British Heart Foundation

Women's Health Strategy: BHF Response to Call for Evidence

June 2021

1 Introduction

The British Heart Foundation (BHF) is the largest independent funder of medical research into heart and circulatory diseases in the UK and the third largest charitable funder of medical research in the UK, as well as a source of trusted information and support for the 7.6 million people living with heart and circulatory diseases. Our funding portfolio extends from laboratory science to clinical trials and population studies. We fund people from PhDs to professors as well as investing in large programme and project grants.

Cardiovascular disease is the world's biggest killer for both women and men and causes 35% of deaths in women worldwide and 26% of deaths in women in the UK. Women comprise around 3.6 million out of 7.6 million people in the UK living with cardiovascular disease - an ageing and growing population- and improved survival rates from heart and circulatory events could see these numbers rise still further. Ischaemic heart disease was the primary cause of cardiovascular mortality in women worldwide in 2019, followed by stroke[i]. Despite coronary heart disease killing twice as many women as breast cancer in the UK, awareness of the scale of the challenge remains low.

But women compared to men are under-aware, under-diagnosed, and under-treated for heart disease and under-represented in heart and stroke research. At every turn, there are differences in women's risk and a unique profile in how and when they develop cardiovascular disease.

Additionally, cardiovascular disease is a disease of inequity, with our most vulnerable populations experiencing the greatest burden of disease. This has only been made worse by the Covid-19 pandemic. Additional factors such as socioeconomic status, race/ethnicity, geography compound that risk, contributing to the widening life expectancy gap we are seeing across the UK.

In 2020, a report commissioned by the Health Foundation found that, for the first time, life expectancy fell for women living in the most deprived communities outside of London[ii]. We know that those living in the most deprived areas of England are more likely to die prematurely from heart and circulatory diseases compared to those living in the least deprived areas[iii], and that addressing inequalities in cardiovascular risk factors is of the utmost importance in closing this mortality gap. While the widening life expectancy gap is driven by complex factors and a diverse group of diseases, CVD remains one of the biggest drivers of this gap and has the greatest opportunity for effective policy interventions to address the inequalities at hand.

The BHF has long funded research that looks at the scope and scale of the inequalities in cardiovascular health, which has led to increased understanding of the impact of the wider social determinants of health and what can be done to address modifiable risk factors that will lead to a more resilient and healthy population.

In the following submission, we present a very brief overview as to the continued challenges in ensuring women's cardiovascular health is supported in the UK from prevention to diagnosis, treatment, and support and suggest a set of recommendations for how to address existing gaps in the evidence. Due to space and time constraints, this submission is by no means exhaustive but rather is meant to highlight the diversity of areas that warrant clear attention in the development of the upcoming Women's Health Strategy, along with recommendations applicable to the UK context. For a recent and more exhaustive analysis on cardiovascular disease in women, we recommend *The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030*, published in May 2021 by Vogel et al.

2 Women's Health Across the Life Course

In the UK, women's health still tends to be defined through reproductive health with a focus on specific, defined periods in a woman's life. The BHF welcomes the Government's focus on taking a holistic approach to forming a coherent Women's Health Strategy that supports women from birth to end of life but also looks beyond reproductive health and sex-specific conditions to better understand the opportunities for preventative action.

As we set out in the following submission, there are notable sex-differences across all major cardiovascular risk factors - hypertension (high blood pressure), high cholesterol (hyperlipidemia), diabetes, living with excess weight

or obesity, physical inactivity, and tobacco use[iv] - as well as in conditions specific to women that can increase their risk of CVD, such as gestational hypertension, gestational diabetes, preterm delivery, premature menopause, and polystic ovary syndrome.

A multitude of studies try to elucidate whether the established sex-specific differences can be explained in part by endogenous and/or exogenous reproductive hormonal differences, with a particular focus on the role of oestrogen. Evidence suggests that, in women who are postmenopausal, the lower concentrations of oestrogen and higher concentrations of androgen might be responsible for the increased CVD seen in that age group. Changing hormone profiles may be one of the many factors that contribute to different cardiovascular disease profiles for women as compared to men but more research is needed to fully understand the impact.

2.1 Prevention of CVD in women

In the UK, there are around 27,000 premature deaths from cardiovascular diseases that are considered to be preventable each year.[v] Additionally, It's estimated that in the UK, nearly 7 million women have high blood pressure. Of these, as many as 2.5 million may be undiagnosed. It's estimated that nearly 2 million women in the UK are living with diabetes, and nearly half of all women in the UK have cholesterol levels above national guidelines[vi].

Current cardiovascular risk prediction tools are limited in their effectiveness for women – sex-specific factors are under-recognised and insufficiently recorded (such as recurrent pregnancy loss. preterm delivery, small for gestational age fetus, hypertensive disorders of pregnancy including pre-eclampsia, gestational diabetes, premature menopause,) and these are poorly incorporated in risk calculators. Cardiovascular disease is the dominant cause of maternal mortality in the UK and women with known heart disease need specific support through pregnancy from cardiologists not only obstetrics and midwifery. There is a dearth of evidence about the role of these sex-specific factors in CVD prediction[vii] that necessitates immediate further research.

Additionally, while there has been an improvement in awareness of CVD risk among healthcare providers and women themselves, it still remains low. In a survey from 2014, only 3% of primary care physicians rated CVD in women as a top concern, after weight and breast health. Only 22% of GPs and 42% of cardiologists felt prepared to appropriately assess CVD risk in women and that number fell further (16% GPs and 22% cardiologists) when asked about whether they comprehensively implemented CVD prevention guidelines when treating women[viii].

In the following sections, we look at how common risk factors for CVD differ in women. While we do not delve into smoking because the evidence around the sex-specific impact of smoking on CVD risk is mixed - one large meta-analysis found that women had a 25% increased risk of CVD associated with smoking as compared to men[ix] while the INTERHEART study found that the risk of myocardial infarction associated with smoking was similar in both men and women [x] - the BHF believes that smoking remains a leading cause of health inequalities and must remain a Government priority as the UK works towards a Smokefree 2030.

