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The Wales Multi-morbidity e-Cohort (WMC): data sources and methods to construct a population-based research platform to investigate multi-morbidity.

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ABSTRACT

Introduction

Multi-morbidity is widely recognised as the presence of two or more concurrent long-term conditions, but remains a poorly understood global issue despite increasing in prevalence.

We have created the Wales Multi-morbidity e-Cohort (WMC) to provide an accessible research ready data asset to further the understanding of multi-morbidity. Our objectives are to create a platform to support research which would help to understand prevalence, trajectories and determinants in multi-morbidity, characterise clusters that lead to highest burden on individuals and healthcare services, and evaluate and provide new multi-morbidity phenotypes and algorithms to the NHS and research communities to support prevention, healthcare planning and the management of individuals with multi-morbidity.

Methods and analysis

The WMC has been created and derived from multi-sourced demographic, administrative and electronic health record (EHR) data relating to the Welsh population in the Secure Anonymised Information Linkage (SAIL) Databank. The WMC consists of 2.9 million people alive and living in Wales on the 1st January 2000 with follow up until 31st December 2019, Welsh residency break or death. Published comorbidity indices and phenotype code lists will be used to measure and conceptualise multi-morbidity.

Study outcomes will include: a) a description of multi-morbidity using published data phenotype algorithms/ontologies, b) investigation of the associations between baseline demographic factors and multi-morbidity c) identification of temporal trajectories of clusters of conditions and multi-morbidity, d) investigation of multi-morbidity clusters with poor outcomes such as mortality and high healthcare service utilisation.

Ethics and dissemination

The SAIL Databank independent Information Governance Review Panel (IGRP) has approved this study (SAIL Project: 0911). Study findings will be presented to policy groups, public meetings, national and international conferences, and published in peer-reviewed journals.

Strengths and limitations of this study

- Creation and access to a multi-sourced population based, deeply phenotyped e-cohort.
- Future use of this resource removes need for data management and cleaning of source data, accelerating research and which could also support efforts for reproducibility of results.
- Variety of individual and household level data on demography, health status, health care utilisation, both primary and secondary healthcare, and mortality to support a wide range of analytical approaches to addressing scientific questions.
- Input from multiple disciplines and institutions from across all four nations of the United Kingdom to help understand, measure and address multi-morbidity.
- Routine data does not capture data on some important aspects, such as quality of life.

INTRODUCTION

Multi-morbidity is defined by the UK's Academy of Medical Sciences (AMS) and the World Health Organisation as the presence of two or more concurrent long-term conditions, which is a global and growing phenomenon.[1,2] Multi-morbidity is more prevalent in older individuals and associated with high healthcare utilisation and mortality, but with large numbers of patients of all age suffering from multi-morbidity.[3-6] With an aging population, it is estimated that two in three people in England aged 65 years or over will experience multi-morbidity by 2035 and nearly one fifth will have complex multi-morbidity (4 or more conditions).[7]

Much of what is known about multi-morbidity is based on a limited and fragmented knowledge base, largely derived from studies of older people in high-income countries or hospital populations.[1,8] The 2018 AMS report concluded that multi-morbidity is an unhelpful term implying random assortment of disease when it often refers to clusters of specific diseases. Once identified, these disease clusters can be addressed specifically through research, healthcare policy development and service delivery.[1,9] The identification of previously unrecognised disease clusters may also provide biological and clinical insights into their aetiology, prevention and treatment. The AMS report identified specific research gaps and proposed a list of priorities (Figure 1). Several can be addressed through a combination of health data science, epidemiology and statistics, and by exploiting the potential from creating deeply phenotyped cohorts from population and clinical data sources.

Figure 1: The Academy of Medical Sciences identified research gaps.

- The scale and nature of multi-morbidity and how it is changing over time.
- Which clusters of conditions cause the biggest problems for patients.
- The causes of the most common clusters including links with sex, ethnicity, income and lifestyle.
- The best ways to prevent the patients developing multi-morbidity, and whether this requires different approaches to just preventing individual conditions.
- How doctors can increase the benefits and reduce the risks of treatment for patients with multi-morbidity.
- How to organise healthcare systems to deal with multi-morbidity more effectively and how best to use digital technology in caring for patients.

Responding to this agenda, we created a privacy protecting total population electronic cohort - the Wales Multi-morbidity e-Cohort (WMC) - as a platform to study these issues in depth, collaborating with scientists from many different institutions and disciplines, clinicians, and members of the public from across the UK to create a broader team science approach.

The objectives of this work are to understand prevalence, trajectories and determinants of multi-morbidity, and identify clusters causing the greatest health care burden. The WMC will also contribute data on incidence, prevalence and burden to the Global Burden of Diseases Study,[10,11] and provide new multi-morbidity phenotypes to e-cohorts with local participants, and phenotyping algorithms to many e-cohorts that utilise routine data.[12]

We expect that findings from these analyses will provide evidence to health policy leads in order to support prevention and the complex healthcare planning and management of multi-morbid individuals. Members of the public are embedded in the research team to ensure the resource focuses on issues of concern to the public.

This paper describes the creation of the WMC and the statistical approaches that will be developed to support the diverse research objectives.

METHODS

The WMC was developed by linking multiple routinely collected population and clinical data sources on the population of Wales from 2000-2019. We used the privacy-protecting Secure Anonymised Information Linkage (SAIL) Databank, to contribute to the Health Data Research UK National Implementation Multi-morbidity Resource (HNIMR) project, and extended to 2020 for the MRC funded Welsh Multi-morbidity Machine Learning (WMML) project .[13,14] SAIL is one of the most comprehensive, privacy protecting, linked data Trusted Research Environments (TRE) in the UK. SAIL utilising data from many different sources and providing linkage at individual and household level.[15] It has supported many different study designs, including, large-scale community-based or clinical condition-based observational studies, disease surveillance, evaluation of natural experiments of environmental interventions, embedded trials, and the Dementias Platform UK.[16-23]

Cohort design and characteristics

WMC is a clearly defined complete population cohort. Cohort entry includes all residents in Wales, alive and living on the 1st January 2000. Cohort censorship was defined by the first date of migration out of Wales/residency break, death or the study endpoint on 31st December 2019 (Figure 2). Within these constraints, the cohort is designed to be without selection bias and to achieve complete follow-up. WMC also provides a fully generalisable population sample against which findings from more selected samples may be compared.

The WMC contains 2,902,101 individuals aged 0-99 at cohort start date with 46 million person years of follow up available (Table 1, Figures 3 & 4, Appendix Table A1 & A2). Individuals have a minimum of 1-day follow up (cohort end date = 2nd January 2000) and maximum of 20-years of follow up (cohort end date = 31st December 2019).

Table 1: WMC baseline demographics

WMC characteristics	n	%
Cohort size	2,902,101	100
Full coverage (01-01-2000 – 31-12-2019)	1,714,484	59.08
Residency break/Emigration	643,472	22.17
Mortality	544,145	18.75
Primary care data available	2,470,874	85.14
Care home residency at cohort end	97,006	3.34
Mean age in years (range) at cohort start	39 (0-99)	
Sex		
Female	1,472,113	50.60
Male	1,436,988	49.40
WIMD 2011 Quintile at cohort start		
1. Most Deprived	605,203	20.85
2	589,479	20.31
3	584,039	20.12
4	557,319	19.20
5. Least Deprived	566,061	19.51

The Heatmap in Figure 4 visualises the person years of follow up by age, sex and area level deprivation. The more years of follow up available the darker the colour. Age is calculated at the cohort start, therefore, younger individuals will have more years of available follow up compared to older individuals. On average, there are less person years of follow up available for the least deprived 15-24 year olds compared to their respective age group in other areas of Wales.

Data Sources

The WMC has utilised and combined anonymised health, social and environmental data held within the SAIL Databank (www.saildatabank.com).

The baseline characteristics for the WMC have been created using the Welsh Demographic Service Dataset (WDSD) and the Annual District Death Extract (ADDE) mortality registry data from the Office for National Statistics. The WDSD contains administrative information concerning the resident population of Wales that are registered to a Welsh General Practice, a free to use National Health Service (NHS) system at the point of primary care registration in the UK. The ADDE data contains information about the dates and causes of all deaths relating to residents in Wales, including those that died outside of Wales. SAIL holds GP data for approximately 80% of the population with coverage extending to all local authorities in Wales. The Welsh Longitudinal General Practice (WLGP) data will be used to identify the sub-population of individuals who are registered to a practice providing data to SAIL to identify which individuals have GP data present and avoid underestimation of conditions or severity of conditions not managed through hospital admission.

The Welsh Health Survey Dataset (WHSD) and the National Survey for Wales Dataset (NSWD) with data on wellbeing measures, social class, education, housing and wealth are available for 9,905 and 33,295 cohort participants respectively. [24]

Anonymised Linkage Fields

Linkage fields are used to anonymously link between data sources in the SAIL Databank and have been previously described elsewhere.[13,14,25] SAIL utilises a multiple encryption system in which a trusted third party, the National Health Service (NHS) Wales Informatics Service (NWIS), uniquely matches identities (NHS number, name, date of birth, and residential address/UPRN) and replaces these with unique identifiers. For individuals this is called an Anonymised Linkage Field (ALF) and Residential Anonymised Linkage Field (RALF) for pseudonymised residences before uploading data to SAIL.

