used in PAD, but we found research activity for this biomarker in other CVDs such as IHD, stroke and a MACE that included a composite of PAD, IHD and stroke. Some biomarker subtypes were limited to specific populations, for example, imaging from scintigraphy (gamma) was only being investigated for risk of IHD in a diabetic population [55].

Interaction with risk factors

For primary prevention of CVD, we captured which risk factors (such as lifestyle or environmental exposures) were being considered if they were a component of the biomarker research including: smoking, exercise, diet, alcohol consumption, air pollution, obesity, family history, and use of preventive drugs. In papers being reviewed these risk factors were being used as a variable or for adjustment as part of the biomarker analysis. Across commonly investigated disease groups (IHD, stroke and AF) all risk factors (except air pollution) were taken into consideration (Figure 2). Smoking behaviour was the only risk factor considered across all disease groups. The next most commonly considered risk factors were obesity, exercise, use of preventive drugs, family history and alcohol consumption. There was limited consideration of diet. Of note was that air pollution, a well-known risk factor for CVD was not considered in the 775 papers reviewed.

During the review considerable variability in how these risk factors were considered in the papers was observed. For example, their use as a variable in a regression model, as an adjustment criterion to display demographic data, or in a complex statistical algorithm. Therefore, there is a caveat to the interpretation of the risk factor information as no inference on causality or association can be made using the data from this scoping review. What can be concluded is that these risk factors are being considered in combination with biomarkers in the research identified.

Role of Artificial Intelligence Technologies

AI technology use was identified for primary and secondary prevention in almost 15% of the 775 papers, more frequently in secondary prevention (Table 2), and usually in conjunction with molecular and imaging biomarkers (Table 2). Novel AI methods that enhance well established technologies such as CT scanning, ECG, MRI and ultrasound using machine learning or convolutional neural networks are being researched for their

accuracy and utility. For secondary prevention a fifth of all imaging papers used AI based methods to aid imaging biomarker research (Table 2).

Our results show that biomarker research activity in population groups with an elevated risk of CVD was focused on diabetes mellitus in primary prevention and high-risk CVD in secondary prevention (Figure 3 and 4). There was little activity in CKD/kidney failure patients and high cholesterol/dyslipidaemia patients. Limited research was identified in population groups with an elevated risk of CVD based on family history, obesity, smoking, and alcohol consumption (Figure 3 and 4).

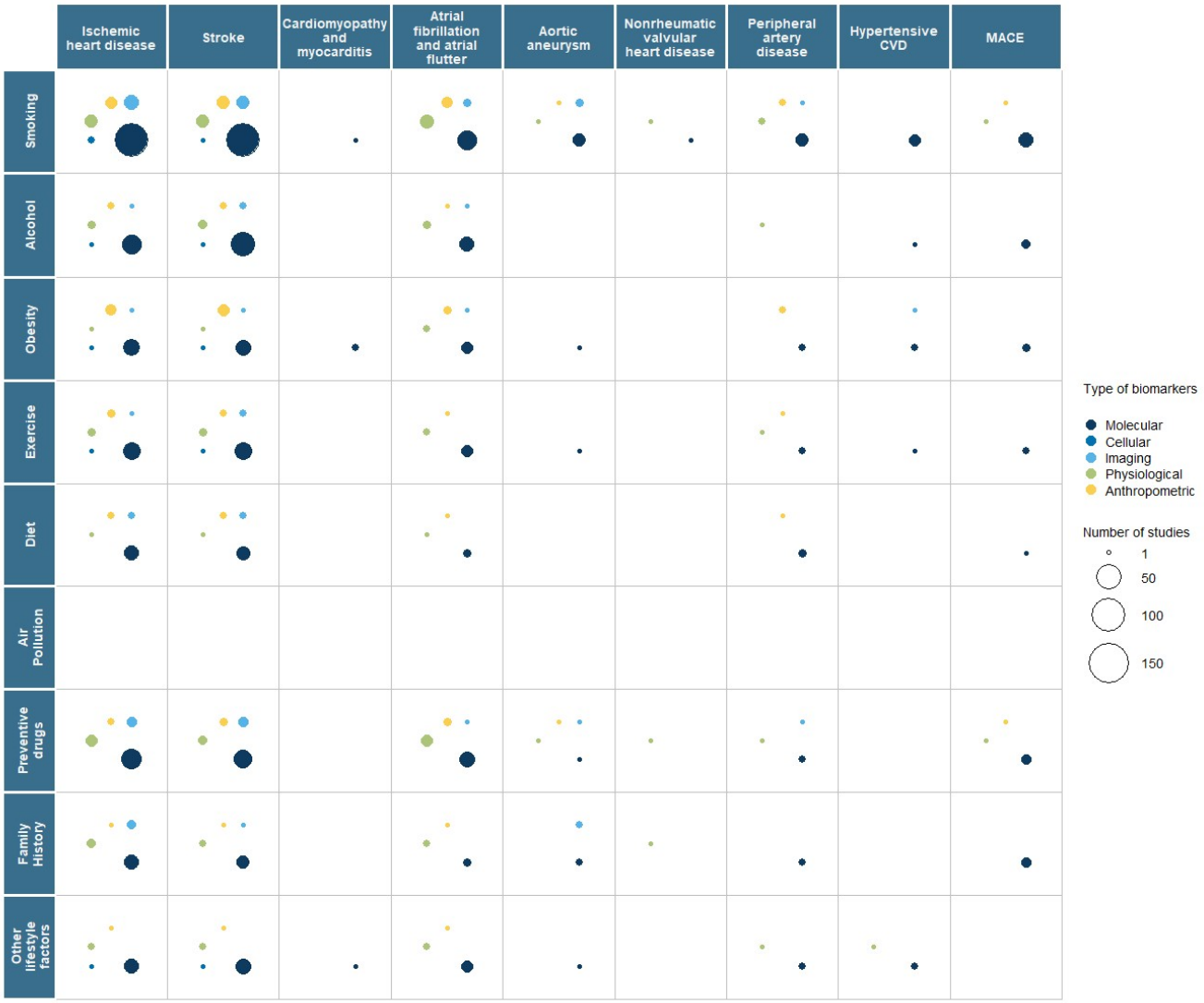

Figure 2. Bubble plot representing the number of papers identified for primary prevention of cardiovascular disease where risk factors were considered - the size of the bubble represents the number of papers and the colour represents a type of biomarker. CVD – cardiovascular disease; MACE – major adverse cardiovascular events.

Table 2. Number of papers found using artificial intelligence for primary and secondary prevention by biomarker categories for cardiovascular diseases.

	Total	Ischemic heart disease	Stroke	Cardiomyopathy and myocarditis	AF	AA	NVHD	PAD	Hypertensive CVD	MACE
Primary prevention										
Total	**22**	**10**	**9**	1	8	2	0	**0**	**0**	**0**
Molecular	**15**	6	4	1	6	2	0	0	0	0
Cellular	0	0	0	0	0	0	0	0	0	0
Imaging	**9**	4	4	1	4	1	0	0	0	0
Physiological	**7**	1	3	0	4	0	0	0	0	0
Anthropometric	**1**	0	1	0	0	0	0	0	0	0
Secondary prevention										
Total	56	24	18	4	8	4	1	3	2	1
Molecular	**22**	15	7	1	1	2	0	**1**	0	0
Cellular	0	0	0	0	0	0	0	0	0	0
Imaging	**28**	8	11	2	3	**2**	1	**1**	2	**1**
Physiological	**15**	4	5	1	5	0	0	**1**	0	0
Anthropometric	**1**	1	0	0	0	0	0	0	0	0