2.1.1 Hypertension

Hypertension is the leading risk factor for CVD morbidity and mortality. The INTERHEART study suggests that women have a higher risk of acute myocardial infarction associated with hypertension than men. Ji et al. suggested in 2020 that there are sex-related differences in the presentation and course of hypertension, with a more rapid increase in progressive blood pressure elevation in women beginning as early as 30-40 years of age[xi]. Additionally, women appear to have more drug-related side effects from antihypertensive therapy than men[xii]. Despite these observations, the underlying mechanisms for these differences remain unclear. It is still not clear whether different blood pressure targets should be used in women as compared to men since women have smaller arterial diameters and arterial stiffness, even when compared to height- and weight-matched men.

For people living with hypertension, early detection is critical in enabling them to understand and manage their condition and access treatment at a point that would reduce the risk of an individual experiencing an acute event. In England, only 34% of people with high blood pressure are currently detected and effectively treated, meaning that there are real gains to be made.[xiii]

2.1.2 Hyperlipidaemia (high cholesterol)

The US 'Study of Women's Health Across the Nation'[xiv] looked at women going through transition to menopause and documented a sharp increase in total cholesterol and LDL cholesterol concentrations (sometimes called the 'bad cholesterol' because high levels of LDL are associated with increased risk of heart disease and stroke) within

a year of the final menstrual period, which was associated with a higher risk of carotid plaque on later follow-up. Another study found that women and men had similar cardiovascular risk associated with hyperlipidaemia but the INTERHEART study found that certain ratios of cholesterol were more powerfully associated with myocardial infarction in women than men. The evidence on high cholesterol and the risk of CVD in women remains mixed and under-developed.

Statins are known to reduce the risk of cardiovascular events and mortality in both men and women with established arterial disease. However, the use of statins in women appears to be significantly lower than in men[xv] – the underlying reasons for those disparities are unclear but physician adherence to guideline recommendations for statin use in women appears to be poor[xvi].

2.1.3 Diabetes

The prevalence of diabetes is on the rise globally– in England, we know that diabetes prevalence increased from 9% to 11% between 2012/13 to 2019/20[xvii]– driven by sedentary lifestyles and the increased prevalence of excess weight across populations. Data published in 2014 from 858,507 people in 64 prospective population-based cohort studies highlighted that the risk of coronary heart disease was 44% greater in women with diabetes than in men with diabetes[xviii]. The UK Biobank found similar risk profiles, with women having a 29% higher risk of myocardial infarction associated with diabetes than men[xix].

The reason for these differences in adverse outcomes in women compared to men is unclear and researchers are looking to understand whether the risk is associated with diabetes itself or is attributable to sex-related differences in baseline factors – studies have highlighted that diagnosis of diabetes occurs later in life and at a higher BMI and more advanced stage of disease progression in women compared to men. It suggests a clear need for vigorous screening and more research to allow for earlier detection of diabetes in women. Women who have been diagnosed with high fasting glucose during pregnancy should be followed up closely throughout their life because of the associated increased risk of type-2 diabetes and CVD later in life[xx].

These risks are equally seen in women diagnosed with type-1 diabetes- those with onset before 10 years of age had almost a 60 times increased risk of coronary heart disease, compared to 17 times in men – and a nearly 90 times increased risk of acute myocardial infarction, as compared to a 15 times increased risk of acute myocardial infarction in men. Reasons for this stark difference between women and men remain unclear but studies suggest that high blood glucose level influences the concentration and activity of oestrogen receptors and prevents any protective effects on the vascular wall.

2.1.4 Obesity and diet

There are strong but complex connections between obesity, type 2 diabetes and heart and circulatory diseases. In 2019, 17% of heart and circulatory disease deaths in the UK were attributable to high BMI, with an estimated 64% of adults in the UK having a BMI classed as overweight or obese. [xxi, xxii] Significant inequalities exist in the prevalence of obesity, the Health Survey for England established a connection between adult obesity and neighbourhood deprivation: in the least deprived areas, 22% of adults are living with obesity, compared to 35% of adults living in the most deprived areas.[xxiii]

As seen with hypertension, data suggest that there is a greater increase in systolic blood pressure in women than men for similar increases in male or female body mass index[xxiv]. The Framingham Heart Study additionally shows that, in women, excess risk attributed to obesity was 64% while in men, it was 46%[xxv]. In England, 2019 data shows that overall, the majority of adults are overweight or obese - 67% of men and 60% of women – but that obesity is slightly higher in women than men (29% as compared to 26%)[xxvi].

While diet can substantially contribute to cardiovascular risk, it can also mitigate it. It is estimated that a balanced diet could prevent one in five premature deaths and curb the obesity epidemic that affects women more than men[xxvii]. While the PURE study shows minimal differences in how men versus women without CVD adhere to a healthy diet, when a CVD diagnosis is established, women were more likely to follow a healthy diet than men[xxviii]. The UK Government's Obesity Strategy, first published in July 2020, has the potential to turn the tide on the high prevalence of obesity - while there are no interventions specifically targeted at women, any population wide intervention will address the growing burden of disease and help protect women's cardiovascular health.

2.2 Differences within specific life stages

There are key life stages that emphasise sex-specific risk factors - pregnancy and menopause drive major changes in a woman's cardiovascular health. However, risks are often not appropriately assessed or a woman is not informed that certain diagnoses during pregnancy are linked to an increased risk of cardiovascular disease later in life. We look at these two phases in a woman's life in more detail below before summarising risks and differences in other cardiovascular diseases in figure 1 – MINOCA, INOCA, STEMI, and stroke, to name a few – also seen predominantly. in women. As stated before, it is beyond the scope of this response to provide an exhaustive review of the many cardiovascular diseases that affect women but we hope to be able to highlight the BHF's strong support for a life course approach to women's health, especially as it pertains to cardiovascular disease.

