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OXFORD POPULATION HEALTH

CEU

The Million Women Study

Answering important questions about women's health

Introduction

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Principal Investigators

In the early 1990s, the use of hormone replacement therapy (HRT) was increasing rapidly amid claims that it could improve women's wellbeing and increase life expectancy. However, emerging evidence suggested that HRT could increase the risk of breast cancer.

In search of some definitive data, a team at the University of Oxford, led by Professor Dame Valerie Beral, worked with the National Health Service Breast Screening Programme to recruit a million women to a new study to investigate whether HRT was associated with breast cancer risk. The Million Women Study would provide reliable information on the risks associated with different types of HRT, as well as on the effects of many other factors that affect women as they age.

Women in the UK in their 50s and early 60s received a recruitment questionnaire along with invitations to attend routine NHS breast screening. By making the process so simple, the one million target was exceeded and between 1996 and 2001, 1.3 million women agreed to participate in the study and be followed indefinitely through their medical records.

Over the past 30 years, study participants have filled out up to five follow-up postal questionnaires and some have completed online questionnaires about their diet and experiences of the COVID-19 pandemic. They have provided the study with a wealth of information on their habits and behaviours, their medical history, and their experiences of caring and disability as they age. Some participants have also provided blood samples and agreed that they can be used for genetic tests. This treasure trove of data has enabled us to provide answers to a range of important questions about women's health.

This report summarises some of the big questions that have been addressed through the Million Women Study, and the changes in policy and practice that have resulted from the commitment of the participants, the foresight of the study's founders, and the dedication of the study team.

1994

- Study shows no adverse impact on breast screening uptake
- Funding from Imperial Cancer Research Fund

1996

- Recruitment involving 66 NHS screening centres
- Linkage to NHS cancer registrations and mortality

1999

- *Breast Cancer Research* paper on study design and methods
- 1st postal re-survey

2000

The Million Women Study website is launched

2001

- Recruitment closes with 1.3 million women recruited
- MRC funding

2003

Landmark paper on HRT and breast cancer is published in *The Lancet*

2005

- Linkage to hospital admission records
- *Lancet* paper on HRT and endometrial cancer

2006

- 2nd postal re-survey
- Collection of blood samples starts

2007

Paper on HRT and ovarian cancer is published in *The Lancet*

2009

- 3rd postal re-survey
- Paper on alcohol and cancer
- *BMJ* paper on VTE after surgery

2013

- 4th postal re-survey
- *Lancet* paper on smoking and mortality
- Linkage to primary care data in England

2014

- Online 24-hour dietary assessment
- Linkage to primary care data in Scotland

2017

British Journal of Cancer paper on disability and screening

2018

5th postal re-survey is sent to participants

2019

- *Lancet* paper on HRT and breast cancer, using worldwide data
- Participant panel established

2020

- *Lancet Public Health* paper on dementia
- Online assessment during COVID pandemic

2022

- GWAS and exome sequencing data
- *JNCI* paper on mobile phone use and brain cancer

2023

Collection of breast screening and digital mammography data begins

2024

- NHS England agreement to share health outcomes data
- Linkage to Mental Health Services data

2025

- *Nature Communications* paper on diet and colorectal cancer
- MRC infrastructure funding

2026

Agreement to join UK Longitudinal Linkage Collaboration for wider data access

At recruitment

1.3m
women aged 50 to 64

20%
current smokers

21%
exercise 2+ times per week

33%
using HRT

Current status

860,000
surviving participants

Average age
82 years

Data collection

Up to 5
postal re-surveys

50,000
donated a blood sample

60,000
surveyed about diet

44,000
surveyed on health and wellbeing during the pandemic

Breast screening information
300,000

Digital mammograms
100,000

Publications and citations

>230
publications

25,000
citations in academic literature

1,200
citations in policy documents

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How does HRT affect the risk of cancer and other conditions?

The challenge

In the 1990s, there was a sharp increase in the number of women taking HRT to help with menopausal symptoms but also because HRT was thought to improve women's wellbeing and prevent coronary heart disease. However, there was a concern that HRT could increase the risk of breast cancer, which is the most common cancer in women worldwide.

Our work

Breast cancer

In a landmark paper published in 2003, the Million Women Study showed that women taking HRT were at an increased risk of developing breast cancer. An estimated 20,000 UK women aged 50-64 may have developed the disease due to HRT use over 10 years. Analyses in the Million Women Study demonstrated that the effects of HRT vary considerably by pattern of use and tumour subtype.

