# Supplementary Information 1

**Events in Early Life are Associated with Female Reproductive Ageing: A UK Biobank Study**

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## Supplementary Methods

### Source of data

UK Biobank invited 9.2 million people to participate, giving a response rate of 5.47% [1]. Participants were registered with the NHS and lived within 25 miles of one of the 22 assessment centres. Participants answered detailed questions about themselves, had measurements taken and provided samples. The data included follow-up data collected in 2012–2013 for 20,000 participants from North West England. In our analysis we analysed baseline data for 266,237 people with a single visit, and follow-up data for 7,237 participants.

### Age at menopause

A total of 166,659 women stated that they were menopausal, and of these 155,658 (93%) gave an age at menopause; of the rest, 10,485 (6%) did not know, 378 (0.2%) preferred not to answer, and 48 (0.03%) had missing values. Of the women with an age at menopause, 9,154 (5.9%) were excluded as they were missing information relating to whether they had had hysterectomy, oophorectomy or HRT, or the age at which this took place. A total of 10,779 women with an age at menopause were excluded as they had menopause due to hysterectomy or oophorectomy (6.9%), with a further 16,782 (10.8%) excluded as HRT was ongoing at time of menopause. Overall we identified 118,943 women with an age at natural menopause. We then restricted our analysis to women with a natural menopause between 20 and 65 years and to women of white ethnicity, giving 113,404 women with natural menopause who were identified.

### Exclusion of outliers

Women with menopause under 20 or over 65 were excluded (n=16) on the basis of biological plausibility. Age at menarche was restricted to a clinically normal range of 9–17 years. Birth weights in excess of 6kg were excluded (n=86) as implausible/extreme outliers.

**Cox proportional hazards model**

Cox proportional hazards regression was run using the stset and stcox commands in Stata using age as the time variable, starting at birth (0 years) and ending at last age at risk of natural menopause, with natural menopause as the event. Women included in the analysis were censored at bilateral oophorectomy and/or hysterectomy, or start of HRT use (where this was ongoing at time of menopause, hysterectomy or oophorectomy). Covariates were considered to be constant throughout the time at risk. The Cox proportional hazards assumption was tested using Schoenfeld residuals, however in most cases this did not hold.

**Variables included**

For further details of the variables included, please see http://www.ukbiobank.ac.uk/

*Questions used to define menopause.*

Age at menopause was derived from the following. Women providing no answer to any of the relevant questions, answering 'Prefer not to answer' or answering 'Not sure' were excluded from the analysis.

2724: Had menopause. Have you had your menopause (periods stopped)?
- Prefer not to answer
- No
- Yes
- Not sure - had a hysterectomy
- Not sure - other reason

3581: Age at menopause. How old were you when your periods stopped?

3591: Ever had hysterectomy?
- Not sure
- Prefer not to answer
- No
- Yes

2824: Age at hysterectomy?

2834: Bilateral oophorectomy?

> Not sure
>
> Prefer not to answer
>
> No
>
> Yes

3882: Age at bilateral oophorectomy?

2814: Ever used HRT?

> Prefer not to answer
>
> Do not know
>
> No
>
> Yes

3536: Age started HRT?

3546: Age last used HRT?


*Questions used to define the early life variables*

Women providing no answer to any of the relevant questions, answering 'Prefer not to answer' or answering 'Not sure' were excluded from the analysis.

34: Year of birth

1787: Maternal smoking around birth

> Prefer not to answer
>
> Do not know
>
> No
>
> Yes

20022: Birth weight

1777: Part of a multiple birth

> Prefer not to answer
>
> Do not know
>
> No
>
> Yes

1677: Breastfed as a baby

    Prefer not to answer

    Do not know

    No

    Yes

1767: Adopted as a child

    Prefer not to answer

    Do not know

    No

    Yes

1707: Handedness (chirality/laterality)

    Prefer not to answer

    Right-handed

    Left-handed

    Use both right and left hands equally

1697: Comparative height at age 10

    Prefer not to answer

    Do not know

    Shorter

    Taller

    About average

1687: Comparative body size at age 10

    Prefer not to answer

    Do not know

    Thinner

    Plumper

    About average

2714: Age when periods started (menarche)

*Questions used to define the potential confounding variables*

Women providing no answer to any of the relevant questions, answering 'Prefer not to answer' or answering 'Not sure' were excluded from the analysis.