2.2.1 Pregnancy

Pregnancy places a large amount of cardiovascular demand on a woman's body[xxix] – Many pregnancy-related disorders are associated with increased cardiovascular risk – pre-eclampsia, gestational diabetes and preterm delivery are all risk factors for a woman developing CVD later in life.[xxx] [xxxi] While the risk is well-established, physicians still often fail to recognise the importance of these pregnancy related-disorders and many do not consider these conditions when evaluating a women's CVD risk profile later in life.

Additionally, there are specific CVD conditions that threaten a woman's life during pregnancy, such as peripartum cardiomyopathy. The causes for peripartum cardiomyopathy remain poorly understood but it is characterised by pregnancy-related left ventricular dysfunction that occurs either at the end of pregnancy or in the months following delivery[xxxii]. Because the initial stages of heart failure can look like normal stages of pregnancy, clinicians may fail to recognise it until the disease is more advanced – late diagnosis increases the risk of complications, including the risk of cardiogenic shock, thromboembolism and arrhythmias.[xxxiii]

Studies suggest that the function of the left side of the heart does improve within 6 months to 5 years with appropriate support, although many women still experience major cardiovascular events or persistent, severe cardiomyopathy.

Spontaneous coronary artery dissection (SCAD) - while normally a rare cause of myocardial infarction (representing only 1-4% of all acute coronary syndrome[xxxiv]) – is a common cause (up to 43%) of myocardial infarction associated with pregnancy. Very little is known or understood about SCAD but it is most often seen in women who do not have any other traditionally recognised CVD risk factors. Women diagnosed with SCAD are at hight risk of recurrent ischemic events and must be monitored closely[xxxv].

Both of these conditions are not only poorly understood but are poorly recognised – there is very limited research in either condition, making clinical interventions empirical in nature rather than evidence-based at a time of incredible vulnerability in a woman's life.

2.2.2 Later years

As mentioned in the introduction to this section, sex-specific differences in how cardiovascular disease develops in women is thought to be partly related to reproductive hormone differences, although there are continued questions about the role of oestrogen in protecting cardiovascular health. Cardiovascular disease typically happens later in life for women than men – the INTERHEART study documents that the first acute myocardial infarction occurs 9 year earlier in men than women[xxxvi]. Men's risk of cardiovascular disease is higher in age-matched women until menopause, after which women's risk increases substantially as compared to men.

Oestrogen affects various mechanisms in endothelial cells, the cells that line the inside of blood vessels, as well as the blood vessels' smooth muscles cells and the cells within the heart itself (cardiac myocytes and fibroblasts) – it is thought that the lower concentrations of oestrogen found in menopause (along with increased concentrations of androgen) might mediate the increased cardiovascular risk found in women who are postmenopausal[xxxvii].

Studies have looked at the use of hormone replacement therapy (HRT) to decrease a woman's risk of developing cardiovascular disease – the use of HRT has been vigorously debated, however, due to the mixed nature of the evidence. Early observational studies showed benefits to HRT. A randomised clinical trial in older women (over 60 years of age) showed no benefit and potential harm[xxxviii]. But a follow up analysis showed this was mainly in women aged 70-79, which is not the usual group in which HRT is sought and prescribed. The increased risk of breast cancer in otherwise healthy women that can be attributed to combined HRT is now understood to be small – the risk translates to an additional 4 in 1000 cases which is higher in those with risk factors such as smoking, obesity or a

family history of breast cancer[xxxix]. More recent studies suggest that there may also be a role for oestrogen only HRT, rather than oestrogen in combination with progestogen in primary prevention of CVD in women[xl]. HRT may have benefits with regards reduction of cardiovascular disease, diabetes, dementia and osteoporosis for women.

The ongoing debate highlights the complexity of women's health and the strong need for robust data-gathering and development of sex-specific guidelines for women at all stages of life and the need for appropriate information to be available to women and healthcare professionals to make informed choices.

2.3 Sex-specific differences in cardiovascular disease

**We have attempted below to highlight some of the main CVD categories that affect women differently than men – the BHF has funded many studies that supports our further understanding of these differences. Where possible, we have included links to BHF-content that provides women with additional information on CVD they might be experiencing. The BHF strongly believes that empowering women with accurate, relevant information is one key pillar to address under-awareness of cardiovascular conditions amongst women and ensuring that women can advocate for their own health.*

Disease Category	Key points	Suggested actions
Ischaemia via non-obstructive coronary arteries (INOCA)	- appears to be more common in women than men, with a high prevalence in women between 45-65 years of age - Associated with increased risk for major CV events as compared to reference populations	- Further research is needed to investigate the underlying mechanism, diagnosis, and approach to treatment
Myocardial Infarction in the absence of obstructive coronary artery disease (MINOCA)	- More common in women than men (10.0% vs 3.4%, respectively) but outcomes are similar for both sexes	- Further research is needed to better understand the mechanism of disease as well as the therapeutic options; additionally, a diagnostic code is needed to allow appropriate classification of disease.
Spontaneous coronary artery disease (SCAD)	- Rare cause of myocardial infarction in men and women but increasingly recognised in women younger than 50 years of age - True prevalence uncertain because often undiagnosed – studies suggest it as the cause of myocardial infarction in 25-35% of women <50 years of age and up to approximately 25% of women <60yrs of age - Most common cause of myocardial infarction associated with pregnancy	- Further research and education is urgently needed on the diagnosis and treatment of SCAD
ST-segment elevation myocardial infarction (STEMI)	- Difference related to sex and gender are especially pronounced (further detail in submission) with women presenting later than men after STEMI, experiencing a longer time from presentation to therapy, and receiving fewer guideline-recommended therapies than men	- Further research is needed to investigate biological differences leading to the sex-related mortality gap - Improved awareness is needed in healthcare professionals and in women