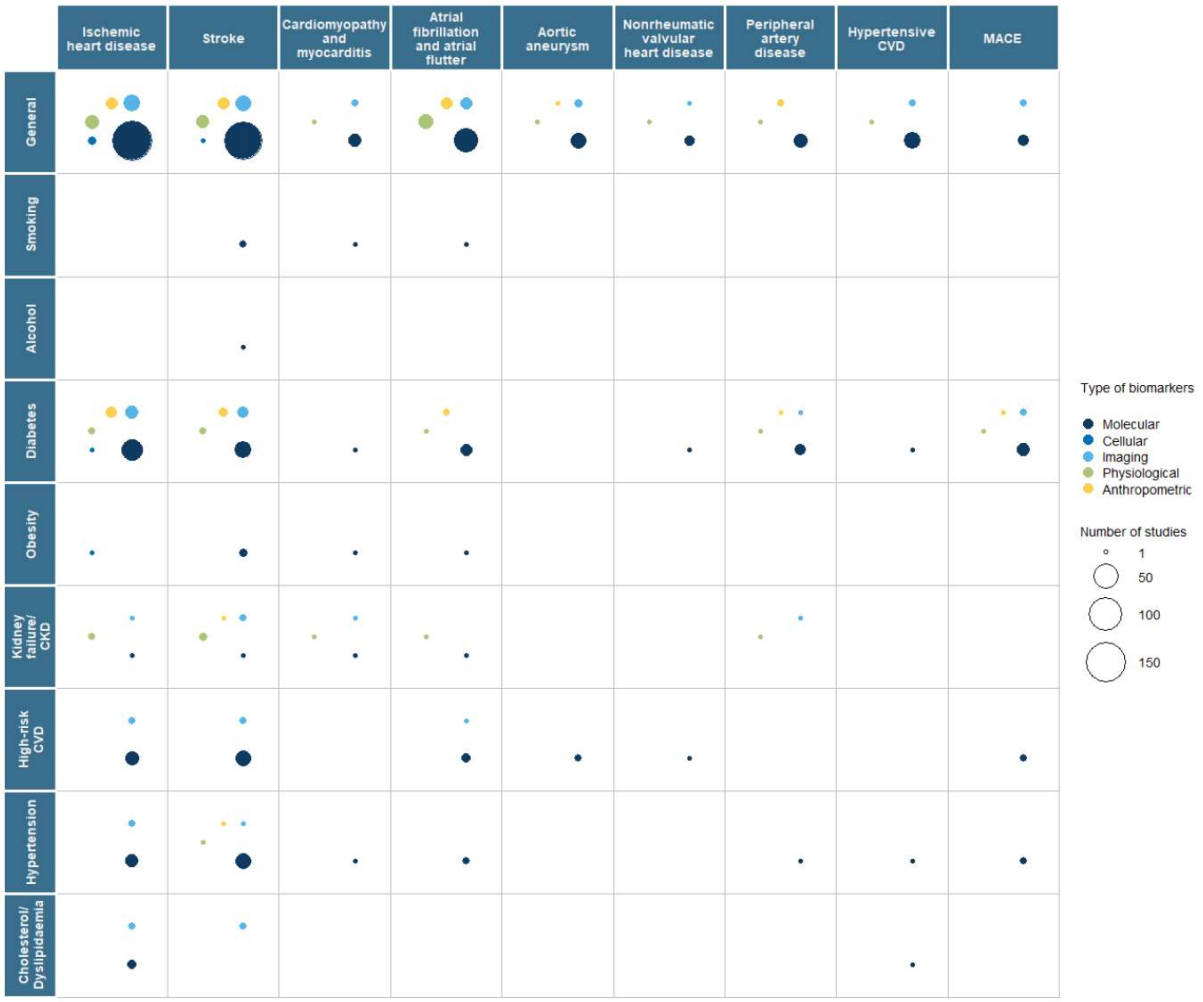

Figure 3. Bubble plot representing the number of papers identified for primary prevention of cardiovascular disease by each population group, where the size of the bubble represents the number of papers and the colour represents a type of biomarker. No papers looked at family history as a population group in primary prevention. Evidence gap map 1: An interactive version linking to the references identified and used in this bubble plot is accessible via: https://phg-foundation.github.io/PROPHET/Phase_1_codes/EGMs/EGM_cvd_primary_segment_biomarker.html .

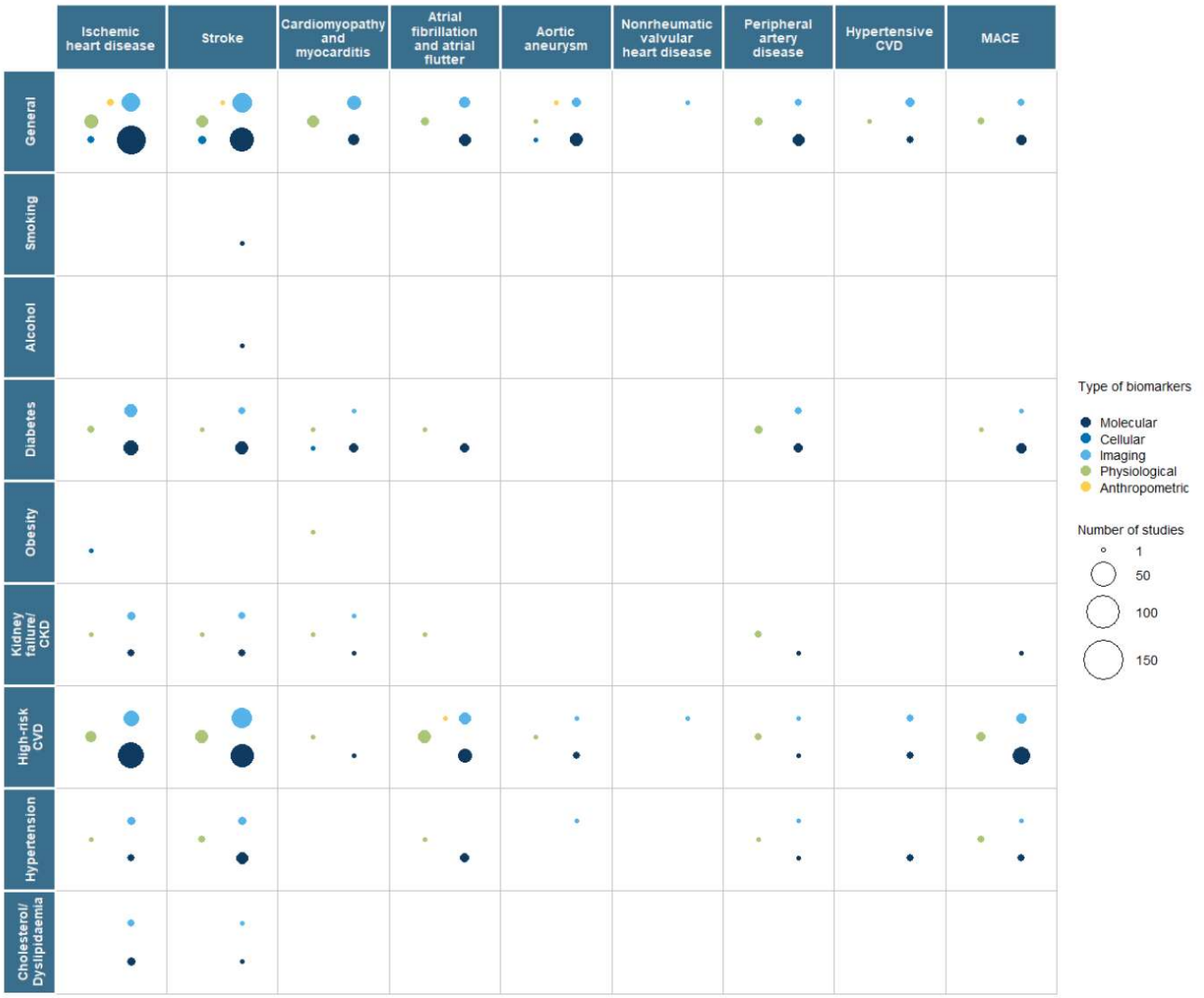

Figure 4. Bubble plot representing the number of papers identified for secondary prevention of cardiovascular disease for each population type, where the size of the bubble represents the number of papers and the colour represents a type of biomarker. CKD – chronic kidney disease; CVD – cardiovascular disease; MACE – major adverse cardiovascular events. There were one papers that looked at family history as a population group in secondary prevention of Cardiomyopathy and myocarditis. Evidence gap map 2: An interactive version linking to the references identified in the scoping review and used in this bubble plot is accessible via: https://phg-foundation.github.io/PROPHET/Phase_1_codes/EGMs/EGM_cvd_secondary_segment_biomarker.html

4. Discussion

In this paper, we present the results of a scoping review of research activity on novel biomarkers for personalised prevention of CVD.

CVD research activity and gaps

The most commonly investigated diseases were IHD and stroke (Table 1), which are the leading causes of CVD death, followed by AF. There was limited or no research activity identified for a number of diseases e.g. NRVHD, cardiomyopathy and myocarditis. However, the total number of biomarkers per CVD identified does not correlate with CVD prevalence in the general population. The limited research activity for less prevalent but

highly morbid conditions like aortic aneurysm highlights a critical research gap, suggesting an opportunity for targeted investigation rather than a confirmed lack of biomarker potential.

Genetic Biomarkers

Genetic biomarker research has advanced significantly in recent years and this progress is reflected in our results. Insights into rare Mendelian diseases that aid diagnosis means genomic medicine has made remarkable progress, offering tailored solutions for patients and their families. It is anticipated that genetic testing will contribute towards personalised prevention of disease. Advances in DNA sequencing enable precision diagnosis, allowing early detection of diseases even before symptoms appear. In the context of CVD, genetic markers could help in assessing risk, guide lifestyle changes, prioritise screening and monitoring at-risk patients.

