Developing a phenotype algorithm to identify natural menopausal women in secondary data: A multi-country, large-scale OHDSI network study

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Background

Approximately 47 million women enter menopause each year globally, with women spending around a third of their lives in the postmenopausal period.[1] Up to 80% of menopausal women will experience vasomotor symptoms (VMS), including hot flashes, which can be debilitating and can affect their daily functioning and quality of life.[2]

Menopause journeys of women in the real-world are under-researched and reported epidemiological data for menopausal symptoms such as VMS vary widely.[3,4] This may be explained by several factors such as study design limitations observed in cross-sectional studies with inconsistent symptom definitions or demographic factors, cultural differences, and healthcare systems.[4-7]

Large anonymized datasets, including administrative claims and electronic health records (EHRs), enable generating simultaneous standardized real-world data (RWD),[8,9] which can contextualize the variability of evidence on menopause. However, several methodological issues exist with these secondary data, including:

- diagnostic challenges and under-reporting by patients, impacting reported incidence of menopause and related symptoms,
- inconsistency and lack of specificity in medical coding through the chronic course of symptoms,
- variation in algorithms used to identify menopause in RWD,
- selection bias toward women with access to healthcare and seeking medical treatment for their symptoms.

This study aims to identify women in natural menopause by developing a common phenotype algorithm across multiple data sources and countries, which can be used for future evidence generation in menopause in the absence of a gold standard definition.

Methods

This was a retrospective, multi-country observational cohort study using administrative claims and EHR databases including more than 312 million women from five countries: France, Germany, Japan, the United Kingdom (UK), and the United States. (US) Databases were standardized to the Observational Medical Outcomes Partnership (OMOP) common data model, which enables the use of standardized analytics and tools through the harmonization of data structure and terminology.

To build different phenotype algorithms, operational definitions listed in published literature and/or medical codes selected by medical experts and epidemiologists based on coding systems in each data source (e.g., Read, ICD-10-CM, NDC) were used. All codes native to a specific data source were mapped to standard OMOP vocabulary.

Fifteen cohort definitions with differing inclusion and exclusion criteria, as outlined in Table 1, were evaluated to define natural menopausal women aged 40-65 from January 2009 up to the latest available date in each database.

For cohort set 1, the likelihood of a medical code to indicate menopause determined *possible* or *probable* diagnosis: for example, the more specific 'Menopausal problem' code is included as *probable* and 'secondary amenorrhea' as *possible*. For cohort set 2 and 3, menopause diagnosis was combined with symptoms or medication use (hormonal and non-hormonal), respectively. Symptoms were categorized based on the presence of a menopause descriptor in medical codes [e.g., 'Menopausal flushing' (symptom *with* menopause descriptor) or 'Hot sweats' (symptom *without* menopause descriptor)].

Table 1. Cohort definitions to identify natural menopause women with differing inclusion and exclusion criteria.

		Inclusion criteria						Exclusion criteria		
		Menopause diagnosis		Symptoms present		Treatment				
	Age 40-65	More specific	Less specific	More specific	Less specific	More specific	Less specific	Prior hormonal or non-hormonal treatment	Prior record of bilateral oophorectomy or radical hysterectomy	Prior exposure to an endocrine adjuvant therapy
		Possible	Probable	With menopause descriptor	Without menopause descriptor	Hormonal	Non-hormonal			
Women aged 40-65	x								x	x
Cohort set 1: Add Diagnosis	x		x						x	x
	x	x							x	x
	x		x					x	x	x
	x	x						x	x	x
Cohort set 2: Add Symptoms	x		x	x					x	x
	x	x		x	x				x	x
	x		x	x				x	x	x
	x	x		x	x			x	x	x
Cohort set 3: Add Treatment	x		x	x		x	x		x	x
	x	x		x	x	x	x		x	x
	x		x	x		x			x	x
	x	x		x	x	x			x	x
	x		x	x			x		x	x
	x	x		x	x		x		x	x

Note: All permutations and combinations of inclusion criteria (x) are assigned using 'OR' logic (except age).

This was a descriptive study without formal hypothesis testing. Patient counts were calculated in each database matching each cohort definition. Study results were aggregated, without identifiable individual patients. Analyses were performed using the R package 'VMSChar' developed by Bayer using the OHDSI Cohort Diagnostics library.[10] Baseline demographics and comorbidities were extracted using an optimized SQL extraction script based on 'FeatureExtraction' package[11] and reported using medians for non-normally distributed continuous variables and proportions for categorical variables. Manual comparison of age distributions, comorbidities and medication use were made for each phenotype algorithm. PheValuator was used to support the review of results.[12]

Results

Results are presented for IBM® MarketScan® (US), CPRD Aurum (UK) and Disease Analyzer (DA) Germany. Phenotypes were evaluated upon their representativeness of a natural menopausal cohort with respect to age distribution, medication use and comorbidities with reference to the literature.[13,14]

There were between 3,746,801 and 16,076,243 women aged 40-65 with no other inclusion criteria in these databases, excluding those with at least one record of bilateral oophorectomy or radical hysterectomy at any time prior to cohort entry and endocrine

adjuvant therapy in the year prior. Having an inclusion criterion of '*possible* menopause diagnosis or symptoms *with/without* menopause descriptors' resulted in a flatter age distribution compared to a more specific phenotype definition, which generated a distribution more representative of a menopausal cohort peaking at age 50-54 (Figure 1). Comorbidities and medication use were also more consistent with baseline characteristics of natural menopausal women when the phenotype algorithm included '*possible* menopause or symptoms *with* menopause descriptors' (data not shown).