Demographic Data

The cohort includes the following variables: Anonymised Linkage Field (ALF), age in years, sex, date of death, date of movement out of Wales, RALF at both cohort inception and cohort end and Care Home Anonymised Linkage Fields (CHALFs) at cohort end date. The CHALF was derived from a data extract from Care Inspectorate Wales in 2020 for all adult care home settings.[18] Geographical variables associated with the RALF and CHALF include Lower layer Super Output Area (LSOA) 2001 at cohort inception and LSOA 2011 at cohort end. These have been mapped to the Welsh Index of Multiple Deprivation (WIMD) version 2011 and 2019 respectively to derive socioeconomic deprivation quintiles and urban/rurality categories.[26,27]

Health Data

All admissions to hospital (inclusive of critical care admissions), outpatient, Emergency Department attendances treated in NHS hospitals as well as disease registries and laboratory test results data are available for cohort participants, GP data for diagnoses and treatments from SAIL providing practices are data for approximately 80% of the population.[28]

All relevant health events recorded in clinical data sources will be joined onto the WMC to identify diagnosis of conditions, treatments and various significant heath events that occur across multi-sourced linked heath data per person (Table 2 &Figure 5).

Table 2: Clinical data sources available for the WMC.

Data source	Period covered	Number and percentage of WMC individuals with data
Critical Care Data Set (CCDS)	01-01-2007 – 31-12-2019	79,521 (2.7%)
Welsh Cancer Incidence Surveillance Unit (WCISU)	01-01-2000 – 31-12-2016	328,792 (11.3%)
Welsh Results Reporting Services (WRRS)	01-01-2015 – 10-12-2018	1,540,754 (53.1%)
Emergency Department Data Set (EDDS)	01-04-2009 – 31-12-2019	1,579,665 (54.4%)
Patient Episode Database for Wales (PEDW)	01-01-2000 – 31-12-2019	2,129,384 (73.4%)
Out Patient Dataset for Wales (OPDW)	01-04-2004 – 31-12-2019	2,177,081 (75.0%)
Welsh Longitudinal General Practice (WLGP)	01-01-2000 – 31-12-2019	2,400,313 (82.7%)
Please note clinical data sources will be updated on a monthly/quarterly basis		

The Upset plot in Figure 5 demonstrates the number of WMC participants that have interacted with the various health care settings from 1st January 2000 to their cohort censorship end date.[29] For example, 780,830 (26.9%) individuals have utilised GP, inpatient, outpatient and emergency department services as well as had at least one laboratory test within their WMC coverage.

Phenotyping the e-cohort

Published comorbidity indices and phenotype code lists (International Classification of Diseases 10th revision (ICD-10), OPCS Classification of Interventions and Procedures version 4 (OPCS4) and primary care Read Codes version 2) will be used to measure and conceptualise multi-morbidity. These include those created by: CALIBER initiative; Charlson Comorbidity Index; Common Mental Disorders (CMD); Elixhauser Comorbidity

Index; Global Burden of Disease Study; and the NHS Quality and Outcomes Framework (QOF).[30-41] Diagnostic codes relating to HIV will not be included in any outputs to conform with SAIL policies. They are part of the list of redacted codes not allowed to be used for research using the data.[42] All ICD-10 and OPCS4 codes provided at the three character level were expanded to include all children terms.

1. CALIBER

Phenotyping algorithms created from the CALIBER resource using ICD-10, OPCS4 and Read Codes will be utilised to identify 300 physical and mental health conditions recorded in both primary and secondary healthcare.[31,39]

There are 1,645 distinct ICD-10 codes (at three and four-character level) for 300 conditions, however, when capturing all ICD-10 codes to include variation in coding entry (e.g. C796– instead of C796) and expanding the code list to the four-character level (F200 instead of F20), there are 3,702 distinct ICD-10 codes (at the four-character level) recorded in the inpatient data. This is important to note as to link solely on standardised codes would result in loss of information and potential reporting of false negatives.

There are 587 distinct OPCS4 codes (at three and four-character level) for 28 conditions and 8,588 distinct Read Codes (at the five-character level) for 275 conditions.

2. Charlson Comorbidity Index

The Aylin and Bottle Charlson amended ICD-10 code list will be utilised for inpatient diagnosis and the Metcalfe et al (2019) Charlson Read Code list will be utilised for primary care recorded diagnosis.[32,33]

The ICD-10 codes have been taken from the pool of diagnosis codes recorded within hospital admissions data, containing 1,024 distinct codes (at the four-character level) for 16 conditions. The GP data contains 4,545 distinct Read Codes at the five-character level.

3. Common Mental Disorders (CMD)

The John et al, 2016 validated algorithm will be used to identify CMD in GP data.[30,40,41] The algorithm has utilised a combination of diagnosis, treatment and symptoms Read Codes in identifying CMD. Individuals with CMD are identified as either having a historical diagnosis code, currently treated or, having a current diagnosis/current symptom code. There are 89 distinct diagnosis codes, 15 symptom codes and 601 treatment codes.

4. Elixhauser Comorbidity Index

The Quan et al (2005) Elixhauser ICD-10 code list will be utilised for inpatient diagnosis and the Metcalfe et al (2019) Elixhauser Read Code list will be utilised for primary care recorded diagnosis.[33,34]

The ICD-10 codes have been taken from the pool of diagnosis codes recorded within hospital admissions data and contains 1,404 distinct codes (at the four-character level) for 30 conditions. The General practice data contains 6,074 distinct Read codes at the five-character level.

5. Global Burden of Disease (GBD) Study

The GBD 2019 ICD-10 codes will be used to identify 130 health conditions in secondary healthcare data. There are 3,497 distinct ICD-10 codes at the three and four-character level.[38]

6. Quality Outcome Framework (QOF)

The QOF conditions business rule V38 will be used to identify 18 health conditions in primary care data.[35] The 18 conditions are asthma, atrial fibrillation, obesity, coronary heart disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, dementia, depression, diabetes, epilepsy, heart failure, hypertension, learning difficulties, peripheral arterial disease, rheumatoid arthritis, serious mental illness and stroke. There are 2,275 distinct Read Codes available at the five-character level for the 18 QOF conditions.

Statistical analysis

The WMC provides an accessible research ready data asset to further understanding of multi-morbidity through the use of bio-statistical and machine learning approaches. Our collaborative team will work across a number of projects to develop and evaluate statistical and machine learning algorithms to address the following broad analytical challenges:

- What is the prevalence of multi-morbidity in the WMC, and how does prevalence of multi-morbidity change over time?
- What are common clusters of multi-morbidity in the WMC, and how do they correspond to or differ from, common clusters of multi-morbidity identified in other datasets?
- Which clusters of multi-morbidity occur less frequently than one would expect based on the prevalence of their constituent conditions?
- How does multi-morbidity develop across the life course (i.e. trajectories)?
- What are the biological, psychological, and social determinants of different clusters and trajectories of multi-morbidity?
- Which clusters and trajectories of multi-morbidity are associated with poor health outcomes?
- Which clusters and trajectories of multi-morbidity are associated with high service utilisation?
- Does multi-morbidity in specific groups (e.g. patients with musculoskeletal conditions) differ from multi-morbidity in general?

The overarching aim is to evaluate and provide new multi-morbidity phenotypes and algorithms to the NHS and research communities to support prevention, healthcare planning and the management of individuals with multi-morbidity.

We will draw upon both methods from statistics (e.g. regression analysis, longitudinal mixed models, multiple correspondence analysis, factor analysis [43], multi-state models, and latent class analysis) and machine learning (e.g. k-means clustering, semantic similarity clustering, market basket analysis, network models [44], and deep learning). We will use resampling methods to assess the stability of identified multi-morbidity clusters, and develop visualisation techniques to summarise multi-morbidity clusters and their associations with risk factors and outcomes.

Analyses will be coded in R, WinBUGS, and Python and made available to WMC users via a Git library to maximise transparency and reproducibility.[45]

Patient and public involvement

The proposal to develop WMC was submitted to the independent Information Governance Review Panel (IGRP) that includes members of the public (IGRP Project: 0911). We worked with this group to refine the study protocol. The scientific steering group includes two members of the public who have contributed to this paper. The HDR UK National Implementation Project Multi-morbidity Resource has a work package on PPI with a panel drawn from across the UK meeting to discuss the research work and feed into the research and dissemination plans.

Ethics and dissemination

The use of de-identified data in SAIL complies with National Research Ethics Service (NRES) guidance.[46] Applications to use data held within the SAIL Databank, an ISO: 27001 and UKSA DEA accredited TRE, must first be approved by the independent Information Governance Review Panel (IGRP). This panel contains individuals with expertise in data governance and protection, including the Chair of the Wales NRES Committee, Caldicott Guardians, and members of the public. WMC was approved by IGRP on 26th June 2019.

Findings from this study will be disseminated widely through a variety of routes, including to health policy and NHS leads across UK, the Academy of Medical Sciences and the Royal Colleges, as well as traditional scientific outlets. The team includes NHS clinicians and informaticians to allow for early NHS adoption of useful findings. Members of the public embedded in the team will create plain English summaries and lead at public facing meetings.