The two main methods used for genetic biomarkers in our review were SNP analysis and PGS. SNP analysis aims to identify associations with disease by testing differences in allele frequencies of genetic variants. However, many of these associations have been weak. To utilise this information there has been a move towards combining these genetic associations using PGS models. These models combine the information of several to millions of genomic variants, accounting for effect sizes and the aggregated impact of multiple variants. PGS can be developed for the disease of interest (e.g. CAD), clinical features (e.g. hypertension), or for a biomarker (e.g. cholesterol or vitamin D levels). In the context of this scoping review, the proposed utility from such genetic information is the possibility of using personalised prevention strategies based on the assessed genetic risk. Genetic biomarkers can be measured in young, asymptomatic adults and present opportunities for implementation of preventive strategies earlier in the life course.

Biochemical, imaging and physiological markers

Biochemical, imaging and physiological markers often rely on detectable changes in specific molecules or structures which usually occur during the progression of a disease, even at the sub-clinical level. Biomarkers from these fields have always played a crucial role in healthcare, being incorporated into essential tools for disease detection, monitoring, and personalised treatment. Many biochemical, imaging and physiological technologies are already commonly available in clinical settings and used for the assessment of patients for the disease of interest, such as ECGs and ankle-brachial measures, CT scans and X-rays. However, our search of recent literature identified limited research activity focused on certain established physiological measures, such as pulse wave velocity or flow-mediated dilation as markers for early vascular aging, suggesting these may be areas of less intensive current investigation for personalised prevention in the examined period.

In this scoping review, the research was focused on innovative measurement techniques and analyses, including the integration of clinical data with biomarker measurements, in at-risk populations. They also explore the repurposing of these biomarkers for CVDs in addition to those for which they were originally intended. Within our results, AI technologies are being used to assess complex regression models with high volumes of genomic and biochemical data or elaborate imaging files (radiomics). In addition, machine learning algorithms are being used to screen detailed health records. AI, including machine learning algorithms, have a pivotal role in facilitating automated assessment of data generated by these technologies. For example, the use of AI with ECG measurements to provide a more accurate coronary artery calcium (CAC) score for risk prediction of CVD in populations such as those with type-2 diabetes [56], [57] or CKD [58]. AI can also be used to review CT scans to detect and triage potential stroke patients in emergency rooms [59], [60], [61].

Risk prediction models

There is growing recognition that combining risk factors with biomarker information enhances prevention strategies by enabling more robust disease prediction. Future applications of biomarkers in prevention will likely involve integrating them into risk scores that use a range of biomarkers from different sources. This scoping review identified such combinations of biomarkers and risk factors, as well as integrated models which included a broad range of variables [62], [63], [64], [65], [66], [67], [68]. Some studies explored multiple biomarker categories simultaneously, such as multi-omic approaches, to capture various disease-associated modalities and improve risk prediction of a number of diseases [33], [69], [70]. These combinations aim to facilitate personalised prevention by integrating socio-demographic, lifestyle, and behavioural information with biological data. Assessment of such combinations of variables was outside the scope of this review, but future research will need to consider how to capture this information to inform biomarker development.

Integration with AI

AI was identified in this scoping review where advances in AI are being used to determine how it can enhance the predictive capabilities of complex, multimodal biomarker data. Risk model research plays a pivotal role in this context, as it helps integrate various biomarkers and other risk factors into comprehensive models that can predict an individual's risk of developing CVD. AI models allow for the integration of sometimes complex data types to accurately stratify patients based on their calculated risk levels, thereby enabling targeted preventive measures and personalised treatment plans.

Limitations

A known caveat of the scoping review methodology is that it does not assess the methodological quality or potential biases of the papers included. This scoping review focused on identifying research on biomarkers for the prevention of CVD. Scoping review are used to identify research priorities, to guide the expansion of research and the generation of new knowledge [71]. Evaluating the clinical utility and integration of these biomarkers into healthcare pathways requires further assessment to fully understand their potential impact and application in clinical settings. As this review synthesizes research activity from a broad range of studies, we acknowledge that this may introduce limitations regarding the direct clinical applicability and generalisability of the findings across different populations.

During the title and abstract screening process, a standard and necessary component of scoping review methodology, a large number of papers were excluded. We acknowledge that abstracts may not always fully capture the relevance of a study, and some papers discussing biomarkers in the full text might have been missed if not mentioned prominently. While our broad search strategy was designed to mitigate this, this limitation is inherent to the review process but is unlikely to have materially affected the overall conclusions given the large volume of literature included.

In this scoping review we observed inconsistent naming of biomarkers, definitions of disease versus risk factors, the lack of description regarding the intended prevention pathway or the clinical care pathway where a biomarker would be used. There was variation in how the clinical manifestation of CVD were described in the papers with a lack of consensus regarding when CVD transitions from sub-clinical (asymptomatic) to symptomatic, and which elements were considered disease versus risk factors for CVD (e.g. hypertension and atherosclerosis). The criteria for this scoping review were carefully formulated and piloted to accommodate for this observed heterogeneity in the literature. We

also noted that International Classification of Diseases (ICD) coding was rarely used in the reviewed studies, further complicating standardisation. This highlights the critical need for adopting more systematic terminology and classification frameworks in future biomarker research.

Due to the variation and lack of standardisation across the papers for biomarker names (including combinations of biomarkers and their derivatives) the creation of a single biomarker list and a count of the biomarkers reported resulted in more names than papers identified. This demonstrates the need for improved standardisation in the nomenclature of biomarker names.

Apart from the general population, population groups known to be at an elevated risk of CVD were also considered in this scoping review. Research that is specifically focused on populations with an elevated or at high risk of CVD would allow for further personalisation and stratification of risk categories. We acknowledge that our definition of high-risk populations focused on established metabolic and lifestyle risk factors; specific comorbid populations with high CVD risk, such as cancer survivors or patients with chronic inflammatory diseases like rheumatoid arthritis, have distinct pathophysiological pathways and were outside the scope of this review, representing important areas for future work. There are additional study populations that were regularly encountered by the reviewers during the scoping review, namely: ethnicity/country of origin, age and sex. Furthermore, congenital heart diseases and studies focused on SARS-CoV-2 were explicitly excluded to maintain a clear focus on the prevention of chronic, non-communicable CVD in adults. Similarly, our definition of a biomarker was strictly focused on biological, physiological, or imaging-based measures, and did not extend to psychosocial or behavioural risk factors such as chronic stress or sleep quality, which are also known to significantly influence cardiovascular health. Future reviews of the research landscape should take these into consideration.

The reviewers also noted that a core number of well-defined large cohorts and databases such as the UK Biobank [72], Gene Expression Omnibus (GEO) [73], and MEGASTROKE [74] are being used for the identification of biomarkers. These cohorts and databases house extensive data allowing for complex analyses without the need for new data gathering. However, relying solely on these resources may perpetuate biases if they do not represent the full spectrum of populations – including demographics and ethnic diversity and can impact on the wider utility of the application of biomarkers developed from these. It is crucial to ensure diverse representation in biomarker research to avoid potential biases and obtain more comprehensive, accurate and widely applicable results. Understanding which cohorts are being utilised for research could also provide a better understanding of the limitations of the research landscape for biomarkers.

Despite significant improvements over the last few decades in decreasing air pollution this exposure remains the largest environmental health risk [75], [76]. Its absence from the papers may be due to the complexity in capturing individual exposure to air pollution.

5. Conclusions

This scoping review provides details of the extensive research activity on biomarkers for the personalised prevention of CVD. Most studies identified focused on IHD and stroke, reflecting their prevalence and impact on public health. Significant research activity for early detection and personalised prevention strategies is taking place with genetic biomarkers, particularly SNP analysis and polygenic scores.

Despite this progress, there are notable gaps in research, particularly for less common CVDs such as aortic aneurysm and nonrheumatic valvular heart disease. Additionally, the variability in how CVD is classified, the lack of clarity on the use of specific biomarkers

in prevention pathways and the limited consideration of certain risk factors, such as air pollution, highlight areas for future research. The integration of AI is emerging as a key enabler, helping to analyse complex, multimodal data to enhance the predictive power of these biomarkers. Ensuring diverse representation in biomarker research and integrating biomarkers with risk factors will be essential for developing comprehensive and effective personalised prevention strategies.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/doi/s1, Supplementary file 1: Search strategies for the different databases and repositories; Supplementary file 2: Eligibility criteria; Supplementary file 3: Data extraction form options that were in Covidence; Supplementary file 4: Definitions.