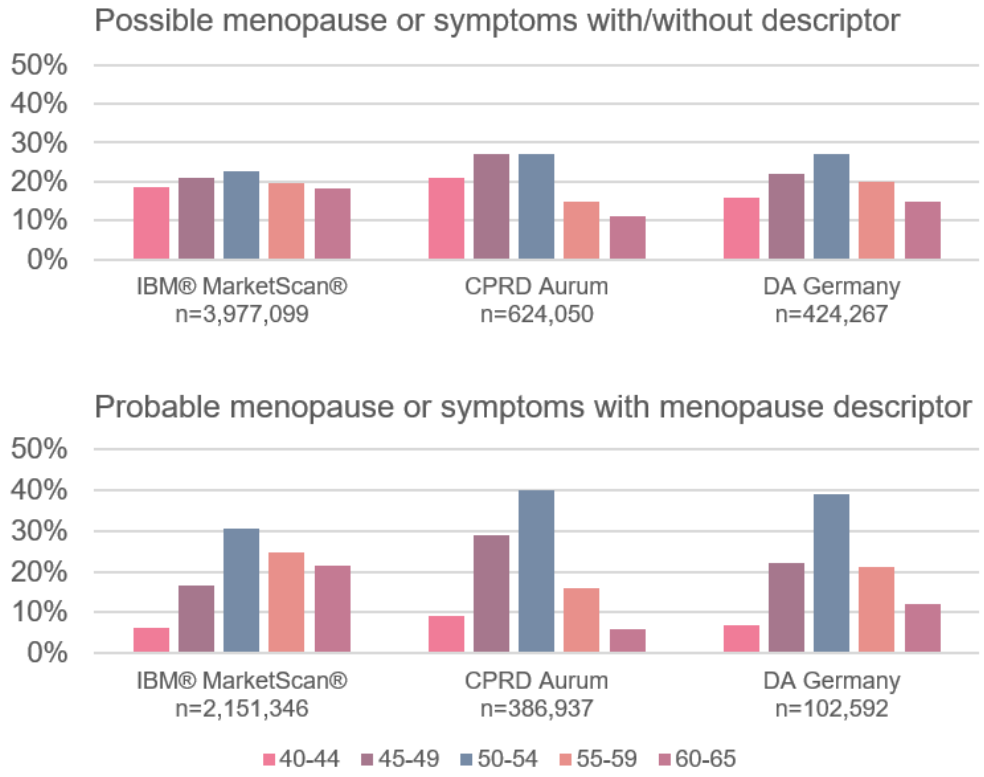

Figure 1. Age distributions at the time of cohort entry in Cohort Set 2 when the phenotype is defined by '*probable* menopause diagnosis or symptoms *with* menopause descriptor' (more specific) and '*possible* menopause diagnosis or symptoms *with/without* menopause descriptor' (less specific)

Several PheValuator implementations were tested and yielded comparable results to manual review in terms of selecting the most suitable cohort definitions. Performance estimates were consistently low for sensitivity and positive predictive value and high for specificity and negative predictive value.

Conclusions

We described a large simultaneous multi-country cohort study of VMS in menopausal women using large-scale network analytics to define a cohort of natural menopausal women. Incorporation of more specific criteria resulted in demographic and clinical characteristics to shift towards a distribution more representative of a menopausal population aligned with literature.[13,14] We conclude that the phenotype algorithm with a more specific cohort definition of probable menopause diagnosis and symptoms with menopause descriptor is preferable to define natural menopausal women in real-world data.

Study strengths include the development of multiple target cohorts based on a range of definitions in secondary data across multiple countries that enable observation of differences in real-world coding patterns and clinical practice specifically for menopause.[8,9,15-18] However, limitations due to selection bias, under-reporting of symptoms by patients, suboptimal coding practices as well as challenges in the accurate assessment of menopause need to be considered. Identified menopausal women with the preferred phenotype algorithm are likely to be more symptomatic and have more interaction with the healthcare system.

Results of our study will enable working towards a standard definition for identifying natural menopause and relevant symptoms in real-world secondary databases by establishing consistent phenotype algorithm. The study will form the basis of subsequent research in treatment pathways for management of menopausal symptoms, which is currently undergoing.

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