Contributors

Conceptualisation of study JL, AA, UA, GH, CM, DOR, RAL; data curation and analysis JL; original draft writing JL, review and editing of manuscript JL, AA, UA, GH, AAL, RB, JR, AW, RF, CM, CD, JPR, NP, CH, SD, RO, KRA, AJ, DOR, SR, MH, CPG, JD, CD,LC, JG, JC, AJB, RAL

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Disclaimer

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Competing interests

None declared.

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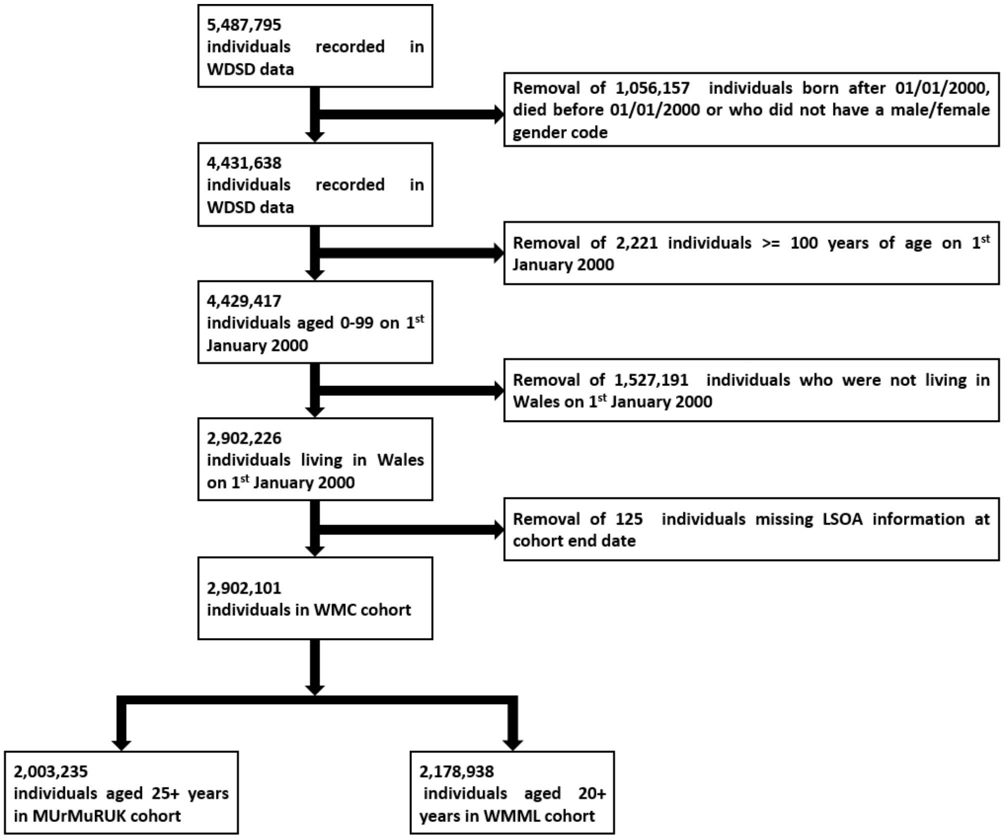

5,487,795 individuals recorded in WDSD data
Removal of 1,056,157 individuals born after 01/01/2000, died before 01/01/2000 or who did not have a male/female gender code
4,431,638 individuals recorded in WDSD data
Removal of 2,221 individuals >= 100 years of age on 1st January 2000
4,429,417 individuals aged 0-99 on 1st January 2000
Removal of 1,527,191 individuals who were not living in Wales on 1st January 2000
2,902,226 individuals living in Wales on 1st January 2000
Removal of 125 individuals missing LSOA information at cohort end date
2,902,101 individuals in WMC cohort
2,003,235 individuals aged 25+ years in MUrMuRUK cohort
2,178,938 individuals aged 20+ years in WMML cohort

Figure 2: WMC flow diagram, based on inclusion criteria.

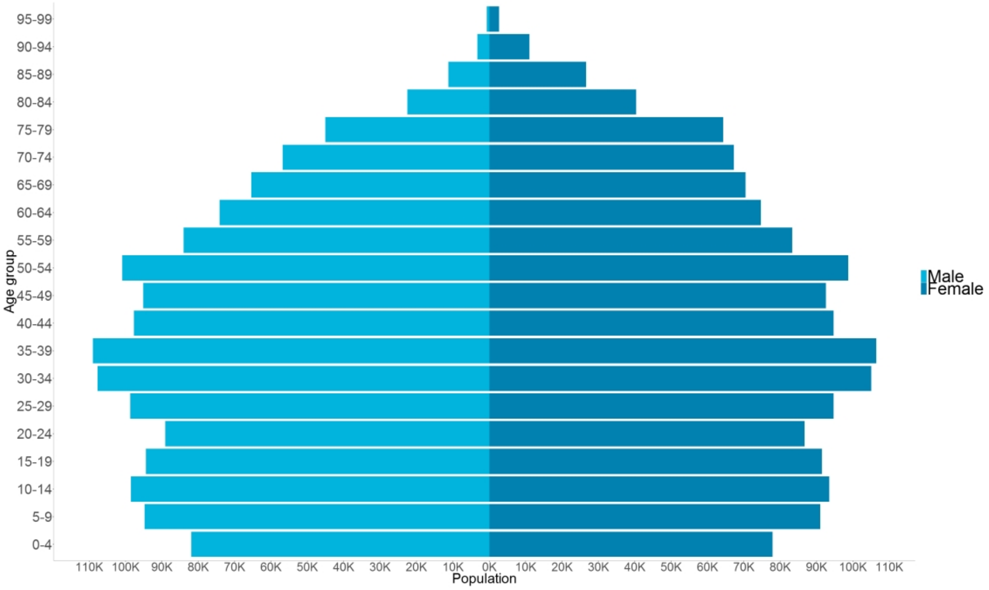


Figure 3: WMC pyramid for age (years) at cohort inception.

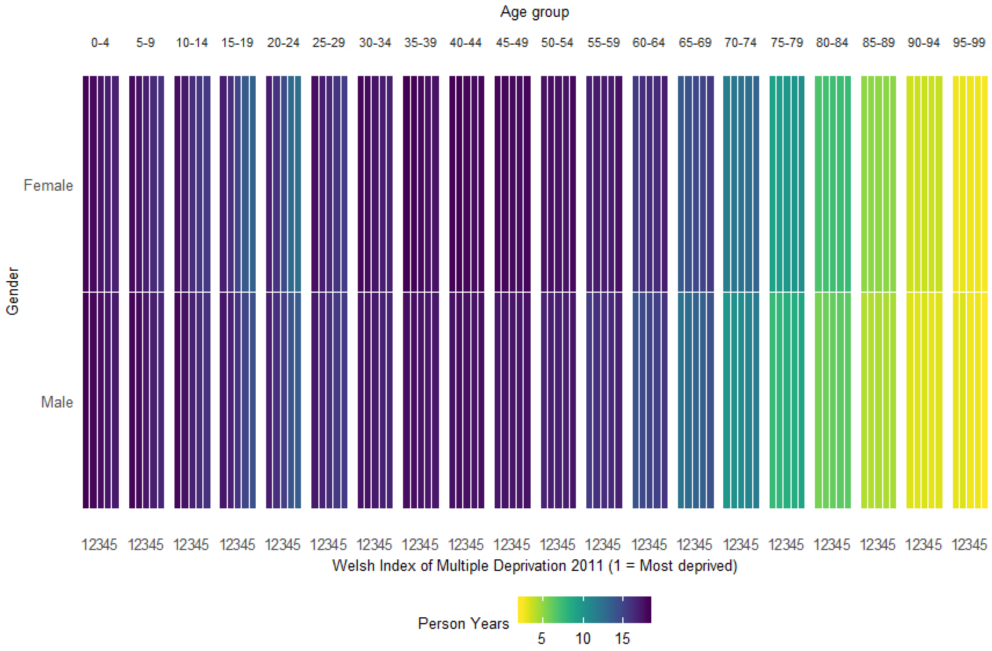
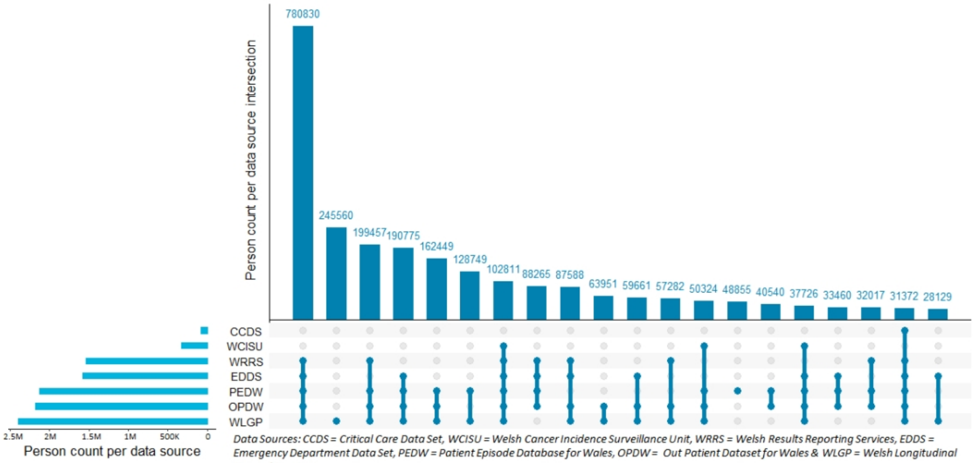


Figure 4: Heatmap of person years of WMC follow up, by age group, sex and area level deprivation at cohort inception.