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Data Availability Statement: Tables summarising the data were created using R package 'reactable (v0.4.4)', and bubble plots were created using R package 'ggplot2 (v3.4.4)'. The R codes are accessible via https://github.com/phg-foundation/PROPHET. Interactive mosaic plots or evidence gap maps (EGMs) [4] available at http://hdl.handle.net/20.500.12105/19630.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations:

The following abbreviations are used in this manuscript:

AA	Aortic Aneurysm
AF	Atrial Fibrillation and Atrial Flutter
AI	Artificial Intelligence
BMI	Body Mass Index
CAD	Coronary Artery Disease
CAC	Coronary Artery Calcium
CKD	Chronic Kidney Disease
CT	Computed Tomography
CVE	Cardiovascular Event(s)
CVD	Cardiovascular Disease
ECG	Electrocardiogram
EEG	Electroencephalogram
EGMs	Evidence Gap Maps
EU	European Union
GEO	Gene Expression Omnibus
GWAS	Genome-Wide Association Study
hs-CRP	High-Sensitivity C-Reactive Protein
IARC	International Agency for Research on Cancer
IHD	Ischemic Heart Disease
lncRNA	Long Non-Coding RNA
MACCE	Major Adverse Cardiac and Cerebrovascular Events
MACE	Major Acute Cardiac Event
MEGASTROKE	Multiancestry Genome-Wide Association Study
MRI	Magnetic Resonance Imaging
MR	Mendelian Randomisation
mtDNA	Mitochondrial DNA
NCD	Non-Communicable Disease
NICE	National Institute for Health and Care Excellence
NRVHD	Nonrheumatic Valvular Heart Disease
NT-proBNP	N-terminal Brain Natriuretic Pro-Peptide
OSF	Open Science Framework
PAD	Peripheral Artery Disease
PET	Positron Emission Tomography
PCC	Population, Concept, Context
PGS	Polygenic Score
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews
PROPHET	PeRsOnalised Prevention Roadmap for the Future HEalThcare
SNP	Single Nucleotide Polymorphism
SPECT	Single-Photon Emission Computed Tomography
SRIA	Strategic Research and Innovation Agenda
UK	United Kingdom
WHO	World Health Organization

Supplementary files (Appendix)

Supplementary file 1.

Search strategies for the different databases and repositories.

The PCC framework was considered to develop the search strategy, and the following topics were obtained for the search: biomarkers, cardiovascular diseases, prevention and personalised. For each of them, the corresponding indexed and free terms were included. As detailed below, "blocks" (biomarkers, diseases, prevention, and personalised) using the "AND" operator to be combined following this general strategy during the search:

#1 biomarkers
#2 diseases
#3 prevention
#4 personalised, precision, prediction or predictive
#5 #1 AND #2 AND #3 AND #4
#6 #5 Filters: from 2020-2023

Our MeSH and free text keyword terms were identified through a rigorous, systematic, multi-step process. The selection began with expert input from content specialists to define the diseases of interest. We then conducted a formal analysis using specialized tools, such as the tools such as SR-Accelerator & Polyglot Search Translator [16], Citationchaser [17] and Yale Mesh Analyzer [18], for an evidence-based selection of the most appropriate terms. The resulting search strategy was subsequently validated by an experienced medical librarian, and finally, it was refined through a pilot study to ensure its accuracy and effectiveness before the full review was conducted. Despite this rigorous, multi-step process, we acknowledge that any search strategy is inherently limited by the initial scope defined for the review and the dynamic nature of database indexing and scientific terminology.

OVID MEDLINE MESH
BIOMARKERS
(exp Biological factors/ or ("biological factor*" or biomarker* or "bio* marker*").ti,ab,kw,kf.)
(exp *carbohydrates/ or exp *lipids/ or exp *amino acids/ or exp *proteins/ or exp *vitamins/ or exp *steroids/ or exp *Hormones/ or exp *Enzymes/)
(exp genetic markers/ or exp genotype/ or exp genetics/ or exp genomics or ("genetic marker*" or "genotype" or "germline biomarker*" or "genetic*" or "genomic*" or "epigen*" or "epigenetic mark*").ti,ab,kw,kf.)
(exp Microchip Analytical Procedures/) or (Microarray*).ti,ab,kw,kf.
(exp Metabolomics/ or exp Proteomics/ or ("metabolomic*" or "proteomic*" or "lipidomic*" or "immunomic*" or "nutriomic*" or "transcriptomic*" or "radiomic*").ti,ab,kw,kf.)
(exp *Diagnostic Imaging/ or imag*.ti,ab,kw,kf.)

DISEASES
(exp *atrial fibrillation/ or exp *atrial flutter/ or 'atrial fibrillation'.ti,ab,kw,kf.)
(exp *cardiomyopathies/ or exp *myocarditis/ or 'cardiomyopath*'.ti,ab,kw,kf. Or 'myocarditis'.ti,ab.)
exp *myocardial ischemia/ or exp *myocardial infarction/ or 'ischemic heart disease'.ti,ab,kw,kf. or 'ischaemic heart disease'.ti,ab,kw,kf. Or 'heart attack'.ti,ab,kw,kf.
exp *heart valve diseases/ OR ("Nonrheumatic valvular heart" OR "calcific aortic valve" OR "degenerative mitral valve" OR "Nonrheumatic heart").ti,ab,kw,kf.
exp *Peripheral Arterial Disease/ or 'Peripheral Arterial Disease'.ti,ab,kw,kf.
exp *Aortic Aneurysm/ OR "'aortic aneurysm".ti,ab,kw,kf.
exp *stroke/ or exp *brain infarction/ or exp *hemorrhagic stroke/ or exp *ischemic stroke/ or 'stroke'.ti,ab,kw,kf. OR exp *Cerebral Hemorrhage/ OR exp *Subarachnoid Hemorrhage/

PREVENTION
(exp Primary Health Care/ or ("public health service*" or "primary health care" or "primary care").ti,ab,kw,kf.)
(exp Primary prevention/ or ("primary disease prevent*" or "preventable disease*").ti,ab,kw,kf.)
(exp Preventive Medicine/ or ("preventive medicine*" or "medical prevent*").ti,ab,kw,kf.)
("protective factor*".ti,ab,kw,kf.)
(susceptibil*.ti,ab,kw,kf.)
(exp *smoking/)
(exp *exercise/ or exp *sedentary behavior/)
(exp *"Diet, food, and nutrition"/ or exp *Overweight/)
(exp *Alcohol Drinking/)
(exp *Type 2 Diabetes Mellitus/)
exp *renal insufficiency, chronic/ or exp *kidney failure, chronic/
(exp *air pollution/)
((exp *blood pressure/ or exp *hypertension/) or ("blood pressure" or "hypertension" or "high blood pressure").ti,ab,kw,kf.)
(exp *hypercholesterolemia/ OR exp lipid metabolism disorders/ or exp dyslipidemias/ or "dyslipedemia*".ti,ab. OR "dyslipidaemia*".ti,ab,kw,kf. OR "high cholesterol".ti,ab,kw,kf.)
exp hyperglycemia/ or exp *Blood Glucose/ or "high blood glucose".ti,ab,kw,kf.
(exp *Community Health Planning/ or ("community setting*" or "health care plan*" or "community health plan*").ti,ab,kw,kf.)
(exp *Preventive health service/ or "preventive health service*".ti,ab,kw,kf.)
(exp *Community Health Center/ or ("community health center*" or "community health centre*" or "community care").ti,ab,kw,kf.)
(exp *Health Education/ or ("health educat*" or "health promot*").ti,ab,kw,kf.)
(exp Mass Screening/ or exp Secondary Prevention/ or ("secondary prevent*" or "screening*").ti,ab,kw,kf.)
(exp Population Surveillance/ or ("population surveillance*" or "population screening*").ti,ab,kw,kf.)
(exp Early Diagnosis/ or ("early diagnos*").ti,ab,kw,kf.)

PERSONALISED
(exp Precision medicine/ or ("personalised medicine*" or "precision medicine*" or "predict*" or "individualized medicine*" or "personalised medicine*" or "individualised medicine*").ti,ab,kw,kf.)
(exp Risk assessment/ or exp Risk adjustment/ or ("risk stratifi*" or "risk scor*" or "risk assess*" or "risk adjust*").ti,ab,kw,kf.)
(exp Machine learning/)

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OVID EMBASE EMTREE
BIOMARKERS
(exp marker/ or ('biological factor*' or 'bio* marker*').ti,ab.)
(exp *'carbohydrate'/ or exp *'lipid'/ or exp *'amino acid'/ or exp *'protein'/ or exp *'vitamin'/ or exp *'steroid'/ or exp *'hormone'/ or exp *'enzyme'/)
(exp 'genetic marker'/ or exp 'genotype'/ or exp 'genetics'/ or exp 'genomics'/ or ('genotype' or 'genetic*' or 'genomic*' or 'epigenetic mark*' or 'germline biomarker*' or 'epigen*' or 'genetic marker*').ti,ab.)
(exp 'microchip analysis'/ or exp 'microarray analysis'/ or ('microarray*').ti,ab.)
(exp metabolomics/ or exp proteomics/ or exp lipidomics/ or exp nutriomics/ or exp transcriptomics/ or exp immunomics/ or exp radiomics/ or (proteomic* or lipidomic* or nutriomic* or metabolomic* or transcriptomic* or immunomic* or radiomic*).ti,ab.)
(exp *'Diagnostic Imaging'/ or (imag*).ti,ab.)

