HSC(6) 29-23 PTN 7

Division of Psychological Medicine and Clinical Neurosciences

Yr Isadran Meddygaeth Seciolegol a Niwrowyddorau Clinigol

Cardiff University
Hadyn Ellis Building
Maindy Road
Cardiff CF24 4HQ
Email:
psychmedadminsupport@cf.ac.uk
www.cardiff.ac.uk

Prifysgol Caerdydd
Adeilad Hadyn Ellis
Heol Maindy
Caerdydd CF24 4HQ
E-bost:
psychmedadminsupport@cf.ac.uk
www.caerdydd.ac.uk

Russell George MS
Health and Social Care Committee
Welsh Parliament

Cardiff September 11th 2023

Dear Mr George

Thank you for your letter, asking for details on the issues I believe are limiting the use of SAIL in some areas of menopause research.

In summary: the limitations presented by SAIL are those of most databanks based on (electronical) health records. SAIL can still be used to explore some questions around reproductive aging, for example, the effects of HRT on long term outcomes.

Background and research context

I have set up and run the only reproductive mental health clinical and research programme in the UK. The programme includes a UK-wide second opinion clinic (run jointly by Cardiff University and Cardiff and Vale University Health Board) and both basic and clinical research. Research focusses on the effects of sex, gender, and reproductive events on the brain and on severe mental illness. With grants from the European Research Council (grant number 947763) and the Medical Research Council (grant number MR/W004658/1), I am studying with my team the association between reproductive aging (i.e. perimenopause and menopause) and severe mental illness.

We are currently focussing on two research questions (which surprisingly have never been addressed):

1) Is the perimenopause a period of increased risk of mental illness?
2) If so, what does make some people more likely than others to developed mental illness at this time?

Variables considered and availability in SAIL:

- **Timing of the final menstrual period -** Menopause is defined by the point in time 12 months after a woman's last period (ref: https://www.nia.nih.gov/health/what-menopause)[1]. Information on whether a person has experienced their final menstrual period is essential for any menopause-related research aimed to assess the impact of the menopause at a population level. Our research has recently "highlight[ed] the importance of considering the final menstrual period rather than chronological age. [..] Given the 20-year range variation in age at final menstrual period, inferring age at menopause on solely chronological age can lead to errors and, in research, to false negatives".

- **Menopausal and other perimenopausal disorders** - The terminology reflects the corresponding International Classification of Diseases code (N95). SAIL would record the presence of menopausal and other perimenopausal disorders if they emerge and they are reported during a GP appointment. If people, as increasingly often happens, seek private healthcare for menopause related issues, this would not be recorded. Moreover, the N95 code 1) covers only some symptoms, mostly physical, and not psychiatric disorders 2) does not specify the timing in relation to the final menstrual period 3) is recorded only if the clinician associates the issues presented by the patient with their menopause status. For example (based on my clinical practice), a first manic episode requiring hospital admission happening in the perimenopause would not be recorded as associated to the perimenopause. Of note, by definition, it is possible to establish the menopause status only one year after the final menstrual

[1] For an international consensus on assessing reproductive aging in research and clinical contexts, please see: Harlow SD, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. Menopause. 2012 Apr;19(4):387-95. doi: 10.1097/gme.0b013e31824d8f40. PMID: 22343510; PMCID: PMC3340903.

period has occurred. In other words: it is not known whether a period is the final menstrual period until 12 months after it has occurred.

Discussion

The limitations presented here are shared by most databanks based on (electronical) health records. When we sought to find the best source of data for our study, we considered accessing national records from countries outside Wales. None of them, however, provided the information on menopause we needed. Large research cohorts with a wealth of menopause related data such as the SWAN cohort in the US (https://www.swanstudy.org) are not large enough to reliably capture severe mental illness. The SWAN study, for example, includes only 3,302 people.

The most useful resource we found to address our research questions was UK Biobank, because it includes a specific variable on age at the final menstrual period. Such variable was collected by asking directly to 177,882 people "How old were you when your periods stopped?" (https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=3581). Using such resource, we have been able to demonstrate for the first time a specific effect of the perimenopause on the risk of severe mental illness in people without history of mental disorders. According to our research, women from the general population have an over 2-fold (2.3, 95% CI 1·43–3·81) increased risk of developing mania[2] in the four years surrounding the final menstrual period compared to the late reproductive stage.

I have not submitted any data request to SAIL, as it does not include some key variables I need for my research. I therefore don't know how many people included in SAIL have information on N95 disorders or how many have been prescribed hormone replacement therapy (HRT). Such data, which could be requested to SAIL, may provide a more

[2] Mania, as defined by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (https://icd.who.int/browse10/2019/en#/F30-F39), is a disorder characterized by a persistent elevation of mood, out of keeping with the patient's circumstances and may vary from carefree joviality to almost uncontrollable excitement. Elation is accompanied by increased energy, resulting in overactivity, pressure of speech, and a decreased need for sleep. Attention cannot be sustained, and there is often marked distractibility. Self-esteem is often inflated with grandiose ideas and overconfidence. Loss of normal social inhibitions may result in behaviour that is reckless, foolhardy, or inappropriate to the circumstances, and out of character. In some cases, delusions (usually grandiose) or hallucinations (usually of voices speaking directly to the patient) are present, or the excitement, excessive motor activity, and flight of ideas are so extreme that the subject is incomprehensible or inaccessible to ordinary communication.

comprehensive picture on the use of SAIL in menopause research. Such assessment would need to integrate estimates and information on private prescriptions of HRT and, more broadly, on people who are using private health care instead of the national health system (NHS). For example, there are five private menopause clinics accredited by the British Menopause Society only within Cardiff. Information on private service users is in fact important to establish the burden of the issues and the representativeness of SAIL data on menopause. If the number of people getting private menopause health care is high, the estimates derived from NHS data (a.k.a. SAIL) may be biased.

I hope this information is helpful.

Please don't hesitate to contact me if you have any questions.

Yours sincerely,

Arianna Di Florio, MD, PhD
Professor of Psychiatry, Cardiff University
Honorary Consultant Psychiatry, Cardiff and Vale University Health Board