Takotsubo Syndrome	- Syndrome of acute and reversible left ventricular systolic dysfunction - Present in up to 7.5% of female patients presenting with acute coronary syndrome - Occurs mainly in women and may be triggered by emotional or physical stress – more than 90% of reported cases are postmenopausal women between 58-75 years of age.	Further research is needed to improve diagnosis and treatment of women with Takotsubo Syndrome
Peripartum cardiomyopathy	- Precise mechanism remains undefined - Most commonly diagnosed at the end of pregnancy or in the immediate months after delivery, without any other identifiable causes	More research at a global scale is needed to better understand prognosis, diagnosis and treatment options possible
Stroke	- Overall, while women have a lower stroke incidence than men, they have a higher lifetime risk - Stroke incidence is affected by age - While the incidence of atrial fibrillation is higher in men than women, women with atrial fibrillation have a higher risk of stroke than men. - Globally, women are less likely to be prescribed oral anticoagulants than men; A European study found that women were less likely to received diagnostics than men, even after adjusting for age and other factors.	- Preventive measures, along with early diagnosis and treatment of hypertension and elevated cholesterol, should be implemented to reduce risk of stroke in women - Rehabilitation programmes that are more tailored to the needs of women should be developed
Systemic inflammatory and autoimmune disorders (e.g rheumatoid arthritis, scleroderma)	- Women are disproportionally affected by systemic autoimmune disease as compared to men, representing 78% of all cases - Chronic inflammation associated with autoimmune disease leads to faster development of atherosclerosis (plaque build up in the arteries), increasing the risk of heart attack and stroke	- Aggressive screening and management of cardiovascular risk factors should be carried out in women with systemic inflammatory and autoimmune diseases

2.4 Bias and Biology - how differences in care lead to worse health outcomes for women

Women experience differences in care in a multitude of conditions, including most cardiovascular conditions. The BHF's Bias and Biology briefing, published in 2019, set out how the gender gap in heart disease is costing women's lives.[xli] The briefing focused specifically on heart disease but many of the themes from the briefing are replicated in many other cardiovascular diseases – at every stage, from diagnosis to treatment and aftercare, women with heart attacks receive poorer care than men:

- Unequal health status. Women are twice as likely to die of coronary heart disease (CHD) than men.
- Unequal public awareness. CHD is often considered to be a man's disease, which may contribute to delays in women seeking help.
- Unequal diagnosis. Women are 50% more likely than men to receive the wrong initial diagnosis for heart attack.
- Unequal treatment. Women do not receive the same standard of care as men.

BHF-funded researchers at the University of Leeds looked at quality indicators recommended by the European Society of Cardiology to better understand whether women were receiving the same degree of care as men. These are lifesaving treatments that are recommended for people having a heart attack. The study highlighted systematic differences in the use of evidence-based medicine that disadvantage women, including:

- Women who have a heart attack where the coronary artery is completely blocked acutely (known as a STEMI) were around 3 per cent less likely to receive timely reperfusion (restoration of blood flow, using procedures such as drugs or stents) than men.
- Women who have a heart attack caused by a partially blocked coronary artery (an NSTEMI) were 34 per cent less likely to receive a coronary angiography imaging test within 72 hours of their hospital admission. Coronary angiography is used to reveal presence and extent of disease in the coronary arteries and is a vital step in treatment because it helps doctors decide on next treatment steps. Research shows that people who receive timely angiography for an NSTEMI have better outcomes as a result.
- Women were less likely to be prescribed drugs that helped to reduce the chance of having a second heart attack; they were 4.2 per cent less likely to receive dual antiplatelet therapy – this involves taking two antiplatelet drugs, often aspirin and an antiplatelet agent

The paper estimated that if parity were achieved, 8243 deaths in women in England and Wales over a ten-year period could have been avoided and recommended that a greater attention to the delivery of guideline recommended care for women having a heart attack has the potential to reduce avoidable deaths among women.

Women are more likely to face challenges in getting a diagnosis of heart attack or angina. Studies from the US and Europe suggest that physicians often classify women as lower risk compared to men and this can have a subsequent impact on whether women receive appropriate treatment. [xlii] [xliii] Studies suggest that women are more likely to delay help-seeking and presentation than men, which could be attributable to a low awareness of personal risk, misinterpretation of symptoms, prioritisation of others over themselves, barriers to accessing care, fear, or embarrassment.[xliv] [xlv] [xlvi] [xlvii] The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients study showed that women were less likely than men to be told they were at risk of heart disease or to have a health-care provider discuss risk modification with them before their index event.[xlviii]

Additionally, there is ongoing debate on whether women who experience a heart attack exhibit different symptoms than men and whether new thresholds for troponin – a protein release from the heart muscle when it is damaged – should be used to diagnose women.[xlix] The ongoing debate has caused confusion within the clinical community, who may dismiss women who show 'typical' signs of a heart attack or who present at a younger age than expected, delaying critical life-saving interventions. A 2019 study by Ferry et al. suggests that women with myocardial infarction report so-called typical and atypical symptoms with the same frequency as men and that international guidelines should be re-evaluated to reduce the risk of underdiagnosis and appropriate treatment of women[l].

Finally, women get differential treatment post-acute event. Another BHF-funded study showed that women in England and Wales were 2.7 per cent less likely to be prescribed statins and 7.4 per cent less likely to be prescribed beta blockers when leaving hospital following a heart attack[li]. More research will be needed to work out why and to test how best to redress these inequalities.

3 Research, Evidence, and Data

3.1 Representation of women in research

Clinical trials have historically been dominated by inclusion of men and continue to be so, meaning their results run the risk of misunderstanding and mistreating diseases which present differently in women. Moreover, underrepresentation of women both in clinical trials as well as in those carrying out research has meant that cardiovascular diseases that predominantly or exclusively affect women remain unidentified, understudied, and misunderstood. The underrepresentation of women in research has significant consequences for resulting diagnostic tests and treatments and, ultimately, on health outcomes.