Data Sources: CCDS = Critical Care Data Set, WCISU = Welsh Cancer Incidence Surveillance Unit, WRRS = Welsh Results Reporting Services, EDDS = Emergency Department Data Set, PEDW = Patient Episode Database for Wales, OPDW = Out Patient Dataset for Wales & WLGP = Welsh Longitudinal General Practice

Figure 5: Number of WMC individuals utilising healthcare services recorded in multi-source data sources, 20 most common combinations presented.

Appendix

Table A1: WMC participants categorised by age group and sex at cohort start

Age group	Sex	Count	Percentage
00-04	Male	81,915	2.82
00-04	Female	77,873	2.68
05-09	Male	94,737	3.26
05-09	Female	90,940	3.13
10-14	Male	98,466	3.39
10-14	Female	93,447	3.22
15-19	Male	94,345	3.25
15-19	Female	91,440	3.15
20-24	Male	89,037	3.07
20-24	Female	86,666	2.99
25-29	Male	98,622	3.40
25-29	Female	94,592	3.26
30-34	Male	107,671	3.71
30-34	Female	104,986	3.62
35-39	Male	108,964	3.75
35-39	Female	106,312	3.66
40-44	Male	97,637	3.36
40-44	Female	94,599	3.26
45-49	Male	95,071	3.28
45-49	Female	92,478	3.19
50-54	Male	100,866	3.48
50-54	Female	98,606	3.40
55-59	Male	83,949	2.89
55-59	Female	83,210	2.87
60-64	Male	74,115	2.55
60-64	Female	74,591	2.57
65-69	Male	65,354	2.25
65-69	Female	70,389	2.43
70-74	Male	56,746	1.96
70-74	Female	67,227	2.32
75-79	Male	45,027	1.55
75-79	Female	64,274	2.21
80-84	Male	22,441	0.77
80-84	Female	40,344	1.39
85-89	Male	11,184	0.39
85-89	Female	26,540	0.91
90-94	Male	3,208	0.11
90-94	Female	10,951	0.38
95-99	Male	633	0.02
95-99	Female	2,648	0.09

Table A2: WMC average person years of follow up, categorised by age group, sex and WIMD 2011 at cohort start

Age group	Sex	WIMD 2011 quintiles	Average Pys
00-04	Male	1	18.16
00-04	Male	2	17.93
00-04	Male	3	17.63
00-04	Male	4	17.28
00-04	Male	5	17.11
05-09	Male	1	18.06
05-09	Male	2	17.81
05-09	Male	3	17.26
05-09	Male	4	16.91
05-09	Male	5	16.50
10-14	Male	1	17.93
10-14	Male	2	17.46
10-14	Male	3	16.76
10-14	Male	4	16.24
10-14	Male	5	15.98
15-19	Male	1	17.30
15-19	Male	2	16.73
15-19	Male	3	15.75
15-19	Male	4	14.89
15-19	Male	5	14.34
20-24	Male	1	16.96
20-24	Male	2	16.04
20-24	Male	3	15.29
20-24	Male	4	14.03
20-24	Male	5	13.59
25-29	Male	1	17.18
25-29	Male	2	16.71
25-29	Male	3	16.22
25-29	Male	4	15.57
25-29	Male	5	15.47
30-34	Male	1	17.44
30-34	Male	2	17.41
30-34	Male	3	17.11
30-34	Male	4	16.82
30-34	Male	5	16.60
35-39	Male	1	17.66
35-39	Male	2	17.63
35-39	Male	3	17.41
35-39	Male	4	17.27

35-39	Male	5	17.22
40-44	Male	1	17.50
40-44	Male	2	17.63
40-44	Male	3	17.55
40-44	Male	4	17.40
40-44	Male	5	17.57
45-49	Male	1	17.23
45-49	Male	2	17.39
45-49	Male	3	17.28
45-49	Male	4	17.24
45-49	Male	5	17.48
50-54	Male	1	16.68
50-54	Male	2	16.96
50-54	Male	3	16.89
50-54	Male	4	16.91
50-54	Male	5	17.30
55-59	Male	1	15.46
55-59	Male	2	16.03
55-59	Male	3	16.20
55-59	Male	4	16.31
55-59	Male	5	16.78
60-64	Male	1	14.07
60-64	Male	2	14.64
60-64	Male	3	14.96
60-64	Male	4	15.19
60-64	Male	5	15.80
65-69	Male	1	12.14
65-69	Male	2	12.70
65-69	Male	3	13.24
65-69	Male	4	13.46
65-69	Male	5	14.21
70-74	Male	1	9.73
70-74	Male	2	10.23
70-74	Male	3	10.59
70-74	Male	4	11.02
70-74	Male	5	11.58
75-79	Male	1	7.46
75-79	Male	2	7.73
75-79	Male	3	8.14
75-79	Male	4	8.29
75-79	Male	5	8.79
80-84	Male	1	5.55
80-84	Male	2	5.82
80-84	Male	3	6.02

80-84	Male	4	6.24
80-84	Male	5	6.30
85-89	Male	1	4.20
85-89	Male	2	4.18
85-89	Male	3	4.28
85-89	Male	4	4.27
85-89	Male	5	4.41
90-94	Male	1	3.09
90-94	Male	2	3.07
90-94	Male	3	3.22
90-94	Male	4	2.95
90-94	Male	5	3.13
95-99	Male	1	2.87
95-99	Male	2	3.19
95-99	Male	3	2.64
95-99	Male	4	2.77
95-99	Male	5	2.32
00-04	Female	1	18.03
00-04	Female	2	17.82
00-04	Female	3	17.37
00-04	Female	4	16.99
00-04	Female	5	16.73
05-09	Female	1	17.84
05-09	Female	2	17.44
05-09	Female	3	16.89
05-09	Female	4	16.27
05-09	Female	5	15.92
10-14	Female	1	17.57
10-14	Female	2	17.09
10-14	Female	3	16.20
10-14	Female	4	15.60
10-14	Female	5	15.51
15-19	Female	1	16.93
15-19	Female	2	16.08
15-19	Female	3	14.88
15-19	Female	4	13.68
15-19	Female	5	13.21
20-24	Female	1	16.94
20-24	Female	2	15.81
20-24	Female	3	14.61
20-24	Female	4	12.89
20-24	Female	5	12.48
25-29	Female	1	17.53
25-29	Female	2	16.99

25-29	Female	3	16.47
25-29	Female	4	15.77
25-29	Female	5	15.34
30-34	Female	1	17.94
30-34	Female	2	17.77
30-34	Female	3	17.39
30-34	Female	4	16.94
30-34	Female	5	16.77
35-39	Female	1	18.18
35-39	Female	2	18.12
35-39	Female	3	17.78
35-39	Female	4	17.47
35-39	Female	5	17.49
40-44	Female	1	18.11
40-44	Female	2	18.16
40-44	Female	3	17.91
40-44	Female	4	17.71
40-44	Female	5	17.92
45-49	Female	1	17.92
45-49	Female	2	17.93
45-49	Female	3	17.82
45-49	Female	4	17.66
45-49	Female	5	17.97
50-54	Female	1	17.49
50-54	Female	2	17.69
50-54	Female	3	17.49
50-54	Female	4	17.44
50-54	Female	5	17.87
55-59	Female	1	16.79
55-59	Female	2	17.09
55-59	Female	3	17.00
55-59	Female	4	17.06
55-59	Female	5	17.54
60-64	Female	1	15.53
60-64	Female	2	16.04
60-64	Female	3	16.23
60-64	Female	4	16.28
60-64	Female	5	16.96
65-69	Female	1	13.76
65-69	Female	2	14.28
65-69	Female	3	14.70
65-69	Female	4	14.92
65-69	Female	5	15.52
70-74	Female	1	11.43

70-74	Female	2	11.93
70-74	Female	3	12.27
70-74	Female	4	12.57
70-74	Female	5	13.12
75-79	Female	1	9.06
75-79	Female	2	9.35
75-79	Female	3	9.70
75-79	Female	4	9.82
75-79	Female	5	10.25
80-84	Female	1	6.78
80-84	Female	2	7.07
80-84	Female	3	7.19
80-84	Female	4	7.26
80-84	Female	5	7.50
85-89	Female	1	4.98
85-89	Female	2	5.02
85-89	Female	3	4.97
85-89	Female	4	5.07
85-89	Female	5	5.07
90-94	Female	1	3.45
90-94	Female	2	3.53
90-94	Female	3	3.61
90-94	Female	4	3.55
90-94	Female	5	3.66
95-99	Female	1	2.66
95-99	Female	2	2.87
95-99	Female	3	2.70
95-99	Female	4	2.75
95-99	Female	5	2.48

BMJ Open

Protocol for the development of the Wales Multi-morbidity e-Cohort (WMC): data sources and methods to construct a population-based research platform to investigate multi-morbidity.

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Protocol for the development of the Wales Multi-morbidity e-Cohort (WMC): data sources and methods to construct a population-based research platform to investigate multi-morbidity.