189: Townsend deprivation index at recruitment

1558: Alcohol intake frequency

>
> Prefer not to answer
>
> Daily or almost daily
>
> Three or four times a week
>
> Once or twice a week
>
> One to three times a month
>
> Special occasions only
>
> Never

2734: Number of live births

20116: Smoking status

>
> Prefer not to answer
>
> Never
>
> Previous
>
> Current

21001: Body mass index (BMI)

Educational level was derived from:

>
> 6138: Qualifications
>
> > None of the above
> >
> > Prefer not to answer
> >
> > College or University degree
> >
> > A levels/AS levels or equivalent
> >
> > O levels/GCSEs or equivalent
> >
> > CSEs or equivalent
> >
> > NVQ or HND or HNC or equivalent
> >
> > Other professional qualifications eg: nursing, teaching

Pack-years was derived using:

    20116: Smoking status

        Prefer not to answer

        Never

        Previous

        Current

    2867: Age started smoking in former smokers

    2887: Number of cigarettes previously smoked daily

    2897: Age stopped smoking

    3436: Age started smoking in current smokers

    3456: Number of cigarettes currently smoked daily (current cigarette smokers)

    21003: Age at recruitment


Whether the participant ate meat  was derived from:

    1359: Poultry intake

        Prefer not to answer

        Do not know

        Never

        Less than once a week

        Once a week

        2-4 times a week

        5-6 times a week

        Once or more daily

    1369: Beef intake

        Prefer not to answer

        Do not know

        Never

        Less than once a week

        Once a week

        2-4 times a week

        5-6 times a week

        Once or more daily

1379: Lamb/mutton intake

    Prefer not to answer

    Do not know

    Never

    Less than once a week

    Once a week

    2-4 times a week

    5-6 times a week

    Once or more daily

1389: Pork intake

    Prefer not to answer

    Do not know

    Never

    Less than once a week

    Once a week

    2-4 times a week

    5-6 times a week

    Once or more daily

*Illnesses included (all have at least one case at under 20 years)*

Cancer aged under 20 was identified from '20007: Interpolated age of participant when cancer first diagnosed'. Other illnesses were identified from '20002: Non-cancer illness code, self-reported' and '20009: Interpolated age of participant when non-cancer illness first diagnosed'.

| Allergy N=16,779 | Cancer N=241 | Diabetes N=332 |
|---|---|---|
| Allergy or anaphylactic reaction to drug | Any self-reported cancer reported under 20 years: | T1 diabetes |
| Allergy or anaphylactic reaction to food | Acute myeloid leukaemia | Diabetes |
| Allergy to house dust mite | Basal cell carcinoma | |
| Allergy/ hypersensitivity/ anaphylaxis | Bladder cancer | |
| Asthma | Brain cancer / primary malignant brain tumour | |
| Blistering/ desquamating skin disorder | Breast cancer | |
| Contact dermatitis | Cancer of lip/ mouth/ pharynx/ oral cavity | |
| Crohn's disease | Cervical cancer | |
| Eczema/ dermatitis | Chronic lymphocytic | |
| Food intolerance | Chronic myeloid | |
| Hay fever/ allergic rhinitis | CIN/ pre-cancer cells cervix | |
| Psoriasis | Colon cancer/ sigmoid cancer | |
| Ulcerative colitis | Ear cancer | |
| | Eye and/ or adnexal cancer | |
| | Female genital tract cancer | |
| | Hodgkin's lymphoma / Hodgkin's disease | |
| | Kidney/ renal cell cancer | |
| | Large bowel cancer/ colorectal cancer | |
| | Leukaemia | |
| | Liver/ hepatocellular cancer | |
| | Lung cancer | |
| | Malignant lymph node, unspecified | |
| | Malignant melanoma | |
| | Meningeal cancer / malignant meningioma | |
| | Non-Hodgkin's lymphoma | |
| | Non-melanoma skin cancer | |
| | Ovarian cancer | |
| | Parotid gland cancer | |
| | Peripheral nerve/ autonomic nerve cancer | |
| | Primary bone cancer | |
| | Retinoblastoma | |
| | Sarcoma/ fibrosarcoma | |
| | Skin cancer | |
| | Small intestine/ small bowel cancer | |
| | Spinal cord or cranial nerve cancer | |
| | Thyroid cancer | |
| | Unclassifiable | |
| | Uterine/ endometrial cancer | |
| | Vaginal cancer | |