Despite the clear benefit of equal representation of women in clinical trials, underrepresentation of women in clinical trials persists right across medical research. A 2020 study reviewed 740 completed cardiovascular trials

and found that 38.2% of clinical trial participants were women. Participation of women in cardiovascular trials was particularly low in trials where the average participants was between 61-65 years of age and in government-supported clinical trials. Looking at the UK specifically, an FDA report Food & Drug Administration (FDA) report highlighted that, in 2015/16, just 36.9% of UK clinical trial participants were women[lii].

There are a multitude of reasons that women may not participate in clinical trials in rates similar to men. In the WIN-Her Initiative (Women Opt-In for Heart Research), an ongoing research effort by Boston Scientific Corporation, women with cardiovascular disease were surveyed to better understand their experiences and attitude towards clinical research. Potential barriers identified included minimal understanding of trial process and logistics, limited information from physicians about clinical trials, and poor understanding of the risks and benefits for participation. Conclusions of the initiative suggested that sex-specific clinical trial education material may increase women's participation clinical trials[liii].

There have been some positive examples of steps taken to address this disparity from around the world. For example, in 1993, a change in federal law attempted to redress the imbalanced and ensure that women and minority groups were included in clinical research supported by all Federal Government departments, including the National Institutes of Health (NIH)[liv]. Moreover, the change mandated that clinical trials be designed and carried out "in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or members of minority groups… differently than other subjects in the trial."

In 2016, NIH also released its policy on 'Sex as a Biological Variable', which mandates that research applicants "explain how relevant biological variables, such as sex, are factored into research designs and analyses for studies in vertebrate animals and humans"[lv]. The European Commission (EC) has taken a similar approach and recognised that "the first step towards excellent research is analysing sex as a biological variable." As part of its 2021-2027 Horizon Europe research programme, the Commission has committed to introducing a default requirement that the "gender dimension" is integrated into the research it funds, to ensure that the biological characteristics of both women and men, alongside environmental and social factors, are taken into consideration within research. From 2022 it will also mandate that all public bodies, higher education institutions and research organisations wishing to participate in Horizon Europe, have a Gender Equality Plan (GEP) in place[lvi]. This will be a public document outlining goals and actions for addressing gender inequalities both within the organisations (e.g., addressing gender balances in recruitment and leadership, and research culture) and the research they fund.

There are also examples of best practice from research funders in the UK. For example, the National Institute for Health Research (NIHR) launched its 'Innovations in Clinical Trial Design and Delivery for the Under-Served' (INCLUDE) project in 2020 which provides guidance for improving the inclusion of under-served groups in UK clinical research[lvii]. Following an extensive literature review, the project shares guidance on identifying under-served groups, evidence on including these groups in clinical research, current barriers to inclusion and template questions for research teams, research funders and delivery teams to consider when designing and undertaking clinical research.

Wellcome has launched a new Clinical Trials Policy[lviii] which points to the INCLUDE guidance and calls for researchers to recruit participants representing the population that the corresponding healthcare intervention is aimed at and to consider recruiting more individuals from under-served groups than statistically necessary to further improve quality of results. The BHF also signposts our research community to INCLUDE[lix] and ensures patient and public involvement to evaluate whether anything in the clinical research protocol can help encourage diversity and successful recruitment and retention of diverse groups within the trial population. However, these efforts remain disparate and lack coordination from national decision-making bodies.

3.2 Representation and experience of women in the clinical and research workforce

The advantages of having a diverse workforce have long been documented across other sectors, and evidence is increasingly emerging to highlight the need to strengthen diversity within the research workforce[lx]. In 2017, the University of Sheffield conducted a review alongside Wellcome to explore the relationship between a diverse health research community and the quality of research they undertake[lxi]. The findings highlighted that researchers from under-represented groups are more likely to undertake research and ask questions that meet the needs of those groups.

Though there does not appear to be an issue around the access of women to higher education within science, engineering, and technology (SET), representation progressively drops in more senior and specialised research roles. 2020 Advance HE student data show that across the UK, 51% of first-degree SET undergraduate students are

female, mirroring the general population. Representation is also high among female SET postgraduate students (55%)[lxii]. However, this figure falls to 45% for research postgraduates, and even further for early year and senior academic roles; just 43% of the UK Higher Education academic workforce and 23% of Professors are female. Women are also under-represented on cardiovascular editorial boards which has the potential to diminish societal value of the content, reduce available role models to encourage a pipeline of women and it has been argued that a more sex-balanced and diverse editorial team adds value by decreasing publication bias against women, providing a favourable impression of the journal, and increasing the likelihood of competitive submissions.

Moreover, these disparities are significantly more pronounced for people from ethnic minority backgrounds; a 2019 University and College Union report highlighted that Black British female professors accounted for just 25 of the 14,770 British professors in UK universities in 2018 (less than 0.169%) while 85 Black British male professors accounted for 85 of those positions (0.575%)[lxiii]. When considered that Black men and women make up 3.4% of the UK population, the disparity is clear both in minority ethnic groups and gender.[lxiv]

Additionally, women are more likely to work part-time than men and be compensated with lower salaries than men, even when adjusted for career breaks. Individuals who work part-time or take career breaks typically progress more slowly to senior positions[lxv]. As in other sectors, it is female academic staff who are more likely to work part-time than their male counterparts. The latest Advance HE staff data show that 34% of all SET female academic staff work part-time, compared to 21% of males (54% of all part-time staff are female, despite only making up 43% of the workforce). The pay gap in research persists even when different working patterns taken into account. This same data shows that 37% of full-time female academic staff earn over £50k per annum, compared with 48% of males[lxvi].