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DISEASES
exp *atrial fibrillation/ or exp *heart atrium flutter/ or 'atrial fibrillation'.ti,ab.
exp *cardiomyopathy/ or exp *myocarditis/ or 'cardiomyopath*'.ti,ab. or 'myocarditis'.ti,ab.
exp *heart muscle ischemia/ or exp *heart infarction/ or 'ischemic heart disease'.ti,ab. or 'ischaemic heart disease'.ti,ab.
exp *aortic valve disease/ or exp *mitral valve disease/ or "nonrheumatic heart".ti,ab.
exp *peripheral occlusive artery disease/ OR 'Peripheral Arterial Disease'.ti,ab.
exp aortic aneurysm/ OR "aortic aneurysm".ti,ab.
exp *cerebrovascular accident/ or exp *ischemic stroke/ OR exp *brain hemorrhage/ OR exp *subarachnoid hemorrhage/ OR 'Stroke'.ti,ab.

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PREVENTION
(exp 'primary health care'/ or exp 'public health service'/ or ('primary health care' or 'primary care' or "public health service*").ti,ab)
(exp 'primary prevention'/ or ('primary disease prevent*' or 'preventable disease*').ti,ab.)
(exp 'preventive medicine'/ or ('medical prevent*' or 'preventive medicine*').ti,ab.)
('protective factor*'.ti,ab.)

(susceptibil*.ti,ab.)
(exp *smoking/)
(exp *exercise/ or exp *'sedentary lifestyle'/)
(exp *nutrition/ or exp *obesity/)
(exp *'drinking behavior'/ or exp *'alcohol consumption'/)
(exp *'non insulin dependent diabetes mellitus'/)
(exp *hypercholesterolemia/ OR exp dyslipidemia/ or "dyslipidemia*".ti,ab. OR "dyslipidaemia*".ti,ab. OR "high cholesterol".ti,ab.)
(exp *'blood pressure'/ or exp *'hypertension'/ or ('blood pressure' or 'high blood pressure' or 'hypertension').ti,ab.)
exp hyperglycemia/ OR exp glucose blood level/ or "high blood glucose".ti,ab.
exp *kidney failure/ or exp *chronic kidney failure/
exp heart infarction prevention/
(exp *'air pollution'/)
('health care plan*' or 'community setting*' or 'community health plan*').ti,ab.
(exp *'preventive health service'/ or ("preventive health service*").ti,ab.)
(exp community care/ or ('community health center*' or 'community health centre*' or 'community care').ti,ab.)
(exp *'health education'/ or exp *'health promotion'/ or ('health educat*' or 'health promot*').ti,ab.)
(exp 'mass screening'/ or exp 'secondary prevention'/ or ('screening*' or 'secondary prevent*').ti,ab.)
(exp 'population surveillance'/ or ('population surveillance*' or 'population screening*').ti,ab.)
(exp Early Diagnosis/ or ("early diagnos*").ti,ab.)

PERSONALISED
(exp 'personalized medicine'/ or ('precision medicine*' or 'predict*' or 'personalized medicine*' or 'individualized medicine*' or 'personalised medicine*' or 'individualised medicine*').ti,ab.)
(exp 'risk assessment'/ or ('risk stratif*' or 'risk scor*' or 'risk adjust*' or 'risk assess*').ti,ab.)
(exp 'Machine learning'/)

Supplementary file 2. Eligibility criteria.

Inclusion	**Exclusion**
Population ✓ Adult general population (> 18 years) (this results in the exclusion of congenital heart disease from this scoping review) ✓ Apart from the general population, we have included relevant specific subgroups of high-risk adults depending on the group of diseases to which they belong: Smoking, alcohol consumption, diabetes, obesity, family history, hypertension, hypercholesterolemia or dyslipidaemia, APOE genotype, hearing impairment. ✓ People who have already had the disease of interest, have it or in whom there is a proxy for the disease. ✓ Any country of origin	**Population** × Pregnancy × SARS-CoV2 infections related
Concept ✓ Studies with a focus on molecular, cellular, physiological, and imaging biomarkers used for individualised primary or secondary prevention of amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, frontotemporal dementia, vascular dementia, Lewy Body disease and multiple sclerosis. ✓ In primary prevention: Biomarkers should stratify individuals into groups ✓ In secondary prevention: Biomarkers should improve the screening or early detection: ◦ stratifying different risk groups ◦ improving the sensitivity, specificity, and time of diagnosis for new subgroups of individuals ✓ Studies with some risk stratification related to the early detection (not to the evolution of the disease)	**Concept** × Basic research in animals, human tissues and cell lines
Context ✓ Clinical or public health settings ✓ English language only ✓ Any geographical setting	**Context** × Studies published before 2020
Type of evidence	**Type of evidence**

✓ Reviews: Umbrella review, systematic review, meta-analysis, scoping review ✓ Experimental and quasi-experimental study designs: Randomised controlled trials, non-randomised controlled trials, before and after studies, interrupted time-series studies ✓ Analytical observational study designs: Prospective and retrospective cohort studies, case–control studies, and analytical cross-sectional studies ✓ Descriptive observational study designs: Descriptive cross-sectional studies **Sources** ✓ MEDLINE via Ovid ✓ Embase via Ovid ✓ Embase preprints via Ovid	× Editorials and opinion pieces × Narrative reviews × Protocols × Qualitative study designs. Delphi studies × Conference abstracts, conference reports × Clinical practice guidelines × Basic research (i.e. laboratory research in animals, human tissues, and cell lines) × Data simulation or modelling studies × Case reports and case series

Biomarkers defining the pre-specified high-risk subpopulations

Condition	Known biomarkers
Diabetes	plasma glucose, fasting plasma glucose, blood sugar levels, glycaemia, glycated haemoglobin, insulin resistance.
Obesity	BMI, weight, waist circumference, waist-hip ratio (WHR) .
Hypertension	(high) blood pressure.
Cholesterol/ dyslipidaemia	high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), Intermediate-density lipoproteins (IDL), cholesterol, atherosclerosis, triglycerides
Smoking	Cotinine.
Alcohol consumption	Blood alcohol level, blood/breath alcohol concentration/content (BAC), ethanol level.
Kidney disease	Serum Creatinine (SCr), Glomerular Filtration Rate (GFR), Cystatin C (CysC), Kidney Injury molecule 1(KIM-1), Neutrophil gelatinase-associated lipocalin (NGAL), Liver-type fatty acid–binding protein (L-FABP), Uromodulin.
Exercise	Metabolic equivalents (METs).
Air pollution	Oxidative stress (GDF-15 and myeloperoxidase), acute inflammation (C-reactive protein), hemostasis (ADAMTS, D-dimer)
CVD-specific	Troponin

It should also be noted that complex indices or scores derived from combinations of well-established biomarkers (e.g., Atherogenic Index of Plasma, Castelli Risk Index) and conditions (e.g., metabolic syndrome) were generally considered part of the established risk assessment landscape. They were only included in this review if they were being validated as a novel biomarker in a new predictive context that otherwise met the inclusion criteria

Supplementary file 3. Data extraction form options that were in Covidence.

The data extraction form in Covidence allowed for the capture of citation details, study design (randomised control trial, cohort, case control, review and other), disease group (IHD, cardiomyopathy and myocarditis, AF, aortic aneurysm, NRVHD, PAD, stroke, hypertensive CVD and MACE), biomarker information (name, type, subtype), technology used (AI, smart watch, pulse oximetry, infrared cameras and other, other), disease type (group, specific disease), prevention type (primary or secondary), and at risk population groups (smoking, alcohol, diabetes, obesity, chronic kidney disease/kidney failure, hypertension, family history, high cholesterol/dyslipidaemia and high risk CVD). A free text field was also included to allow reviewers to capture any relevant observations from the papers. For primary prevention papers, the data extraction sheet allowed

for capture of risk factors assessed alongside a biomarker such as lifestyle factors and included: smoking, exercise, diet, alcohol consumption, air pollution, obesity, family history and use of preventive drugs.

Information on the use of various technologies could also be captured. The use of wearable technology included personal sensors or computing devices incorporated into accessories to provide healthcare information about people wearing them. Artificial intelligence was also considered under technologies, and when considering healthcare we included image processing, computer vision, artificial neural network (ANN), machine learning, convolutional neural network (CNN) and deep learning.

The IHD category included coronary artery disease (CAD), myocardial infarction, heart attack, heart muscle ischemia, heart infarction, coronary heart disease, myocardial ischemia and acute coronary syndrome (ACS). The stroke category included ischemic stroke (including embolic stroke and transient ischemic stroke), intracerebral haemorrhage, and subarachnoid haemorrhage.