| Gynaecological problems N=660 | Infections N=10,164 | Migraine/ headache N=4,667 |
|---|---|---|
| Abnormal smear (cervix) | Acute infective polyneuritis/ Guillain-Barre | Migraine |
| Cervical erosion | syndrome | Headaches (not migraine) |
| Cervical polyps | Appendicitis | |
| Cervical problem | Blepharitis/ eyelid infection | |
| Dysmenorrhoea / dysmenorrhea | Bronchitis | |
| Ectopic pregnancy | Cellulitis | |
| Female infertility | Chickenpox | |
| Fibrocystic disease | Dengue fever | |
| Gynaecological disorder (not cancer) | Diphtheria | |
| Menopausal symptoms / menopause | Encephalitis | |
| Menorrhagia (unknown cause) | Gastroenteritis/dysentery | |
| Miscarriage | Helicobacter pylori | |
| Ovarian cyst or cysts | Hepatitis | |
| Ovarian problem | Hepatitis A | |
| Pelvic inflammatory disease/PID | Hepatitis B | |
| Polycystic ovaries/ polycystic ovarian | Hepatitis C | |
| syndrome | Herpes simplex | |
| Uterine fibroids | Infection of nervous system | |
| Uterine polyps | Infectious mononucleosis/ glandular fever/ | |
| Vaginal prolapse/ uterine prolapse | Epstein Barr virus (EBV) | |
| | Infective/ viral hepatitis | |
| | Lung abscess | |
| | Malaria | |
| | Measles/ morbillivirus | |
| | Meningitis | |
| | Mumps/ epidemic parotitis | |
| | Non-infective hepatitis | |
| | Pericarditis | |
| | Peritonitis | |
| | Pneumonia | |
| | Polio/ poliomyelitis | |
| | Rheumatic fever | |
| | Rubella/ German measles | |
| | Scarlet fever/ scarlatina | |
| | Schistosomiasis/ bilharzia | |
| | Septicaemia/ sepsis | |
| | Shingles | |
| | Tonsillitis | |
| | Tuberculosis (TB) | |
| | Typhoid fever | |
| | Whooping cough/ pertussis | |
| | Yellow fever | |

*N* is number of women of white ethnicity recorded with illness. Note: each person can have more than one illness.


## References (Supplementary Methods)

1       Allen, N. *et al.* UK Biobank: Current status and what it means for epidemiology. *Health Policy and Technology* **1**, 123-126, doi:http://dx.doi.org/10.1016/j.hlpt.2012.07.003 (2012).

# Supplementary Results

**Supplementary Figure 1.** Distribution of age at recruitment in early menopause cases and controls.
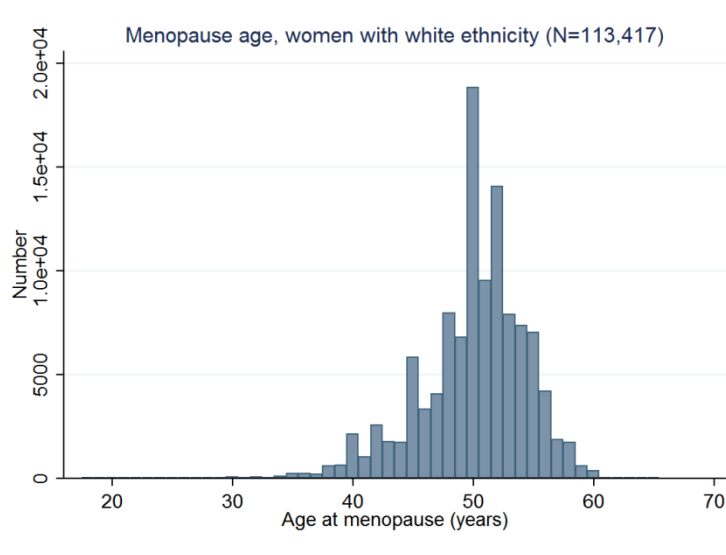
(i) All cohort.
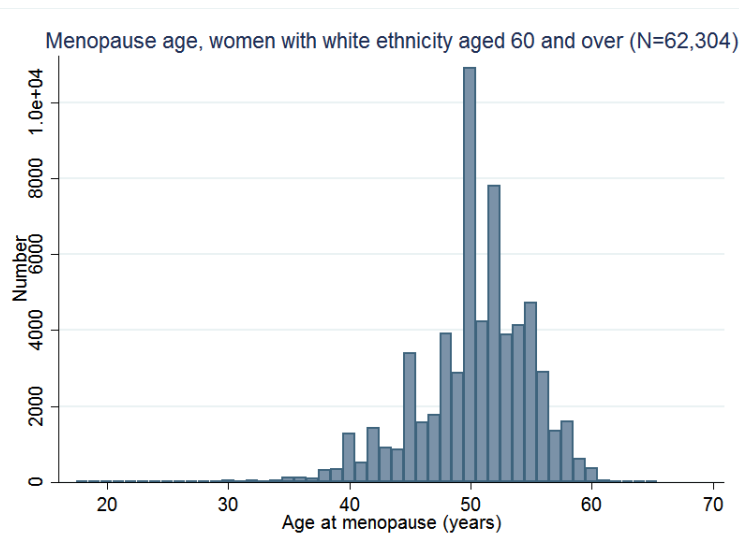


(ii) Aged 60 and over at recruitment.

**Supplementary Figure 2.** Distribution of age at menopause in all women and women aged 60 and over at recruitment.

(i) All cohort.



Median=50 years. Interquartile range (48,53). Mean=50.0 years. Range (18,65).

(ii) Aged 60 and over at recruitment.



Median=51 years. Interquartile range (48,54). Mean=50.4 years. Range (18,65).