The gender inequalities in the research workforce are reflected in authorship on research publications. According to a 2017 study that looked at 1.5 million research papers, female first authorship was seen in just 40% of papers. This value falls considerably for authorship in more prestigious journals (as measured by their impact factors)[lxvii]. Across six high-impact medical journals (*Annals of Internal Medicine*, *Archives of Internal Medicine*, *The British Medical Journal*, the *Journal of the American Medical Association*, *The Lancet*, and the *New England Journal of Medicine*) over the past 20 years worldwide, only 34% of articles had a female first author. Further, in two of the world's leading journals, *Nature* and *Science*, women accounted for just 25% of first authors and 15% of senior authorship positions (typically the last author) in papers published between 2005 and 2017. In the UK, between 2014 and 2017, just 30% of publications from British universities listed women as authors, up slightly from 26% between 2006 and 2009.

These effects are seen in cardiovascular science and medicine, with lack of diversity in authorship and lack of diversity in cardiology. A 2020 study highlighted that heart failure trials with a woman as a first or senior author were associated with better recruitment of women to heart failure trials (39% enrolment of female participants as compared to 26% for male authors)[lxviii]. Despite these findings, the study noted that the proportion of women authors in guidelines and heart failure trials are consistently low.

This effect is also seen in medicine and is particularly pronounced in cardiology where women are a minority amongst UK cardiologists. Despite making up over half of medical students in the UK, recent data shows that women represent 28 per cent of cardiology trainees and only 13 per cent of cardiology consultants[lxix]. The disparities are most marked in interventional specialities and academic cardiology. Given the burden of cardiovascular disease, it is clear that the academic and clinical cardiovascular workforce needs to be drawn from the widest pool of talent and the status quo is not acceptable. Tangible questions around gender or ethnicity related pay disparity within the taxpayer funded NHS and in the university sector need to be asked.

3.2.1 The impact of Covid-19 on women in the research workforce

In November 2020, the Academy of Medical Sciences released a report that explored the impact of Covid-19 on medical research careers [lxx]. The report highlighted that female academics, especially those with caring responsibilities, were more likely to have been negatively impacted by the pandemic, with anticipated gaps in research activity and publication records resulting from the lockdown. A separate analysis by the British Medical Journal (BMJ) confirmed this finding, reporting that women had made up just 29% of first authors, and 34% of all authors, across the 1445 Covid-19 research papers that had been published worldwide as of 1 May 2020[lxxi]. For context, a 2017 study of 1.5 million research papers found that female first authorship was seen in 40% of papers[lxxii]. The BMJ attributes this disparity to "competing demands from parenting, home-schooling and other caring duties, [which] are predominantly assumed by women."

3.3 Harassment and bullying

Findings have shown that women report experiencing substantially higher levels of bullying and harassment in research environments than do their male counterparts, which likely contributes to the inequalities in representation in the STEM workforce highlighted above. Wellcome's 2020 research culture report[lxxiii], which surveyed over 4,200 researchers found that 60% of survey respondents felt their working environment was biased in favour of certain groups of people. It also found that women were more likely (49%) to have experienced bullying or harassment than men (34%). Additionally, 44% of surveyed women reported they had personally experienced discrimination in their workplace, 51% of women reported witnessing discrimination. In the survey, female respondents were less likely than their male counterparts to believe that their concerns relating to these issues would be acted on appropriately if they were to raise them (22% versus 30%, respectively).

These findings are noted quite starkly in the clinical workforce as well. A third of female cardiologists have reported sexual harassment and, in surveys, non-cardiology trainee respondents decided not to choose a career in cardiology after witness and experiencing the bullying and sexism by cardiologist and cardiology trainees[lxxiv].

4 Conclusions and Recommendations

Inequalities loom large in all of the priority areas discussed in this submission, from stark gaps in prevalence of major modifiable risk factors such as smoking and obesity, to variation in access to heart disease testing and support programmes. These differences in experience, environment, and access to services across social groups, ethnic groups, genders, and geographies must be addressedWe suggest the following recommendations to better address women's cardiovascular health:

- **Develop a Women's Health Strategy that includes both near-term and further-off policy interventions** - the BHF welcome the Government's approach to the Women's Health Strategy and the deliberate engagement of a multitude of voices to define the scale of the issue across all of women's health.
    - There are clear opportunities to implement the lesson learned from this call for evidence in the roll-out of the integrated care systems (ICS) in England.
    - Championing women's health at all levels through the health and care system and ensuring that cardiovascular health is prioritised within that will make a meaningful difference in the resilience of the UK population at large and progress towards the Government's ambition for everyone to have five extra year of healthy, independent life by 2035 and narrow the gap between the richest and poorest.
- **Improve cardiovascular risk assessments in women** - We need to ensure risk factors identified during pregnancy are seamlessly incorporated into the main health record from ante-natal or maternity notes and routinely followed up by healthcare professionals considering cardiovascular risk. CVD prevention will empower women to recognise their own CVD risk and encourage healthcare professionals to appropriately assess and treat risk factors.
- **Target further research in cardiovascular diseases that disproportionately affect women or where the outcomes affect women differently than men** . Consideration should be given on whether policies that mandate research applicants to explain how relevant biological variables, such as sex, are factored into research designs and analyses for studies in vertebrate animals and humans should be implemented more widely across the UK.
- **Increase women's participation in clinical trials** - Increasing participation in clinical trials will require a multi-pronged approach that
    - incorporates, where appropriate, adjustment of exclusion criteria in clinical research
    - Investigates and addresses the barriers to women participating in clinical trials (e.g. offering flexible hours or at home follow-up)
    - Increases awareness in women of the benefits of clinical trial participation
- **Coordinate engagement between key stakeholders to address noted gender inequalities in the cardiovascular research workforce and in cardiology as a speciality** – Stakeholder such as the British Cardiovascular Society and British Junior Cardiologists' Association are working to address the disparities in cardiology while research funders have multiple mechanisms in place to support women throughout their research careers – despite these efforts, gender inequalities persist. Coordinated efforts at all levels of the research ecosystem and the health and care system are needed to encourage and support women in pursuing careers in cardiology and cardiovascular science.
- **Enhance awareness of cardiovascular disease in women** – Developing campaigns to increase awareness of CVD in women and in healthcare professionals is crucial, especially as it relates to prevention, risk factor management and interventions across a woman's life course.