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ABSTRACT

Introduction

Multi-morbidity is widely recognised as the presence of two or more concurrent long-term conditions, but remains a poorly understood global issue despite increasing in prevalence.

We have created the Wales Multi-morbidity e-Cohort (WMC) to provide an accessible research ready data asset to further the understanding of multi-morbidity. Our objectives are to create a platform to support research which would help to understand prevalence, trajectories and determinants in multi-morbidity, characterise clusters that lead to highest burden on individuals and healthcare services, and evaluate and provide new multi-morbidity phenotypes and algorithms to the NHS and research communities to support prevention, healthcare planning and the management of individuals with multi-morbidity.

Methods and analysis

The WMC has been created and derived from multi-sourced demographic, administrative and electronic health record (EHR) data relating to the Welsh population in the Secure Anonymised Information Linkage (SAIL) Databank. The WMC consists of 2.9 million people alive and living in Wales on the 1st January 2000 with follow up until 31st December 2019, Welsh residency break or death. Published comorbidity indices and phenotype code lists will be used to measure and conceptualise multi-morbidity.

Study outcomes will include: a) a description of multi-morbidity using published data phenotype algorithms/ontologies, b) investigation of the associations between baseline demographic factors and multi-morbidity c) identification of temporal trajectories of clusters of conditions and multi-morbidity, d) investigation of multi-morbidity clusters with poor outcomes such as mortality and high healthcare service utilisation.

Ethics and dissemination

The SAIL Databank independent Information Governance Review Panel (IGRP) has approved this study (SAIL Project: 0911). Study findings will be presented to policy groups, public meetings, national and international conferences, and published in peer-reviewed journals.

Strengths and limitations of this study

- Creation and access to a multi-sourced population based, deeply phenotyped e-cohort.
- Future use of this resource removes need for data management and cleaning of source data, accelerating research and which could also support efforts for reproducibility of results.
- Variety of individual and household level data on demography, health status, health care utilisation, both primary and secondary healthcare, and mortality to support a wide range of analytical approaches to addressing scientific questions.
- Input from multiple disciplines and institutions from across all four nations of the United Kingdom to help understand, measure and address multi-morbidity.
- Routine data does not capture data on some important aspects, such as quality of life.

INTRODUCTION

Multi-morbidity is defined by the UK's Academy of Medical Sciences (AMS) and the World Health Organisation as the presence of two or more concurrent long-term conditions, which is a global and growing phenomenon.[1,2] Multi-morbidity is more prevalent in older individuals and associated with high healthcare utilisation and mortality, but with large numbers of patients of all age suffering from multi-morbidity.[3-6] With an aging population, it is estimated that two in three people in England aged 65 years or over will experience multi-morbidity by 2035 and nearly one fifth will have complex multi-morbidity (4 or more conditions).[7]

Much of what is known about multi-morbidity is based on a limited and fragmented knowledge base, largely derived from studies of older people in high-income countries or hospital populations.[1,8] The 2018 AMS report concluded that multi-morbidity is an unhelpful term implying random assortment of disease when it often refers to clusters of specific diseases. Once identified, these disease clusters can be addressed specifically through research, healthcare policy development and service delivery.[1,9] The identification of previously unrecognised disease clusters may also provide biological and clinical insights into their aetiology, prevention and treatment. The AMS report identified specific research gaps and proposed a list of priorities (Textbox 1). Several can be addressed through a combination of health data science, epidemiology and statistics, and by exploiting the potential from creating deeply phenotyped cohorts from population and clinical data sources.

Textbox 1: The Academy of Medical Sciences identified research gaps.

- The scale and nature of multi-morbidity and how it is changing over time.
- Which clusters of conditions cause the biggest problems for patients.
- The causes of the most common clusters including links with sex, ethnicity, income and lifestyle.
- The best ways to prevent the patients developing multi-morbidity, and whether this requires different approaches to just preventing individual conditions.
- How doctors can increase the benefits and reduce the risks of treatment for patients with multi-morbidity.
- How to organise healthcare systems to deal with multi-morbidity more effectively and how best to use digital technology in caring for patients.

Responding to this agenda, we created a privacy protecting total population electronic cohort - the Wales Multi-morbidity e-Cohort (WMC) - as a platform to study these issues in depth, collaborating with scientists from many different institutions and disciplines, clinicians, and members of the public from across the UK to create a broader team science approach.

The objectives of this work are to understand prevalence, trajectories and determinants of multi-morbidity, and identify clusters causing the greatest health care burden. The WMC will also contribute data on incidence, prevalence and burden to the Global Burden of Diseases Study,[10,11] and provide new multi-morbidity phenotypes to e-cohorts with local participants, and phenotyping algorithms to many e-cohorts that utilise routine data.[12]

We expect that findings from these analyses will provide evidence to health policy leads in order to support prevention and the complex healthcare planning and management of multi-morbid individuals. Members of the public are embedded in the research team to ensure the resource focuses on issues of concern to the public.

This paper describes the creation of the WMC and the statistical approaches that will be developed to support the diverse research objectives.

METHODS

The WMC was developed by linking multiple routinely collected population and clinical data sources on the population of Wales from 2000-2019. We used the privacy-protecting Secure Anonymised Information Linkage (SAIL) Databank, to contribute to the Health Data Research UK National Implementation Multi-morbidity Resource (HNIMR) project, and extended to 2020 for the MRC funded Welsh Multi-morbidity Machine Learning (WMML) project .[13,14] SAIL is one of the most comprehensive, privacy protecting, linked data Trusted Research Environments (TRE) in the UK. SAIL utilising data from many different sources and providing linkage at individual and household level.[15] It has supported many different study designs, including, large-scale community-based or clinical condition-based observational studies, disease surveillance, evaluation of natural experiments of environmental interventions, embedded trials, and the Dementias Platform UK.[16-23]

Cohort design and characteristics

WMC is a clearly defined complete population cohort. Cohort entry includes all residents in Wales, alive and living on the 1st January 2000. Cohort censorship was defined by the first date of migration out of Wales/residency break, death or the study endpoint on 31st December 2019 (Figure 1). Within these constraints, the cohort is designed to be without selection bias and to achieve complete follow-up. WMC also provides a fully generalisable population sample against which findings from more selected samples may be compared.

The WMC contains 2,902,101 individuals aged 0-99 at cohort start date with 46 million person years of follow up available (Table 1, Figures 2 & 3, Appendix Table A1 & A2). Individuals have a minimum of 1-day follow up (cohort end date = 2nd January 2000) and maximum of 20-years of follow up (cohort end date = 31st December 2019).

Table 1: WMC baseline demographics

WMC characteristics	n	%
Cohort size	2,902,101	100
Full coverage (01-01-2000 – 31-12-2019)	1,714,484	59.08
Residency break/Emigration	643,472	22.17
Mortality	544,145	18.75
Primary care data available	2,470,874	85.14
Care home residency at cohort end	97,006	3.34
Mean age in years (range) at cohort start	39 (0-99)	
Sex		
Female	1,472,113	50.60
Male	1,436,988	49.40
WIMD 2011 Quintile at cohort start		
1. Most Deprived	605,203	20.85
2	589,479	20.31
3	584,039	20.12
4	557,319	19.20
5. Least Deprived	566,061	19.51

The Heatmap in Figure 3 visualises the person years of follow up by age, sex and area level deprivation. The more years of follow up available the darker the colour. Age is calculated at the cohort start, therefore, younger individuals will have more years of available follow up compared to older individuals. On average, there are less person years of follow up available for the least deprived 15-24 year olds compared to their respective age group in other areas of Wales.

Data Sources

The WMC has utilised and combined anonymised health, social and environmental data held within the SAIL Databank (www.saildatabank.com).

The baseline characteristics for the WMC have been created using the Welsh Demographic Service Dataset (WDSD) and the Annual District Death Extract (ADDE) mortality registry data from the Office for National Statistics. The WDSD contains administrative information concerning the resident population of Wales that are registered to a Welsh General Practice, a free to use National Health Service (NHS) system at the point of primary care registration in the UK. The ADDE data contains information about the dates and causes of all deaths relating to residents in Wales, including those that died outside of Wales. SAIL holds GP data for approximately 80% of the population with coverage extending to all local authorities in Wales. The Welsh Longitudinal General Practice (WLGP) data will be used to identify the sub-population of individuals who are registered to a practice providing data to SAIL to identify which individuals have GP data present and avoid underestimation of conditions or severity of conditions not managed through hospital admission.

The Welsh Health Survey Dataset (WHSD) and the National Survey for Wales Dataset (NSWD) with data on wellbeing measures, social class, education, housing and wealth are available for 9,905 and 33,295 cohort participants respectively. [24]

Anonymised Linkage Fields

Linkage fields are used to anonymously link between data sources in the SAIL Databank and have been previously described elsewhere.[13,14,25] SAIL utilises a multiple encryption system in which a trusted third party, the National Health Service (NHS) Wales Informatics Service (NWIS), uniquely matches identities (NHS number, name, date of birth, and residential address/UPRN) and replaces these with unique identifiers. For individuals this is called an Anonymised Linkage Field (ALF) and Residential Anonymised Linkage Field (RALF) for pseudonymised residences before uploading data to SAIL.