Data Extraction form CODE		
Methods	Study design	Umbrella reviews Systematic review (With meta analysis) Systematic review (Without meta analysis) RCT Cohort study Case-control study Other design N/P (Not Provided)
	Mendelian Randomization	Has Mendelian randomization been used in the study?
Biomarker(s)	Name	Name of the biomarker(s) in text format
	Molecular	Genetics/Genomics Epigenetics/Epigenomics Transcription/Transcriptomics Metabolites/Metabolomics Proteins/Proteomics Microbiomics/Microbiology Biochemistry Other molecular biomarker N/P
	Cellular	Histology (tissue abnormalities) Cytology (cell types) Other cellular biomarker N/P
	Imaging	X-Rays Ultrasound (echography, etc) CT Scan PET/SPECT Spectrometry MRI Scintigraphy (Gamma) Other image biomarker N/P
	Physiological	Blood Pressure Ankle-brachial Index Electrocardiogram Electromiography Other physiological biomarker N/P
	Anthropometric measures	Body mass index Body perimeters

		Other anthropometric biomarker N/P

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Data Extraction form CODE		
Clinical Utility	Does the paper mention the clinical utility of the biomarker? (explicitly)	
AI	Did they use AI technology or methods related to AI? (Deep learning, machine learning, clinical trial simulation, etc.)	
Radiomics	Does the paper mention radiomics?	
Technology	If they used a new technology/wearable to measure the biomarker, specify which one	Smart watch Pulse oximetry Infrared cameras Other
Diseases	CVD	Ischemic heart disease Cardiomyopathy and myocarditis Atrial fibrillation and atrial flutter Aortic aneurysm Nonrheumatic valvular heart disease Peripheral artery disease Stroke Stroke -ischemic stroke Stroke - intracerebral haemorrhage Stroke - subarachnoid haemorrhage Hypertensive heart disease MACE
Prevention	Type	Primary Secondary: Screening, early diagnosis, and early detection N/P
	If Primary: Lifestyle (Risk factors)	Smoking Exercise Diet Alcohol Air pollution Obesity Preventive drugs Other: Specify which one N/P
Population	Population type	General: without any other condition or healthy participants. (Included in all disease groups) Smoking Alcohol consumption Family history Diabetes Hypertension Dyslipidaemia Obesity Kidney failure / chronic kidney disease N/P
Observations		

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Supplementary file 4. Eligibility criteria. Definitions.

Prevention: reduction of the likelihood of developing a disease, sustaining an injury, or experiencing an unfavourable outcome. This study includes both collective (e.g., population screening) and individual (e.g., individual risk stratification) preventive measures.

Primary prevention is targeted at individuals that have not developed clinical manifestations of the diseases but are considered at risk of developing them, thus efforts are focused on preventing the onset of the disease.

Secondary prevention involves the time in which an intervention might be made to avoid disease progression. Screening programmes also play a role in secondary prevention. Screening is actively offered to defined population groups who do not have symptoms and have not sought medical help but are defined as being at risk of the disease.

Biomarkers were classified in the following categories:

1. **Molecular Biomarkers**: These biomarkers involve the analysis of specific molecules such as DNA, RNA, proteins, metabolites, or genetic variations. This category encompasses both studies using specific, more targeted molecules and those using high-throughput, hypothesis-free approaches such as arrays. They are subclassified into the following groups: genetic/ genomics; epigenetic/ epigenomics; transcriptomics; metabolites/ metabolomics; proteins/ proteomics; microbiological/ microbiomics; biochemistry, and others. Within genetic/genomics, we have also extracted specifically information on the use of mendelian randomization.
2. **Cellular Biomarkers**: In this category, we have included both cytological and histological biomarkers. These include the analysis of cells or cell components to provide information about cellular processes, dysfunction, or disease states, or examination of tissue samples through techniques such as staining or immunohistochemistry to identify specific cellular or tissue characteristics associated with a disease.
3. **Physiological Biomarkers**: Physiological biomarkers reflect functional changes in the body and can include measurements such as blood pressure or heart rate. This group also includes patterns of movement (i.e. derived from accelerometery).
4. **Imaging Biomarkers**: Imaging biomarkers utilize medical imaging techniques, such as X-rays, MRI (magnetic resonance imaging), PET (positron emission tomography), or CT (computed tomography), to visualize and measure structural, functional, or molecular changes in organs or tissues.
5. **Anthropometric Biomarkers**: Anthropometric biomarkers involve the measurement of physical characteristics of the body, such as body mass index (BMI), waist circumference, or body fat percentage. In almost all the cases, they are covariables in multivariate models that include other biomarkers and/or personal characteristics of the individuals.

Lifestyles and subpopulations explored: the strategy we have used to incorporate existing information and knowledge on prevention into the review is as follows:

In primary prevention, there are lifestyle-related factors that, similar to family history, clearly influence the likelihood of developing the disease. Biomarkers should add additional value to what it is already known. In addition, we have explored, both in primary and secondary prevention, whether scientific papers examined differences or provided specific risk estimators for subgroups defined by certain risk factors and/or clinical conditions or diseases associated with clear increases in the risk of our target diseases. These studies are likely to be particularly valuable as they could help refine or personalised prevention strategies.

Wearable technology, the use of personal sensors or computing devices incorporated into accessories to provide healthcare information about people bearing them.

Artificial intelligence, when referring to the medical field, includes mainly image processing, computer vision, artificial neural network (ANN), machine learning, convolutional neural network (CNN) and Deep learning (DL).

References

1. A. Timmis et al., 'European Society of Cardiology: Cardiovascular Disease Statistics 2017.', Eur. Heart J., vol. 39, no. 7, pp. 508–579, Feb. 2018, doi: 10.1093/eurheartj/ehx628.
2. C. Antoniades, A. S. Antonopoulos, and J. Deanfield, 'Imaging residual inflammatory cardiovascular risk', Eur. Heart J., vol. 41, no. 6, pp. 748–758, Feb. 2020, doi: 10.1093/eurheartj/ehz474.
3. P. O. of the E. Union, 'Council conclusions on personalised medicine for patients', Publ. Off. EU, Dec. 2015, Accessed: Feb. 20, 2025. Available: https://op.europa.eu/en/publication-detail/-/publication/f416ce37-a48c-11e5-b528-01aa75ed71a1/language-en
4. E. Plans-Beriso et al., 'Biomarkers for personalized prevention of chronic diseases', Mar. 2023, doi: 10.17605/OSF.IO/WG62B.
5. GBD 2019 Collaborators, 'Global mortality from dementia: Application of a new method and results from the Global Burden of Disease Study 2019', Alzheimers Dement. N. Y. N, vol. 7, no. 1, p. e12200, 2021, doi: 10.1002/trc2.12200.
6. Global Burden of Disease 2019 Cancer Collaboration, 'Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019', JAMA Oncol., vol. 8, no. 3, pp. 420–444, Mar. 2022, doi: 10.1001/jamaoncol.2021.6987.
7. G. A. Roth et al., 'Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study', J. Am. Coll. Cardiol., vol. 76, no. 25, pp. 2982–3021, Dec. 2020, doi: 10.1016/j.jacc.2020.11.010.
8. WHO, 'Non communicable diseases', 12 2024. Accessed: Feb. 20, 2025. Available: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases
9. E. U. OECD, 'Health at a Glance: Europe 2022: State of Health in the EU Cycle', OECD Publ., Dec. 2022, doi: doi.org/10.1787/507433b0-en.
10. Y. Luo, J. Liu, J. Zeng, and H. Pan, 'Global burden of cardiovascular diseases attributed to low physical activity: An analysis of 204 countries and territories between 1990 and 2019.', Am. J. Prev. Cardiol., vol. 17, p. 100633, Mar. 2024, doi: 10.1016/j.ajpc.2024.100633.
11. F. L. J. Visseren 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., vol. 42, no. 34, pp. 3227–3337, Sep. 2021, doi: 10.1093/eurheartj/ehab484.
12. S. Boccia et al., 'How to Integrate Personalized Medicine into Prevention? Recommendations from the Personalized Prevention of Chronic Diseases (PRECeDI) Consortium', Public Health Genomics, vol. 22, no. 5–6, pp. 208–214, 2019, doi: 10.1159/000504652.
13. L. H. Goetz and N. J. Schork, 'Personalized medicine: motivation, challenges, and progress', Fertil. Steril., vol. 109, no. 6, pp. 952–963, Jun. 2018, doi: 10.1016/j.fertnstert.2018.05.006.
14. E. Plans-Beriso et al., 'Biomarkers for personalised prevention of chronic diseases: a common protocol for three rapid scoping reviews', Syst. Rev., vol. 13, no. 1, p. 147, Jun. 2024, doi: 10.1186/s13643-024-02554-9.
15. A. C. Tricco et al., 'PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation', Ann. Intern. Med., vol. 169, no. 7, pp. 467–473, Oct. 2018, doi: 10.7326/M18-0850.
16. J. Clark, P. Glasziou, C. Del Mar, A. Bannach-Brown, P. Stehlik, and A. M. Scott, 'A full systematic review was completed in 2 weeks using automation tools: a case study', J. Clin. Epidemiol., vol. 121, pp. 81–90, May 2020, doi: 10.1016/j.jclinepi.2020.01.008.
17. N. R. Haddaway, M. J. Grainger, and C. T. Gray, 'Citationchaser: A tool for transparent and efficient forward and backward citation chasing in systematic searching', Res. Synth. Methods, vol. 13, no. 4, pp. 533–545, 2022, doi: 10.1002/jrsm.1563.
18. H. G. Nardini, 'The Yale MeSH Analyzer', Harvey Cushing John Hay Whitney Med. Libr., Feb. 2015, Accessed: Feb. 19, 2025. Available: https://library.medicine.yale.edu/news/yale-mesh-analyzer