[i] Vogel B, Acevedo M, Appelman Y et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet*. May 16 2021

[ii]The Health Foundation's *'Health Equity in England: The Marmot Review 10 years on'*. February 2020. Available here: Health Equity in England: The Marmot Review 10 Years On | The Health Foundation

[iii] British Heart Foundation analysis of Office for National Statistics mortality data for 2013-15, 2017

[iv] https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

[v] British Heart Foundation analysis using Public Health England Outcomes Framework data for under 75 mortality rate from cardiovascular diseases considered preventable 2015-2017.

[vi] BHF estimates based on latest UK health survey data (NHS Digital & Scottish Government)

[vii] Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; **37:** 2315–81.

[viii] Bairey Merz CN, Andersen H, Sprague E, et al. Knowledge, attitudes, and beliefs regarding cardiovascular disease in women: the Women's Heart Alliance. *J Am Coll Cardiol* 2017; **70:** 123–32.

[ix] Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet* 2011; **378:** 1297–305.

[x] Anand SS, Islam S, Rosengren A, et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J* 2008; **29:** 932–40.

[xi] Ji H, Kim A, Ebinger JE, et al. Sex differences in blood pressure trajectories over the life course. *JAMA Cardiol* 2020; **5:** 19–26.

[xii] Wenger NK, Arnold A, Bairey Merz CN, et al. Hypertension across a woman's life cycle. *J Am Coll Cardiol* 2018; **71:** 1797–813.

[xiii] Imperial College Health Partners analysis for the BHF using Sheffield/Public Health England CVD Return on Investment tool.

[xiv] Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K. Menopause and the metabolic syndrome: the Study of Women's Health Across the Nation. *Arch Intern Med* 2008; **168:** 1568–75.

[xv] Peters SAE, Colantonio LD, Zhao H, et al. Sex differences in high-intensity statin use following myocardial infarction in the United States. *J Am Coll Cardiol* 2018; **71:** 1729–37.

[xvi] Nanna MG, Wang TY, Xiang Q, et al. Sex differences in the use of statins in community practice. *Circ Cardiovasc Qual Outcomes* 2019; **12:** e005562.

[xvii] PHE data – accessible here: https://fingertips.phe.org.uk/profile-group/cardiovascular-disease-diabetes-kidney-disease/profile/diabetes-ft/data#page/4/gid/1938133138/pat/44/ati/154/are/E38000004/iid/241/age/187/sex/4/cid/4/tbm/1/page-options/ovw-do-1

[xviii] Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858 507 individuals and 28 203 coronary events. *Diabetologia* 2014; **57:** 1542–51.

[xix] de Jong M, Woodward M, Peters SAE. Diabetes, glycated hemoglobin, and the risk of myocardial infarction in women and men: a prospective cohort study of the UK Biobank. *Diabetes Care* 2020; **43:** 2050–59

[xx] Retnakaran R. Hyperglycemia in pregnancy and its implications for a woman's future risk of cardiovascular disease. *Diabetes Res Clin Pract* 2018; **145:** 193–99.

[xxi] British Heart Foundation analysis of UK estimates from Global Health Data Exchange, 2019, Global Burden of Disease (GBD) Results Tool, [online] Available at: http://ghdx.healthdata.org/gbd-results-tool

[xxii] British Heart Foundation analysis of latest UK health surveys

[xxiii] Health survey for England (2019) Overweight and obesity in adults and children data tables [online] Available at: Health Survey for England, 2019: Overweight and obesity in adults and children data tables

[xxiv] Wilsgaard T, Schirmer H, Arnesen E. Impact of body weight on blood pressure with a focus on sex differences: the Tromso Study, 1986–1995. *Arch Intern Med* 2000; **160:** 2847–53

[xxv] Wilson PWF, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med* 2002; **162:** 1867–72.

[xxvi] NHS Statistics on obesity. Statistics on Obesity, Physical Activity and Diet, England, 2020 - NHS Digital

[xxvii] Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. *Lancet* 2018; **392:** 2052–90.

[xxviii] Walli-Attaei M, Joseph P, Rosengren A, et al. Variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet* 2020; **396:** 97–109.

[xxix xxix] Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. Atherosclerosis 2015; 241: 211–18

[xxx] Leon LJ, McCarthy FP, Direk K, et al. Preeclampsia and cardiovascular disease in a large UK pregnancy cohort of linked electronic health records: a CALIBER study. Circulation 2019; 140: 1050–60.

[xxxi] Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia 2019; 62: 905–14.

[xxxii] Sliwa K, Hilfiker-Kleiner D, Petrie MC, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. *Eur J Heart Fail* 2010; **12:** 767–78.

[xxxiii] Azibani F, Sliwa K. Peripartum cardiomyopathy: an update. Curr Heart Fail Rep 2018; 15: 297–306.

[xxxiv] Hayes SN, Kim ESH, Saw J, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation* 2018; **137:** e523–57.

[xxxv] Elkayam U, Jalnapurkar S, Barakkat MN, et al. Pregnancy-associated acute myocardial infarction: a review of contemporary experience in 150 cases between 2006 and 2011. *Circulation* 2014; **129:** 1695–702.

[xxxvi] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; **364:** 937–52

[xxxvii] Zhao D, Guallar E, Ouyang P, et al. Endogenous sex hormones and incident cardiovascular disease in post-menopausal women. *J Am Coll Cardiol* 2018; **71:** 2555–66.

[xxxviii] Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288:** 321–33.

[xxxix] Hamoda H et al. The British Menopause Society and Women's Health concern 2016 recommendations on hormone replacement threapy in menopausal women. Post Reproductive Health. 22(4): 165-183.