Demographic Data

The cohort includes the following variables: Anonymised Linkage Field (ALF), age in years, sex, date of death, date of movement out of Wales, RALF at both cohort inception and cohort end and Care Home Anonymised Linkage Fields (CHALFs) at cohort end date. The CHALF was derived from a data extract from Care Inspectorate Wales in 2020 for all adult care home settings.[18] Geographical variables associated with the RALF and CHALF include Lower layer Super Output Area (LSOA) 2001 at cohort inception and LSOA 2011 at cohort end. These have been mapped to the Welsh Index of Multiple Deprivation (WIMD) version 2011 and 2019 respectively to derive socioeconomic deprivation quintiles and urban/rurality categories.[26,27]

Health Data

All admissions to hospital (inclusive of critical care admissions), outpatient, Emergency Department attendances treated in NHS hospitals as well as disease registries and laboratory test results data are available for cohort participants, GP data for diagnoses and treatments from SAIL providing practices are data for approximately 80% of the population.[28]

All relevant health events recorded in clinical data sources will be joined onto the WMC to identify diagnosis of conditions, treatments and various significant heath events that occur across multi-sourced linked heath data per person (Table 2 &Figure 4).

Table 2: Clinical data sources available for the WMC.

Data source	Period covered	Number and percentage of WMC individuals with data
Critical Care Data Set (CCDS)	01-01-2007 – 31-12-2019	79,521 (2.7%)
Welsh Cancer Incidence Surveillance Unit (WCISU)	01-01-2000 – 31-12-2016	328,792 (11.3%)
Welsh Results Reporting Services (WRRS)	01-01-2015 – 10-12-2018	1,540,754 (53.1%)
Emergency Department Data Set (EDDS)	01-04-2009 – 31-12-2019	1,579,665 (54.4%)
Patient Episode Database for Wales (PEDW)	01-01-2000 – 31-12-2019	2,129,384 (73.4%)
Out Patient Dataset for Wales (OPDW)	01-04-2004 – 31-12-2019	2,177,081 (75.0%)
Welsh Longitudinal General Practice (WLGP)	01-01-2000 – 31-12-2019	2,400,313 (82.7%)
Please note clinical data sources will be updated on a monthly/quarterly basis		

The Upset plot in Figure 4 demonstrates the number of WMC participants that have interacted with the various health care settings from 1st January 2000 to their cohort censorship end date.[29] For example, 780,830 (26.9%) individuals have utilised GP, inpatient, outpatient and emergency department services as well as had at least one laboratory test within their WMC coverage.

Phenotyping the e-cohort

Published comorbidity indices and phenotype code lists (International Classification of Diseases 10th revision (ICD-10), OPCS Classification of Interventions and Procedures version 4 (OPCS4) and primary care Read Codes version 2) will be used to measure and conceptualise multi-morbidity. These include those created by: CALIBER initiative; Charlson Comorbidity Index; Common Mental Disorders (CMD); Elixhauser Comorbidity

Index; Global Burden of Disease Study; and the NHS Quality and Outcomes Framework (QOF).[30-41] Diagnostic codes relating to HIV will not be included in any outputs to conform with SAIL policies. They are part of the list of redacted codes not allowed to be used for research using the data.[42] All ICD-10 and OPCS4 codes provided at the three character level were expanded to include all children terms.

1. CALIBER

Phenotyping algorithms created from the CALIBER resource using ICD-10, OPCS4 and Read Codes will be utilised to identify 300 physical and mental health conditions recorded in both primary and secondary healthcare.[31,39]

There are 1,645 distinct ICD-10 codes (at three and four-character level) for 300 conditions, however, when capturing all ICD-10 codes to include variation in coding entry (e.g. C796– instead of C796) and expanding the code list to the four-character level (F200 instead of F20), there are 3,702 distinct ICD-10 codes (at the four-character level) recorded in the inpatient data. This is important to note as to link solely on standardised codes would result in loss of information and potential reporting of false negatives.

There are 587 distinct OPCS4 codes (at three and four-character level) for 28 conditions and 8,588 distinct Read Codes (at the five-character level) for 275 conditions.

2. Charlson Comorbidity Index

The Aylin and Bottle Charlson amended ICD-10 code list will be utilised for inpatient diagnosis and the Metcalfe et al (2019) Charlson Read Code list will be utilised for primary care recorded diagnosis.[32,33]

The ICD-10 codes have been taken from the pool of diagnosis codes recorded within hospital admissions data, containing 1,024 distinct codes (at the four-character level) for 16 conditions. The GP data contains 4,545 distinct Read Codes at the five-character level.

3. Common Mental Disorders (CMD)

The John et al, 2016 validated algorithm will be used to identify CMD in GP data.[30,40,41] The algorithm has utilised a combination of diagnosis, treatment and symptoms Read Codes in identifying CMD. Individuals with CMD are identified as either having a historical diagnosis code, currently treated or, having a current diagnosis/current symptom code. There are 89 distinct diagnosis codes, 15 symptom codes and 601 treatment codes.

4. **Elixhauser Comorbidity Index**

The Quan et al (2005) Elixhauser ICD-10 code list will be utilised for inpatient diagnosis and the Metcalfe et al (2019) Elixhauser Read Code list will be utilised for primary care recorded diagnosis.[33,34]

The ICD-10 codes have been taken from the pool of diagnosis codes recorded within hospital admissions data and contains 1,404 distinct codes (at the four-character level) for 30 conditions. The General practice data contains 6,074 distinct Read codes at the five-character level.

5. Global Burden of Disease (GBD) Study

The GBD 2019 ICD-10 codes will be used to identify 130 health conditions in secondary healthcare data. There are 3,497 distinct ICD-10 codes at the three and four-character level.[38]

6. Quality Outcome Framework (QOF)

The QOF conditions business rule V38 will be used to identify 18 health conditions in primary care data.[35] The 18 conditions are asthma, atrial fibrillation, obesity, coronary heart disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, dementia, depression, diabetes, epilepsy, heart failure, hypertension, learning difficulties, peripheral arterial disease, rheumatoid arthritis, serious mental illness and stroke. There are 2,275 distinct Read Codes available at the five-character level for the 18 QOF conditions.

Statistical analysis

The WMC provides an accessible research ready data asset to further understanding of multi-morbidity through the use of bio-statistical and machine learning approaches. Our collaborative team will work across a number of projects to develop and evaluate statistical and machine learning algorithms to address the following broad analytical challenges:

- What is the prevalence of multi-morbidity in the WMC, and how does prevalence of multi-morbidity change over time?
- What are common clusters of multi-morbidity in the WMC, and how do they correspond to or differ from, common clusters of multi-morbidity identified in other datasets?
- Which clusters of multi-morbidity occur less frequently than one would expect based on the prevalence of their constituent conditions?
- How does multi-morbidity develop across the life course (i.e. trajectories)?
- What are the biological, psychological, and social determinants of different clusters and trajectories of multi-morbidity?
- Which clusters and trajectories of multi-morbidity are associated with poor health outcomes?
- Which clusters and trajectories of multi-morbidity are associated with high service utilisation?
- Does multi-morbidity in specific groups (e.g. patients with musculoskeletal conditions) differ from multi-morbidity in general?

The overarching aim is to evaluate and provide new multi-morbidity phenotypes and algorithms to the NHS and research communities to support prevention, healthcare planning and the management of individuals with multi-morbidity.

We will draw upon both methods from statistics (e.g. regression analysis, longitudinal mixed models, multiple correspondence analysis, factor analysis [43], multi-state models, and latent class analysis) and machine learning (e.g. k-means clustering, semantic similarity clustering, market basket analysis, network models [44], and deep learning). We will use resampling methods to assess the stability of identified multi-morbidity clusters, and develop visualisation techniques to summarise multi-morbidity clusters and their associations with risk factors and outcomes.

Analyses will be coded in R, WinBUGS, and Python and made available to WMC users via a Git library to maximise transparency and reproducibility.[45]

Patient and public involvement

The proposal to develop WMC was submitted to the independent Information Governance Review Panel (IGRP) that includes members of the public (IGRP Project: 0911). We worked with this group to refine the study protocol. The scientific steering group includes two members of the public who have contributed to this paper. The HDR UK National Implementation Project Multi-morbidity Resource has a work package on PPI with a panel drawn from across the UK meeting to discuss the research work and feed into the research and dissemination plans.

Ethics and dissemination

The use of de-identified data in SAIL complies with National Research Ethics Service (NRES) guidance.[46] Applications to use data held within the SAIL Databank, an ISO: 27001 and UKSA DEA accredited TRE, must first be approved by the independent Information Governance Review Panel (IGRP). This panel contains individuals with expertise in data governance and protection, including the Chair of the Wales NRES Committee, Caldicott Guardians, and members of the public. WMC was approved by IGRP on 26th June 2019.

Findings from this study will be disseminated widely through a variety of routes, including to health policy and NHS leads across UK, the Academy of Medical Sciences and the Royal Colleges, as well as traditional scientific outlets. The team includes NHS clinicians and informaticians to allow for early NHS adoption of useful findings. Members of the public embedded in the team will create plain English summaries and lead at public facing meetings.