19. 'Covidence - Better systematic review management', Covidence, 2024, Accessed: Feb. 19, 2025. Available: https://www.covidence.org/
20. FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource. Silver Spring (MD): Food and Drug Administration (US), 2016. Accessed: Jun. 01, 2023. Available: http://www.ncbi.nlm.nih.gov/books/NBK326791/
21. M. Porta, 'A Dictionary of Epidemiology', in A Dictionary of Epidemiology, Oxford University Press, 2016. Accessed: Feb. 19, 2025. Available: https://www.oxfordreference.com/display/10.1093/acref/9780199976720.001.0001/acref-9780199976720
22. S. Jaskulski, C. Nuszbaum, and K. B. Michels, 'Components, prospects and challenges of personalized prevention', Front. Public Health, vol. 11, Feb. 2023, doi: 10.3389/fpubh.2023.1075076.
23. K. Bíró, V. Dombrádi, A. Jani, K. Boruzs, and M. Gray, 'Creating a common language: defining individualized, personalized and precision prevention in public health', J. Public Health, vol. 40, no. 4, pp. e552–e559, Dec. 2018, doi: 10.1093/pubmed/fdy066.
24. R: A language and environment for statistical computing. (2020). R Foundation for statistical computing, Vienna, Austria. Available: https://www.r-project.org/https://www.r-studio.com/
25. G. Lin, 'reactable: Interactive Data Tables for R.', R Package Version 0449001, Accessed: Feb. 19, 2025. Available: https://glin.github.io/reactable/
26. G. Van Rossum and F. L. Drake, Python 3 Reference Manual. Scotts Valley, CA: CreateSpace, 2009.
27. Digital Solution Foundry and EPPI Centre, 'EPPI-Mapper, Version 2.2.4', EPPI Cent. UCL Soc. Res. Inst. Univ. Coll. Lond., Accessed: Feb. 19, 2025. Available: https://eppi.ioe.ac.uk/cms/default.aspx?tabid=3790
28. P. Brennan and G. Davey-Smith, 'Identifying Novel Causes of Cancers to Enhance Cancer Prevention: New Strategies Are Needed', JNCI J. Natl. Cancer Inst., vol. 114, no. 3, pp. 353–360, Nov. 2021, doi: 10.1093/jnci/djab204.
29. S. Guo, S. Yin, G. Tse, G. Li, L. Su, and T. Liu, 'Association Between Caliber of Retinal Vessels and Cardiovascular Disease: a Systematic Review and Meta-Analysis', Curr. Atheroscler. Rep., vol. 22, no. 4, p. 16, May 2020, doi: 10.1007/s11883-020-0834-2.
30. A. R. Rudnicka et al., 'Artificial intelligence-enabled retinal vasculometry for prediction of circulatory mortality, myocardial infarction and stroke', Br. J. Ophthalmol., vol. 106, no. 12, pp. 1722–1729, Dec. 2022, doi: 10.1136/bjo-2022-321842.
31. M. Kocamaz, O. Karadağ, and S. E. Onder, 'Comparison of choroidal thicknesses in patients with coronary artery disease and patients at risk of coronary artery disease', Int. Ophthalmol., vol. 41, no. 6, pp. 2117–2124, Jun. 2021, doi: 10.1007/s10792-021-01769-2.
32. L. Zhao, H. Wang, X. Yang, B. Jiang, H. Li, and Y. Wang, 'Multimodal Retinal Imaging for Detection of Ischemic Stroke', Front. Aging Neurosci., vol. 13, Feb. 2021, doi: 10.3389/fnagi.2021.615813.
33. L. Zhao et al., 'Risk Stratification Tool for Ischemic Stroke: A Risk Assessment Model Based on Traditional Risk Factors Combined With White Matter Lesions and Retinal Vascular Caliber', Front. Neurol., vol. 12, p. 696986, 2021, doi: 10.3389/fneur.2021.696986.
34. J. L. Romero-Trevejo et al., 'Choroidal thickness and granulocyte colony-stimulating factor in tears improve the prediction model for coronary artery disease', Cardiovasc. Diabetol., vol. 21, no. 1, p. 103, Jun. 2022, doi: 10.1186/s12933-022-01538-0.
35. Y. Huang et al., 'Integrating oculomics with genomics reveals imaging biomarkers for preventive and personalized prediction of arterial aneurysms', EPMA J., vol. 14, no. 1, pp. 73–86, Mar. 2023, doi: 10.1007/s13167-023-00315-7.
36. W. Osman et al., 'Genetics of type 2 diabetes and coronary artery disease and their associations with twelve cardiometabolic traits in the United Arab Emirates population', Gene, vol. 750, p. 144722, Aug. 2020, doi: 10.1016/j.gene.2020.144722.
37. J. Burrello et al., 'An extracellular vesicle epitope profile is associated with acute myocardial infarction', J. Cell. Mol. Med., vol. 24, no. 17, pp. 9945–9957, Sep. 2020, doi: 10.1111/jcmm.15594.
38. I. Marei et al., 'Angiogenic content of microparticles in patients with diabetes and coronary artery disease predicts networks of endothelial dysfunction', Cardiovasc. Diabetol., vol. 21, no. 1, p. 17, Feb. 2022, doi: 10.1186/s12933-022-01449-0.
39. C. Eyileten et al., 'Diagnostic Performance of Circulating miRNAs and Extracellular Vesicles in Acute Ischemic Stroke', Int. J. Mol. Sci., vol. 23, no. 9, p. 4530, Apr. 2022, doi: 10.3390/ijms23094530.
40. M. Lown et al., 'Machine learning detection of Atrial Fibrillation using wearable technology.', PloS One, vol. 15, no. 1, p. e0227401, 2020, doi: 10.1371/journal.pone.0227401.
41. N. Forghani, K. Maghooli, N. Jafarnia Dabanloo, A. Vasheghani Farahani, and M. Forouzanfar, 'Intelligent Oscillometric System for Automatic Detection of Peripheral Arterial Disease', IEEE J. Biomed. Health Inform., vol. 25, no. 8, pp. 3209–3218, Aug. 2021, doi: 10.1109/JBHI.2021.3065379.
42. H. A. Lumley et al., 'A scoping review of pre-hospital technology to assist ambulance personnel with patient diagnosis or stratification during the emergency assessment of suspected stroke', BMC Emerg. Med., vol. 20, no. 1, p. 30, Apr. 2020, doi: 10.1186/s12873-020-00323-0.