[xl] Roger A. Lobo – Nature Reviews: Endocrinology 13, 220-231 (2017)

[xli] BHF, Bias and Biology, (2019).

[xlii] Lehto, H. R, Lehto, S., Havulinna, A. S., Jousilahti, P., Salomaa, V. (2012). Gender differences in the prevalence, causes and treatment of high cardiovascular risk: findings from the FINRISK Survey, European Journal of Preventive Cardiology, Vol 19, pp. 1153-1160.

[xliii] Mosca L, Linfante AH, Benjamin EJ, et al. (2005). National study of physician awareness and adherence to cardiovascular disease prevention guidelines. Circulation, Vol 111, p 499–510.

[xliv] 2 Kaul P, Armstrong PW, Sookram S, Leung BK, Brass N, Welsh RC. Temporal trends in patient and treatment delay among men and women presenting with ST-elevation myocardial infarction. Am Heart J 2011; 161: 91–97

[xlv] 3 Kang SH, Suh JW, Yoon CH, et al. Sex differences in management and mortality of patients with ST-elevation myocardial infarction (from the Korean Acute Myocardial Infarction National Registry). Am J Cardiol 2012; 109: 787–93.

[xlvi] Pagidipati NJ, Peterson ED. Acute coronary syndromes in women and men. Nat Rev Cardiol 2016; 13: 471–80.

[xlvii] Lichtman JH, Leifheit-Limson EC, Watanabe E, et al. Symptom recognition and healthcare experiences of young women with acute myocardial infarction. Circ Cardiovasc Qual Outcomes 2015; 8 (suppl 1): S31–38.

[xlviii] Leifheit-Limson EC, D'Onofrio G, Daneshvar M, et al. Sex differences in cardiac risk factors, perceived risk, and health care provider discussion of risk and risk modification among young patients with acute myocardial infarction: the VIRGO study. J Am Coll Cardiol 2015; 66: 1949–57.

[xlix] Shah AS, Griffiths M, Lee K et al. (2015). High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study, BMJ, Vol 350.

[l] Ferry A, Anand A, Strachnan FE et al (2019). Presenting symptoms in men and women diagnosed with myocardial infarction using sex-specific criteria. Journal of the American Heart Association; 8(17).

[li] Wilkinson C, Bebb O, Dondo TB et al. Sex differences in quality indicator attainment for myocardial infarction; a nationwide cohort study. Heart. 2018;105(7): 516-523.

[lii] US Food and Drug Administration. 2015-16 Global participation in clinical trials report. Can be accessed here: 2015-2016 Global Participation in Clinical Trials Report (fda.gov)

[liii] X Jin, C Cahndramouli, B Allocco, et al. Women's participation in cardiovascular clinical trials from 2010 to 2017. Circulation (2020). Vol 141 (7).

[liv] Reports on Women's Participation in Clinical Studies, 1977-1993 - Women and Health Research - NCBI Bookshelf (nih.gov)

[lv]NIH Policy on Sex as a Biological Variable- full policy can be accessed here: NOT-OD-15-102_Guidance.pdf (nih.gov)

[lvi] Gender equality in research and innovation | European Commission (europa.eu)

[lvii] Improving inclusion of under-served groups in clinical research: Guidance from INCLUDE project (nihr.ac.uk)

[lviii] Clinical trials policy – Grant funding | Wellcome

[lix]https://www.bhf.org.uk/for-professionals/information-for-researchers/how-to-apply/clinical-study-guidelines

[lx] Saxena A. Workforce diversity: a key to improve productivity. Procedica Economics and Finance. 2014. Vol 11: 76-85

[lxi] University of Sheffield in partnership with Wellcome. Review of diversity and inclusion literature and an evaluation of methodologies and metrics relating to health research. May 2017. Available at review-of-diversity-and-inclusion-literature.pdf (wellcome.org)

[lxii] Equality in higher education: statistical report 2020 | Advance HE (advance-he.ac.uk)

[lxiii] UCU 2019 Report by N Rollock. 'Staying power: the career experiences and strategies of UK black female professors'. Can be accessed here: UCU_Rollock_February_2019.pdf

[lxiv] Gov.uk Population of England and Wales [online] available at: https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest

[lxv] Van Osch Y and Schaveling J. The effects of part-time employment and gender on organisation career growth. Journal of Career Development. (2020) Vol 47 (3): 328-343.

[lxvi] Equality in higher education: statistical report 2020 | Advance HE (advance-he.ac.uk)

[lxvii] MW Nielsen, JP Andersen, L Shiebinger & JW Schneider. 'One and a half million medical papers reveal a link between author gender and attention to gender and sex analysis'. Nature Human Behaviour (2017) 1, 791-796

[lxviii] N Reza, AS Tahhan, et al. Representation of women authors in international heart failure guidelines and contemporary clinical trials. Circulation: Heart Failure. August 2020. 13(8)

[lxix] HC Sinclair, A Josh, C Allen et al. Women in Cardiology: the British Junior Cardiologist' Association identifies the challenges. *European Heart Journal*, Volume 40, Issue 3, January 2019, Pages 227–231

[lxx] The impact of COVID-19 on biomedical research careers | The Academy of Medical Sciences (acmedsci.ac.uk) (July 2020)

[lxxi] AC Pimho-Gomes, S Peters, K Thompson et al. 'Where are the women? Gender inequalities in covid-19 research authorship'. BMJ Global Health (2020). Vol 5, Issue 7.

[lxxii] MW Nielsen, JP Andersen, L Schiebinger & JW Schneider. 'One and a half million medical papers reveal a link between author gender and attention to gender and sex analysis'. Nature Human Behaviour (2017). 1: 701-796

[lxxiii] 2020 Report: what-researchers-think-about-the-culture-they-work-in.pdf (wellcome.org)

[lxxiv] SV Babu-Narayan, Simon Ray. 'Women in cardiology: no progress in the pace of change'. Heart (2021). Vol 107, Issue 11.