Contributors

Conceptualisation of study JL, AA, UA, GH, CM, DOR, RAL; data curation and analysis JL; original draft writing JL, review and editing of manuscript JL, AA, UA, GH, AAL, RB, JR, AW, RF, CM, CD, JPR, NP, CH, SD, RO, KRA, AJ, DOR, SR, MH, CPG, JD, CD,LC, JG, JC, AJB, RAL

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Disclaimer

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the funding agencies, NHS organisations or Welsh Government.

Competing interests

None declared.

Figure captions

Figure 1**:** WMC flow diagram, based on inclusion criteria.

Figure 2: WMC pyramid for age (years) at cohort inception.

Figure 3: Heatmap of person years of WMC follow up, by age group, sex and area level deprivation at cohort inception.

Figure 4: Number of WMC individuals utilising healthcare services recorded in multi-source data sources, 20 most common combinations presented.

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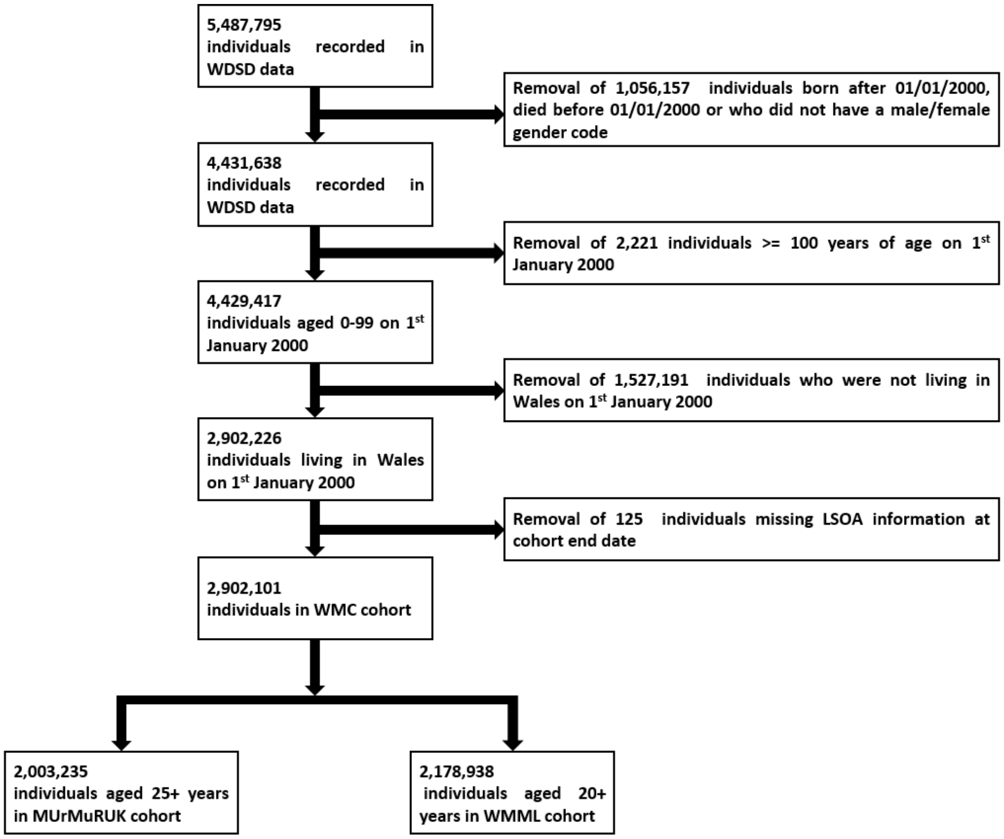

5,487,795 individuals recorded in WDSD data
Removal of 1,056,157 individuals born after 01/01/2000, died before 01/01/2000 or who did not have a male/female gender code
4,431,638 individuals recorded in WDSD data
Removal of 2,221 individuals >= 100 years of age on 1st January 2000
4,429,417 individuals aged 0-99 on 1st January 2000
Removal of 1,527,191 individuals who were not living in Wales on 1st January 2000
2,902,226 individuals living in Wales on 1st January 2000
Removal of 125 individuals missing LSOA information at cohort end date
2,902,101 individuals in WMC cohort
2,003,235 individuals aged 25+ years in MUrMuRUK cohort
2,178,938 individuals aged 20+ years in WMML cohort

Figure 1: WMC flow diagram, based on inclusion criteria.

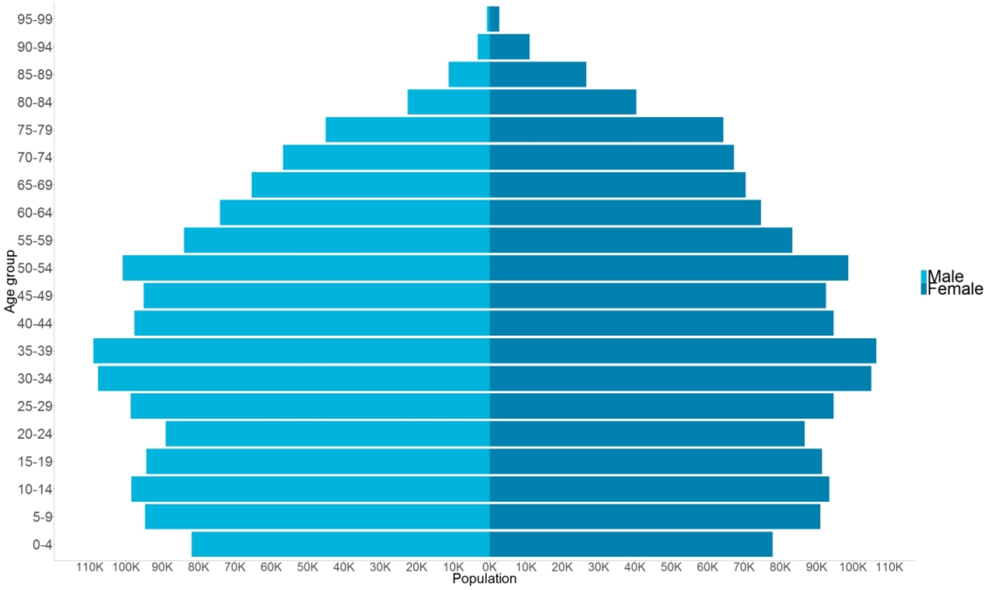


Figure 2: WMC pyramid for age (years) at cohort inception.

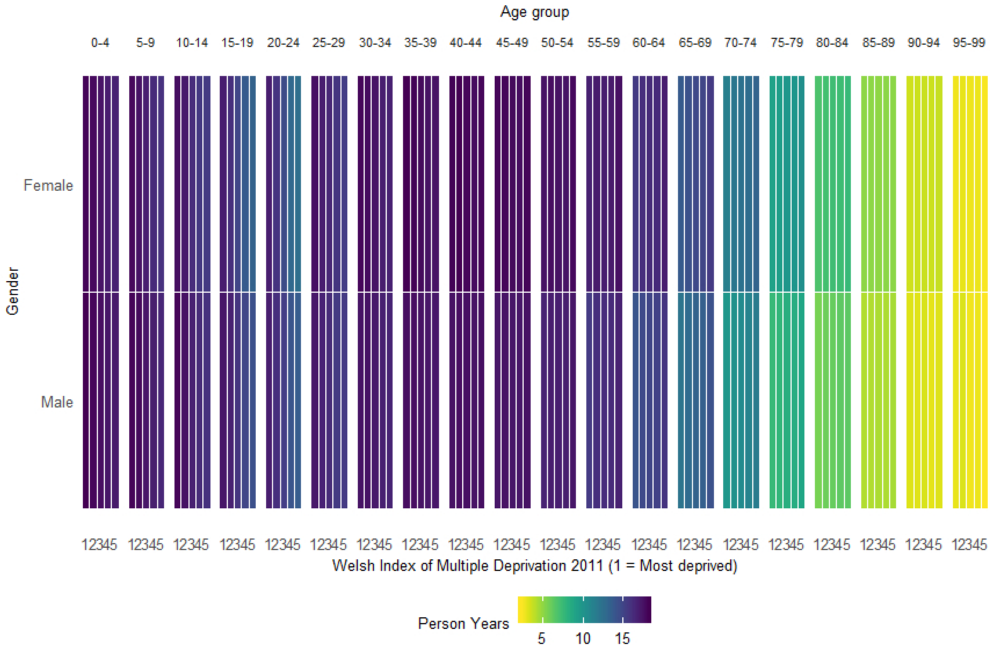
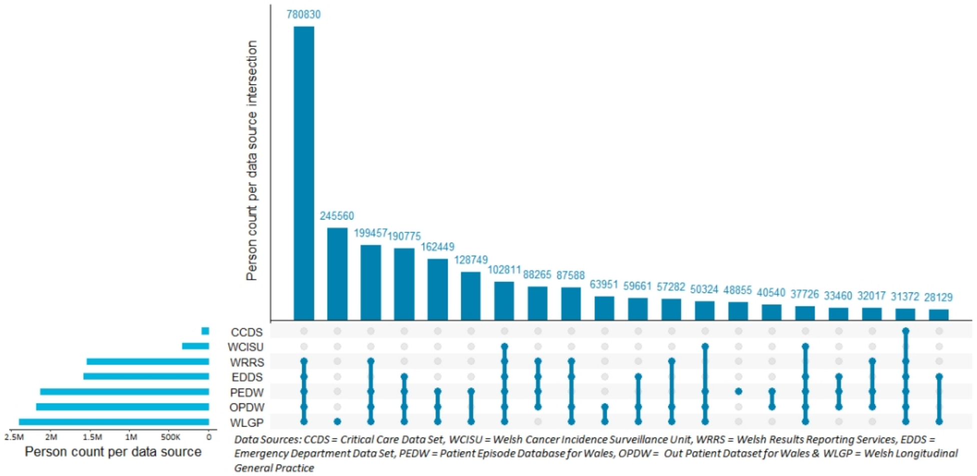


Figure 3: Heatmap of person years of WMC follow up, by age group, sex and area level deprivation at cohort inception.