Endometrial cancer

In 2005, the Million Women Study confirmed that post-menopausal women who have not had a hysterectomy and are taking oestrogen-only HRT, are at an increased risk of endometrial cancer. The study also showed that the risk of endometrial cancer increases in women who take the HRT drug tibolone, but may be reduced in

women taking combined oestrogen-progestogen HRT.

Ovarian cancer

Results from the Million Women Study published in 2007 showed that women taking HRT were at a slightly higher risk of ovarian cancer. The study, analysing 948,576 postmenopausal women over five years, found that for every 1,000 women taking HRT, 2.6 developed ovarian cancer, compared to 2.2 in those not taking HRT.

The study has also provided valuable evidence regarding the association of HRT with many other conditions, including venous thromboembolism, gallbladder disease, cataracts, and fracture risk, providing a more complete overview of the risks and benefits associated with HRT use.

The impact

These findings had a major impact on attitudes towards HRT and led to significant changes in its use worldwide.

The results, together with findings from the US Women's Health Initiative trials, influenced a number of health agencies in Europe and around the world to change their guidelines. In the UK, agencies citing the Million Women Study results included the Medicines and Healthcare products Regulatory Agency (MHRA), the

National Institute for Health and Care Excellence (NICE), and the Royal College of Obstetricians and Gynaecologists. Around the world, clinical guidelines citing the study results included those produced by the European Medicines Agency and health agencies in Finland, France, Germany, Ireland, Norway, and the USA.

Prescribing practice changed – women were no longer given HRT as a first line therapy for osteoporosis, and were advised to take HRT for as short a time as possible. Women at a high risk of breast cancer were advised to consider alternatives to HRT.

The fall in usage of HRT in many countries was followed by corresponding decreases in breast cancer incidence rates of about 10% in post-menopausal women.

In 2019, the Million Women Study was a major contributor to a report using data from 58 studies around the world which provided definitive evidence on the long-term effects of taking HRT on the risk of breast cancer. Compared with women who had never taken HRT, women who started taking HRT after menopause had a significantly increased risk of invasive breast cancer. The longer women took HRT, the greater the risk. In women who stopped taking HRT, their risks of breast cancer were lower but remained elevated more than 10 years after stopping.

This persistence in effect meant that the estimates of absolute excess risk associated with HRT use were around twice as large as had previously been thought. The 2019 report, which was commended for its scope and robustness, prompted the MHRA to issue an urgent update for health care professionals.

In recent years, HRT use has been increasing again amidst greater focus on the menopause in public discourse. The Million Women Study team will continue to assess the benefits and risks of taking HRT.

Women should be aware of this new information, so that it can be considered with the other risks and benefits of using HRT.

Dr Sarah Branch, Former Director of Vigilance and Risk Management of Medicines, MHRA

This is a "tour de force" in what has been done and the way it has been done – the findings cannot be dismissed.

Emeritus Professor Stephen Evans, Professor of Pharmacoepidemiology, London School of Hygiene & Tropical Medicine

What are the risks of smoking for women?

The challenge

Women born in the 1930s and 1940s were among the first generation of women in the UK to start smoking substantial numbers of cigarettes regularly in early adulthood and throughout their lives. The British Doctors Study, which began in 1951, established a convincing link between tobacco smoking and premature death, but women were excluded from most of the analyses because the majority of participants were men.

Earlier studies that had reported on the effects of smoking in women could have underestimated the effects since young women did not start smoking in large numbers until the 1940s. The Million Women Study provided an opportunity to investigate the risks of smoking for women who had smoked all their adult lives.

Our work

Our study, published in 2013, showed that the hazards of smoking in women were greater than previously thought. We showed that smokers were three times more likely to die prematurely than women who had never smoked, the equivalent of losing 11 years of life, on average. We also found that stopping smoking is more effective in reducing the excess risk than previously thought – a woman who stops smoking at age 40 can avoid about 90% of the excess risk of death associated with continued smoking.

The impact

The results on both the risks related to smoking and the benefits of giving up have been widely cited in academic literature and in policy documents and clinical guidelines. For example, our findings were cited in the US Surgeon General's reports on the *Health Consequences of Smoking*, and on *Smoking Cessation*, and in France's National Authority for Health's *Good practice recommendation for stopping smoking*.