43. S. Z. Diederichsen et al., 'Incidence and predictors of atrial fibrillation episodes as detected by implantable loop recorder in patients at risk: From the LOOP study', Am. Heart J., vol. 219, pp. 117–127, Jan. 2020, doi: 10.1016/j.ahj.2019.09.009.
44. Y. Miyazaki et al., 'Atrial Fibrillation After Ischemic Stroke Detected by Chest Strap-Style 7-Day Holter Monitoring and the Risk Predictors: EDUCATE-ESUS', J. Atheroscler. Thromb., vol. 28, no. 5, pp. 544–554, May 2021, doi: 10.5551/jat.58420.
45. J. Y. Lin et al., 'Serial 7-Day Electrocardiogram Patch Screening for AF in High-Risk Older Women by the CHARGE-AF Score', JACC Clin. Electrophysiol., vol. 8, no. 12, pp. 1523–1534, Dec. 2022, doi: 10.1016/j.jacep.2022.08.024.
46. S. Khurshid et al., 'Accelerometer-derived physical activity and risk of atrial fibrillation', Eur. Heart J., vol. 42, no. 25, pp. 2472–2483, Jul. 2021, doi: 10.1093/eurheartj/ehab250.
47. R. Balasubramanian et al., 'Metabolomic Profiles Associated With Incident Ischemic Stroke', Neurology, vol. 98, no. 5, pp. e483–e492, Feb. 2022, doi: 10.1212/WNL.0000000000013129.
48. F. Guo, X. Qiu, Y. Zhu, Z. Tan, Z. Li, and D. Ouyang, 'Association between plasma betaine levels and dysglycemia in patients with coronary artery disease', Biosci. Rep., vol. 40, no. 8, p. BSR20200676, Aug. 2020, doi: 10.1042/BSR20200676.
49. H. Li, Y. Liu, J. Huang, Y. Liu, and Y. Zhu, 'Association of genetic variants in lncRNA GAS5/miR-21/mTOR axis with risk and prognosis of coronary artery disease among a Chinese population', J. Clin. Lab. Anal., vol. 34, no. 10, p. e23430, Jun. 2020, doi: 10.1002/jcla.23430.
50. J. Li et al., 'The Mediterranean diet, plasma metabolome, and cardiovascular disease risk', Eur. Heart J., vol. 41, no. 28, pp. 2645–2656, Jul. 2020, doi: 10.1093/eurheartj/ehaa209.
51. S. Noerman et al., 'Associations of the serum metabolite profile with a healthy Nordic diet and risk of coronary artery disease', Clin. Nutr. Edinb. Scotl., vol. 40, no. 5, pp. 3250–3262, May 2021, doi: 10.1016/j.clnu.2020.10.051.
52. C. Razquin et al., 'Circulating Amino Acids and Risk of Peripheral Artery Disease in the PREDIMED Trial', Int. J. Mol. Sci., vol. 24, no. 1, p. 270, Dec. 2022, doi: 10.3390/ijms24010270.
53. W. Yin et al., 'Plasma Ceramides and Cardiovascular Events in Hypertensive Patients at High Cardiovascular Risk', Am. J. Hypertens., vol. 34, no. 11, pp. 1209–1216, Nov. 2021, doi: 10.1093/ajh/hpab105.
54. J. K. Nicholls, J. Ince, J. S. Minhas, and E. M. L. Chung, 'Emerging Detection Techniques for Large Vessel Occlusion Stroke: A Scoping Review', Front. Neurol., vol. 12, p. 780324, 2021, doi: 10.3389/fneur.2021.780324.
55. C.-H. Lu et al., 'Predictors of abnormality in thallium myocardial perfusion scans for type 2 diabetes', Heart Vessels, vol. 36, no. 2, pp. 180–188, Feb. 2021, doi: 10.1007/s00380-020-01681-2.
56. [56] M. Nassar, N. Nso, K. Emmanuel, M. Alshamam, M. S. Munira, and A. Misra, 'Coronary Artery Calcium Score directed risk stratification of patients with Type-2 diabetes mellitus', Diabetes Metab. Syndr. Clin. Res. Rev., vol. 16, no. 6, p. 102503, Jun. 2022, doi: 10.1016/j.dsx.2022.102503.
57. M.-H. Lei, Y.-L. Wu, S.-L. Chung, C.-C. Chen, W.-C. Chen, and Y.-C. Hsu, 'Coronary Artery Calcium Score Predicts Long-Term Cardiovascular Outcomes in Asymptomatic Patients with Type 2 Diabetes', J. Atheroscler. Thromb., vol. 28, no. 10, pp. 1052–1062, Oct. 2021, doi: 10.5551/jat.59386.
58. X.-R. Wang, L.- Yuan, R.- Shi, H.- Li, D.-G. Wang, and Y.-G. Wu, 'Predictors of coronary artery calcification and its association with cardiovascular events in patients with chronic kidney disease', Ren. Fail., vol. 43, no. 1, pp. 1172–1179, Dec. 2021, doi: 10.1080/0886022X.2021.1953529.
59. J. Pan, G. Wu, J. Yu, D. Geng, J. Zhang, and Y. Wang, 'Detecting the Early Infarct Core on Non-Contrast CT Images with a Deep Learning Residual Network', J. Stroke Cerebrovasc. Dis., vol. 30, no. 6, p. 105752, Jun. 2021, doi: 10.1016/j.jstrokecerebrovasdis.2021.105752.
60. R. Cao et al., 'BNP on Admission Combined with Imaging Markers of Multimodal CT to Predict the Risk of Cardioembolic Stroke', Dis. Markers, vol. 2022, p. 3327967, Jul. 2022, doi: 10.1155/2022/3327967.
61. T. Sorimachi et al., 'Benefits and Risks of CT Angiography Immediately after Emergency Arrival for Patients with Intracerebral Hematoma', Neurol. Med. Chir. (Tokyo), vol. 60, no. 1, pp. 45–52, Jan. 2020, doi: 10.2176/nmc.oa.2019-0152.
62. J. C. L. Himmelreich et al., 'Validating risk models versus age alone for atrial fibrillation in a young Dutch population cohort: should atrial fibrillation risk prediction be expanded to younger community members?', Feb. 2022, doi: 10.1136/bmjopen-2021-057476.
63. S. Khurshid et al., 'Predictive Accuracy of a Clinical and Genetic Risk Model for Atrial Fibrillation', Circ. Genomic Precis. Med., vol. 14, no. 5, p. e003355, Oct. 2021, doi: 10.1161/CIRCGEN.121.003355.
64. J. Lyu et al., 'A potent risk model for predicting new-onset acute coronary syndrome in patients with type 2 diabetes mellitus in Northwest China', Acta Diabetol., vol. 57, no. 6, pp. 705–713, Jun. 2020, doi: 10.1007/s00592-020-01484-x.

65. V. Viswanathan et al., 'Integration of estimated glomerular filtration rate biomarker in image-based cardiovascular disease/stroke risk calculator: a south Asian-Indian diabetes cohort with moderate chronic kidney disease', Int. Angiol. J. Int. Union Angiol., vol. 39, no. 4, pp. 290–306, Aug. 2020, doi: 10.23736/S0392-9590.20.04338-2.
66. J. Elliott, B. Bodinier, M. Whitaker, I. Tzoulaki, P. Elliott, and M. Chadeau-Hyam, 'Improving cardiovascular risk prediction beyond pooled cohort equations: a prospective cohort of 304,356 participant', 2023. doi: 10.1101/2023.01.09.23284368.
67. T. A. Buchan et al., 'Predictive models for cardiovascular and kidney outcomes in patients with type 2 diabetes: systematic review and meta-analyses', Heart Br. Card. Soc., vol. 107, no. 24, pp. 1962–1973, Dec. 2021, doi: 10.1136/heartjnl-2021-319243.
68. S. M. Devaraj, A. M. Kriska, T. J. Orchard, R. G. Miller, and T. Costacou, 'Cardiovascular health in early adulthood predicts the development of coronary heart disease in individuals with type 1 diabetes: 25 year follow-up from the Pittsburgh Epidemiology of Diabetes Complications study', Diabetologia, vol. 64, no. 3, pp. 571–580, Mar. 2021, doi: 10.1007/s00125-020-05328-9.
69. J. Liu, E. L. Chou, K. K. Lau, P. Y. M. Woo, J. Li, and K. H. K. Chan, 'Machine learning algorithms identify demographics, dietary features, and blood biomarkers associated with stroke records', J. Neurol. Sci., vol. 440, p. 120335, Sep. 2022, doi: 10.1016/j.jns.2022.120335.
70. B. Liu et al., 'A model combining rest-only ECG-gated SPECT myocardial perfusion imaging and cardiovascular risk factors can effectively predict obstructive coronary artery disease', BMC Cardiovasc. Disord., vol. 22, no. 1, p. 268, Jun. 2022, doi: 10.1186/s12872-022-02712-8.
71. H. Khalil et al., 'Scoping reviews and their role in identifying research priorities', J. Clin. Epidemiol., vol. 181, p. 111712, May 2025, doi: 10.1016/j.jclinepi.2025.111712.
72. C. Sudlow 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., vol. 12, no. 3, p. e1001779, Mar. 2015, doi: 10.1371/journal.pmed.1001779.
73. R. Edgar, M. Domrachev, and A. E. Lash, 'Gene Expression Omnibus: NCBI gene expression and hybridization array data repository.', Nucleic Acids Res., vol. 30, no. 1, pp. 207–210, Jan. 2002, doi: 10.1093/nar/30.1.207.
74. R. Malik et al., 'Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes.', Nat. Genet., vol. 50, no. 4, pp. 524–537, Apr. 2018, doi: 10.1038/s41588-018-0058-3.
75. 'Chief Medical Officer's annual report 2022: air pollution'. Accessed: Feb. 19, 2025. Available: https://www.gov.uk/government/publications/chief-medical-officers-annual-report-2022-air-pollution
76. 'Air pollution', Dec. 2024. Accessed: Feb. 19, 2025. Available: https://www.eea.europa.eu/en/topics/in-depth/air-pollution

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