Data Sources: CCDS = Critical Care Data Set, WCISU = Welsh Cancer Incidence Surveillance Unit, WRRS = Welsh Results Reporting Services, EDDS = Emergency Department Data Set, PEDW = Patient Episode Database for Wales, OPDW = Out Patient Dataset for Wales & WLGP = Welsh Longitudinal General Practice

Figure 4: Number of WMC individuals utilising healthcare services recorded in multi-source data sources, 20 most common combinations presented.

Appendix

Table A1: WMC participants categorised by age group and sex at cohort start

Age group	Sex	Count	Percentage
00-04	Male	81,915	2.82
00-04	Female	77,873	2.68
05-09	Male	94,737	3.26
05-09	Female	90,940	3.13
10-14	Male	98,466	3.39
10-14	Female	93,447	3.22
15-19	Male	94,345	3.25
15-19	Female	91,440	3.15
20-24	Male	89,037	3.07
20-24	Female	86,666	2.99
25-29	Male	98,622	3.40
25-29	Female	94,592	3.26
30-34	Male	107,671	3.71
30-34	Female	104,986	3.62
35-39	Male	108,964	3.75
35-39	Female	106,312	3.66
40-44	Male	97,637	3.36
40-44	Female	94,599	3.26
45-49	Male	95,071	3.28
45-49	Female	92,478	3.19
50-54	Male	100,866	3.48
50-54	Female	98,606	3.40
55-59	Male	83,949	2.89
55-59	Female	83,210	2.87
60-64	Male	74,115	2.55
60-64	Female	74,591	2.57
65-69	Male	65,354	2.25
65-69	Female	70,389	2.43
70-74	Male	56,746	1.96
70-74	Female	67,227	2.32
75-79	Male	45,027	1.55
75-79	Female	64,274	2.21
80-84	Male	22,441	0.77
80-84	Female	40,344	1.39
85-89	Male	11,184	0.39
85-89	Female	26,540	0.91
90-94	Male	3,208	0.11
90-94	Female	10,951	0.38
95-99	Male	633	0.02
95-99	Female	2,648	0.09

Table A2: WMC average person years of follow up, categorised by age group, sex and WIMD 2011 at cohort start

Age group	Sex	WIMD 2011 quintiles	Average Pys
00-04	Male	1	18.16
00-04	Male	2	17.93
00-04	Male	3	17.63
00-04	Male	4	17.28
00-04	Male	5	17.11
05-09	Male	1	18.06
05-09	Male	2	17.81
05-09	Male	3	17.26
05-09	Male	4	16.91
05-09	Male	5	16.50
10-14	Male	1	17.93
10-14	Male	2	17.46
10-14	Male	3	16.76
10-14	Male	4	16.24
10-14	Male	5	15.98
15-19	Male	1	17.30
15-19	Male	2	16.73
15-19	Male	3	15.75
15-19	Male	4	14.89
15-19	Male	5	14.34
20-24	Male	1	16.96
20-24	Male	2	16.04
20-24	Male	3	15.29
20-24	Male	4	14.03
20-24	Male	5	13.59
25-29	Male	1	17.18
25-29	Male	2	16.71
25-29	Male	3	16.22
25-29	Male	4	15.57
25-29	Male	5	15.47
30-34	Male	1	17.44
30-34	Male	2	17.41
30-34	Male	3	17.11
30-34	Male	4	16.82
30-34	Male	5	16.60
35-39	Male	1	17.66
35-39	Male	2	17.63
35-39	Male	3	17.41
35-39	Male	4	17.27

35-39	Male	5	17.22
40-44	Male	1	17.50
40-44	Male	2	17.63
40-44	Male	3	17.55
40-44	Male	4	17.40
40-44	Male	5	17.57
45-49	Male	1	17.23
45-49	Male	2	17.39
45-49	Male	3	17.28
45-49	Male	4	17.24
45-49	Male	5	17.48
50-54	Male	1	16.68
50-54	Male	2	16.96
50-54	Male	3	16.89
50-54	Male	4	16.91
50-54	Male	5	17.30
55-59	Male	1	15.46
55-59	Male	2	16.03
55-59	Male	3	16.20
55-59	Male	4	16.31
55-59	Male	5	16.78
60-64	Male	1	14.07
60-64	Male	2	14.64
60-64	Male	3	14.96
60-64	Male	4	15.19
60-64	Male	5	15.80
65-69	Male	1	12.14
65-69	Male	2	12.70
65-69	Male	3	13.24
65-69	Male	4	13.46
65-69	Male	5	14.21
70-74	Male	1	9.73
70-74	Male	2	10.23
70-74	Male	3	10.59
70-74	Male	4	11.02
70-74	Male	5	11.58
75-79	Male	1	7.46
75-79	Male	2	7.73
75-79	Male	3	8.14
75-79	Male	4	8.29
75-79	Male	5	8.79
80-84	Male	1	5.55
80-84	Male	2	5.82
80-84	Male	3	6.02

80-84	Male	4	6.24
80-84	Male	5	6.30
85-89	Male	1	4.20
85-89	Male	2	4.18
85-89	Male	3	4.28
85-89	Male	4	4.27
85-89	Male	5	4.41
90-94	Male	1	3.09
90-94	Male	2	3.07
90-94	Male	3	3.22
90-94	Male	4	2.95
90-94	Male	5	3.13
95-99	Male	1	2.87
95-99	Male	2	3.19
95-99	Male	3	2.64
95-99	Male	4	2.77
95-99	Male	5	2.32
00-04	Female	1	18.03
00-04	Female	2	17.82
00-04	Female	3	17.37
00-04	Female	4	16.99
00-04	Female	5	16.73
05-09	Female	1	17.84
05-09	Female	2	17.44
05-09	Female	3	16.89
05-09	Female	4	16.27
05-09	Female	5	15.92
10-14	Female	1	17.57
10-14	Female	2	17.09
10-14	Female	3	16.20
10-14	Female	4	15.60
10-14	Female	5	15.51
15-19	Female	1	16.93
15-19	Female	2	16.08
15-19	Female	3	14.88
15-19	Female	4	13.68
15-19	Female	5	13.21
20-24	Female	1	16.94
20-24	Female	2	15.81
20-24	Female	3	14.61
20-24	Female	4	12.89
20-24	Female	5	12.48
25-29	Female	1	17.53
25-29	Female	2	16.99

25-29	Female	3	16.47
25-29	Female	4	15.77
25-29	Female	5	15.34
30-34	Female	1	17.94
30-34	Female	2	17.77
30-34	Female	3	17.39
30-34	Female	4	16.94
30-34	Female	5	16.77
35-39	Female	1	18.18
35-39	Female	2	18.12
35-39	Female	3	17.78
35-39	Female	4	17.47
35-39	Female	5	17.49
40-44	Female	1	18.11
40-44	Female	2	18.16
40-44	Female	3	17.91
40-44	Female	4	17.71
40-44	Female	5	17.92
45-49	Female	1	17.92
45-49	Female	2	17.93
45-49	Female	3	17.82
45-49	Female	4	17.66
45-49	Female	5	17.97
50-54	Female	1	17.49
50-54	Female	2	17.69
50-54	Female	3	17.49
50-54	Female	4	17.44
50-54	Female	5	17.87
55-59	Female	1	16.79
55-59	Female	2	17.09
55-59	Female	3	17.00
55-59	Female	4	17.06
55-59	Female	5	17.54
60-64	Female	1	15.53
60-64	Female	2	16.04
60-64	Female	3	16.23
60-64	Female	4	16.28
60-64	Female	5	16.96
65-69	Female	1	13.76
65-69	Female	2	14.28
65-69	Female	3	14.70
65-69	Female	4	14.92
65-69	Female	5	15.52
70-74	Female	1	11.43

70-74	Female	2	11.93
70-74	Female	3	12.27
70-74	Female	4	12.57
70-74	Female	5	13.12
75-79	Female	1	9.06
75-79	Female	2	9.35
75-79	Female	3	9.70
75-79	Female	4	9.82
75-79	Female	5	10.25
80-84	Female	1	6.78
80-84	Female	2	7.07
80-84	Female	3	7.19
80-84	Female	4	7.26
80-84	Female	5	7.50
85-89	Female	1	4.98
85-89	Female	2	5.02
85-89	Female	3	4.97
85-89	Female	4	5.07
85-89	Female	5	5.07
90-94	Female	1	3.45
90-94	Female	2	3.53
90-94	Female	3	3.61
90-94	Female	4	3.55
90-94	Female	5	3.66
95-99	Female	1	2.66
95-99	Female	2	2.87
95-99	Female	3	2.70
95-99	Female	4	2.75
95-99	Female	5	2.48