The results have also been presented in World Health Organization (WHO) documents, such as *Empower Women – facing the challenge of Tobacco Use in Europe*, which provided evidence of the health consequences of smoking and examples of effective tobacco-control measures.

If women smoke like men, they die like men. The Million Women Study allowed us to observe directly the full effects of smoking, and the benefits of stopping.

Emeritus Professor
Sir Richard Peto,
Oxford Population Health

How long does the risk of venous thrombo-embolism last after an operation?

The challenge

Venous thromboembolism (VTE) encompasses two serious blood-clotting conditions – deep vein thrombosis and pulmonary embolism, and is a common cause of preventable death in surgical patients. However, information was lacking on how long the risk of VTE lasted after surgery and whether this risk varied by the type of surgery.

Our work

Our research in the Million Women Study showed that the risk of VTE after surgery reached a peak about three weeks after surgery, but that the risks were substantially higher for up to 12 weeks after an operation. The risks were much greater for patients undergoing inpatient surgery than day case surgery, but were still significantly elevated after day case surgery. The highest risks were after surgery for joint replacement and cancer. At the time of publication, surgical patients were typically only receiving preventive treatment for VTE while they were in hospital, with an average stay of six days. This meant that, in most cases, prophylaxis was stopped before the peak incidence of VTE.

The impact

These results, published in the *BMJ* in 2009, added to growing evidence that the duration of prophylaxis provided for VTE should be extended beyond the typical length of a hospital stay, for up to 12 weeks. The *BMJ* editorial called it a 'wake-up call to all surgeons', not only in terms of the need to extend the length of prophylaxis, but also the need to expand the use of prophylaxis following all types of surgery, including outpatient surgery.

Our work in this area has been cited in many guidelines, including Scotland's national clinical guidelines for the prevention and management of venous thromboembolism in 2010, and in specialty-specific guidelines, such as the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines and the Enhanced Recovery After Surgery Society guidelines for perioperative care in gynaecological oncology.

Following a recommendation by the National Institute for Health and Care Excellence (NICE) to use a risk assessment tool for all adult patients admitted to hospital, there has been a reduction in hospital-acquired thrombosis.

Does moderate drinking increase the risk of cancer and other conditions?

The challenge

Most of the evidence for an association between alcohol intake and cancer risk has come from studies of men, who typically drink more alcohol than women. Although there was evidence that drinking alcohol was linked to a higher risk of breast cancer, little was known about the risk of cancer associated with more moderate drinking. It was also unclear what effect moderate drinking had on women's risks of other alcohol-related diseases, such as liver cirrhosis.

Our work

Cancer

In 2009, we published a paper on alcohol and cancer incidence in women which concluded that even low to moderate alcohol consumption increases women's risk of certain cancers. Those findings indicated that for every additional drink consumed per day, the increase in incidence per 1,000 women up to age 75 years in developed countries is estimated to be about 11 for breast cancer, one for cancers of the oral cavity and pharynx, one for cancer of the rectum, and 0.7 each for cancers of the oesophagus, larynx and liver, giving a total excess of about 15 cancers.

In 2023, we showed that for aero-digestive cancers, alcohol worsens the adverse effect of smoking, with a 10-fold greater risk of aero-digestive cancers in women who are heavy smokers and heavy drinkers compared to women who have never smoked and drink a low amount of alcohol (one to two drinks per week). Most of the increased risk of aero-digestive cancers associated with higher alcohol consumption was confined to smokers. The findings also provided robust evidence that greater alcohol intake, even within relatively moderate ranges, increases the risk of many common cancers.

Liver cirrhosis

In 2019, we reported on the effects of alcohol drinking on the risk of liver cirrhosis. Women who drank more than 14 drinks per week had a three times higher risk of liver cirrhosis compared to women who drank one to two drinks per week; but even those who drank moderate amounts were at higher risk. We also found that certain habits around drinking were associated with an increased risk. Among women who drank seven or more drinks per week, those who drank daily and who tended not to drink with meals were at even greater risk of liver cirrhosis.

The impact

The Million Women Study's results on alcohol and women's health have been cited in policy documents on the effects of alcohol produced by the WHO, and by the International Agency for Research on Cancer, and by the World Cancer Research Fund on the causes of cancer. Other government agencies citing the results include the Australian Department of Health, France's National Authority for Health, and Health New Zealand.

Is disability a barrier to accessing cancer screening?

The challenge

The UK Equality Act 2010 requires equitable access to all National Health Service (NHS) screening programmes. However, people with disabilities may be less likely to participate in cancer screening than people without disabilities. Evidence was lacking for England, where all people in relevant age ranges are routinely invited for free cancer screening, regardless of their health status or ability to pay.

Our work

In collaboration with the International Centre for Evidence in Disability, we conducted research on the impact of disability on participation in cancer screening, which was published in 2017. Most previous work had used self-reported participation in screening rather than screening records, and came from the US, which does not have population-wide screening. This analysis had the great advantage of having an objective measure of participation because the Million Women Study is linked to data from the NHS Screening Programme.

We found that, despite having been invited for screening by the NHS Screening Programme, women with disabilities were 36% less likely than other women to participate in breast cancer screening and 25% less likely to participate in bowel cancer screening. Difficulties with self-care and with vision were associated with the greatest reduction in participation.

The impact

This evidence was cited by Public Health England in 2019 in their guidance to support the health system to reduce inequalities in screening and by the WHO in a policy brief on developing disability-inclusive health systems. In 2024, the NHS announced that they would offer a specially designed tool to support people who are blind or partially sighted to complete a FIT (faecal immunochemical test) for bowel cancer at home.

Do mobile phones cause brain cancer?

The challenge

There has been a long-standing concern that mobile phone users may be at an increased risk of developing brain tumours, with the International Agency for Research on Cancer (IARC) classifying radiofrequency waves as 'possibly carcinogenic'. However, most of the studies that investigated this question were retrospective studies in which individuals reported mobile phone use after a diagnosis of cancer, meaning that the results may have been biased.

Our work

In collaboration with IARC, we produced two reports on mobile phone use and brain tumour risk in 2013 and an updated paper in 2022. Both reports concluded that mobile phone use did not increase brain tumour risk in this cohort. The updated paper included over 770,000 women, among whom there were 3,200 cases of brain cancer. These substantial numbers meant that it was also possible to conclude that patterns of mobile phone use that were typical in women of this generation, including using a mobile phone for 20 minutes a week and use spanning at least 10 years, were not associated with any subtype of brain cancer.

The impact

The results were covered by numerous media outlets and have been cited in multiple policy documents looking at the health impacts of 5G and earlier mobile phone technologies. These include policy documents produced by the European Parliament. Findings were also cited by the French Agency for Food, Environmental and Occupational Health & Safety, Japan's Ministry of Internal Affairs and Communication, Netherlands Health Council, New Zealand Ministry of Health, Royal Society of Canada, Swedish Radiation Safety Authority, Swiss Federal Office for the Environment, UK National Infrastructure Commission, US Congress, and the US National Toxicology Program.

How does diet affect cancer risk?

The challenge

Diet is known to be a determinant of health, but many questions remain about whether and how dietary and nutritional factors may affect the risk of different cancers.

Our work

The Million Women Study has contributed valuable insights into the role of diet in both breast cancer and bowel cancer.

In the largest study to date into the link between diet and bowel cancer, we found that an additional 300mg of calcium each day is associated with a 17% decrease in bowel cancer risk. We used dietary data from more than 500,000 women and looked at their consumption of 97 food products and nutrients. The findings showed that consuming foods and drinks rich in calcium, such as milk and yoghurt, was associated with a lower risk of a bowel cancer diagnosis. The reduction in risk was similar for both dairy and non-dairy sources, suggesting that calcium was the main factor responsible for cutting risk. Further evidence was provided by an analysis of genetically-predicted milk intake, which is likely to also reflect calcium intake.

The study confirmed the link between alcohol consumption and increased risk of bowel cancer, with each additional large glass of wine per day

being associated with a 15% increase in bowel cancer risk. We also found an 8% higher risk of bowel cancer for every 30g of red and processed meat consumed per day.

In contrast to the findings on bowel cancer, results from the Million Women Study suggest that diet does not play a significant role in breast cancer risk, except for the known association between alcohol and breast cancer.

The study was also a major contributor to the largest ever study of non-meat diets and cancer risk. The study found that vegetarian diets are associated with lower risks of several cancers — breast, prostate, kidney and pancreatic cancers, and multiple myeloma — but a higher risk of squamous cell carcinoma of the oesophagus.

Press coverage for both the diet and bowel cancer study and for the cancer risk in vegetarians study was widespread, with over 425 media outlets covering the bowel cancer study and over 290 covering the vegetarian diets study.

The impact

Until recently, dairy intake, and hence calcium intake, have only been classed as probable factors affecting the risk of colorectal cancer. This work considerably strengthens the case for consideration of dietary calcium intake as a potential target for prevention of colorectal cancer.

How do lifestyles in middle age affect the risk of dementia later in life?

The challenge

It can take about 10 years from the first, very early symptoms of dementia until a person receives a diagnosis. As a result, studies on dementia can be affected by reverse causation, whereby behaviours that may appear to affect the risk of getting dementia are actually a consequence of the disease. It is therefore important to have long-term studies, with follow-up periods of 10 to 20 years, in order to disentangle cause and effect.

Our work

The Million Women Study is ideally suited to investigate risk factors for dementia because of its long-term follow-up and, given the age of the cohort, large number of dementia cases. We have investigated different risk factors, including: obesity, lack of physical activity, poor diet, hypertension, and lack of participation in social and cognitive activities. We have shown that there is substantial reverse causation, but that this bias can be avoided by disregarding at least the first 10 years of follow-up and concentrating on the longer-term associations. Our studies on risk factors for dementia have concluded that obesity and hypertension are likely to be true causal risk factors for dementia, but that the association between physical inactivity and poor diet and dementia is likely to be due to reverse causation, and disappears once the early years of follow-up are removed. A similar phenomenon occurs for social and cognitive activities, where any association between lack of participation and dementia is likely to reflect the impact of the disease on a person's ability to participate.

The impact

Our work was cited by a review of the UK health data landscape commissioned by the Chief Medical Officer for England, the UK National Statistician and NHS England's National Director for Transformation. Our studies of potential causes of dementia were used to illustrate the benefits of long-term follow-up. Our work has also been cited by the Lancet Commission report on dementia prevention, intervention, and care, which noted the issue of reverse causation.

[The study] shows why follow-up for so many years is crucial for understanding a condition such as dementia, which starts to develop many years before obvious symptoms appear or a diagnosis is made.

Sudlow, CLM (2024). Uniting the UK's Health Data: A Huge Opportunity for Society

The future: emerging research questions

The Million Women Study will continue to be important for many research questions that are yet to be answered.

We aim to expand our research on cardiovascular disease in women. The cohort is in an excellent position to respond to the Lancet Commission's call for prioritising research in an area which is 'understudied, under-recognised, underdiagnosed, and undertreated' despite the fact that cardiovascular disease is responsible for causing 35% of deaths in women each year.

Given the age of the cohort, research on risk factors for medical conditions of older age, such as dementia, stroke and fractures will be possible at a scale not previously seen. Participants have given a wealth of detail about their lives as they have grown older, providing us with information on the 'exposures' of older age, which could include retirement, frailty, disability and caring responsibilities. We are investigating the impact of caring responsibilities on a carer's mental and physical health.

The size of the cohort also enables researchers to investigate risks for rare but potentially devastating diseases like motor neurone disease, which tend to be understudied.

We will continue to augment the data with disease biomarkers, imaging and histopathology. These valuable new biomarkers can be used to better characterise susceptibility to disease and disease mechanisms.

Working with the public and our participants

Our Participant Panel and public contributors will continue to provide us with advice and insights into the key issues we should be tackling.

> **I'm very proud of having participated in something that was ground-breaking. The research must continue.**
>
> Lesley Laxton,
> MWS Participant

Working with the wider research community

We will continue to provide access to study data through the use of secure data access platforms for approved researchers, with the knowledge and consent of participants. This enables this rich resource to be fully exploited so we can deepen our understanding of the effects of many different factors on women's health as they age.

Acknowledgements

We are indebted to the 1.3 million women who have given their time and energy to fill in questionnaires about their health. The impact of the study on health policy and practice would not have been possible without the involvement of these women, the contribution of breast screening centres to their recruitment, and the efforts of the Million Women Study coordination centre staff in overseeing the collection of vast amounts of data and preparing it for analyses. Many academic researchers have also contributed to the success of the study.

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