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Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice

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The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Abstract

Objectives – Prevalence estimates of multimorbidity vary widely due to inconsistent definitions and measurement methods. This study examines independent effect on prevalence estimates of the number of chronic conditions studied, number of disease entities required for multimorbidity, and how 'disease entity' is defined — as single chronic condition or chapters/domains in the International Classification of Primary Care (Version 2) (ICPC-2), International Classification of Disease (10th revision) (ICD-10) or the Cumulative Illness Rating Scale (CIRS).

Design – National prospective cross sectional study

Setting – Australian general practice

Participants 8,707 random consenting de-identified patients sampled from encounters with 290 randomly selected general practitioners

Main outcome measures – Prevalence estimates of multimorbidity measured using different definitions

Results - Health data classified to ICPC-2 chapters, ICD-10 chapters, or CIRS domains produce similar multimorbidity prevalence estimates. When multimorbidity was defined as two or more (2+) disease entities: counting individual chronic conditions and groups of chronic conditions produced similar estimates; twelve most prevalent chronic conditions identified about 80% of those identified using all chronic conditions; age-specific prevalence plateaued in patients aged 70+ years. When multimorbidity was defined as 3+ disease entities: counting individual chronic conditions produced significantly higher estimates than counting groups of chronic conditions; twelve most prevalent chronic conditions identified only two-thirds of patients identified using all chronic conditions; age-specific prevalence of multimorbidity had greater differentiation among older patients.

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Conclusion - For the first time, a large prospective study has tested the independent effect of multimorbidity measurement methods on prevalence estimates. Multimorbidity defined as 2+ disease entities can be measured using different definitions of disease entity with as few as 12 prevalent chronic conditions, but lacks specificity to be useful, especially in older people. Multimorbidity, defined as 3+, requires more measurement conformity and inclusion of all chronic conditions, but provides greater specificity than 2+ definition.

ARTICLE SUMMARY

Strengths and limitations of the study

- A large, representative, prospective study of multimorbidity, involving 290 general practitioners and 8,707 patients, allowed testing of the independent effect of variables on prevalence estimates, something not possible with systematic reviews.
- This study investigated all chronic conditions, not a selection of conditions.
- This study used the general practitioner as an "expert interviewer", drawing upon the patient's knowledge, the patient's health record and their own knowledge to indicate the patient's current chronic conditions. Most multimorbidity studies rely on only one of these sources of data.
- This study only considered chronic conditions, whereas some authors now include acute conditions when defining multimorbidity.

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Introduction

Research into coexistence of multiple chronic health conditions in an individual was initially concerned with comorbidity, defined as 'the existence or occurrence of any distinct additional disease entity in a patient who has the index disease under study'.(1) However since the early nineties, interest has progressed to 'multimorbidity', commonly defined as the "co-occurrence of two or more diseases within one person without defining an index disease".(2)

Interest in multimorbidity is growing due to its expected increase resulting from the ageing of the world's population.(3;4) Studies have shown that multimorbidity is associated with increased patient mortality, demand on health resources, complexity of care, and with reduced patient quality of life.(5;6) However, prevalence estimates of multimorbidity have ranged from 3.5%(7) to 98.5%,(8) the wide variance thought to be due to the lack of standards defining multimorbidity, and how it is measured. A recent systematic review found 132 definitions involving 1,631 different criteria.(9) There have been many calls for standards and guidelines for research into multimorbidity.(10-12) Recent systematic reviews have raised specific issues regarding the way multimorbidity is defined and/or measured.(11;12)

The first issue is the number of conditions studied. Fortin et al(11) found this ranged from 5 to all conditions. Diederichs et al(12) reported a range of 4 to 102 conditions, (mean,18.5,median 14) and suggested that conditions may be chosen for pragmatic reasons (such as data availability), as the majority of authors did not give reasons for their selection. Where they did, the most common was those conditions with a high prevalence or high impact on patients.(12) Both Diederichs et al(12) and Fortin et al(11) suggested studies considering only a few conditions produced lower prevalence estimates than those examining many conditions. Diederichs et al(12) suggested a list of 11 chronic conditions prevalent in the elderly as a minimum (cancer, diabetes mellitus, depression, hypertension, myocardial infarction, chronic ischeamic heart disease, heart arrhythmias, heart

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insufficiency, stroke, CODP, arthritis). Fortin et al(11) suggested that any 12 prevalent conditions should suffice to measure multimorbidity accurately.

The second issue is how 'disease entity' was defined in multimorbidity studies. Ideally, morbidities being counted should be "distinct" disease entities. However, disease entities used across studies varied from very specific conditions to groups of conditions. Even Diederich et al's suggested list(12) (above), includes some disease entities that are groups of conditions (such as arthritis and cancer) and some very specific, closely related conditions (eg. myocardial infarction and chronic ischaemic heart disease). It is debatable whether both myocardial infarction and chronic ischaemic heart disease should be considered as two separate disease entities in measuring multimorbidity. Some multimorbidity studies have tried to overcome this problem by only counting chronic conditions that affect different body systems, to ensure the count was of distinct disease entities.(4;13) These studies used the Cumulative Illness Rating Scale (CIRS)(14) domains to group chronic conditions by body system.(4;13) Fortin et al suggested that while the use of the CIRS needed further research, this approach may simplify coding and data collection.(11) The impact of counting the different body systems affected by chronic conditions, on multimorbidity prevalence estimates is not known.

Most primary care based multimorbidity studies rely on health record review.(11) A disadvantage of using CIRS in such reviews is that it requires additional mapping of diagnoses from the classification system in which the health records were coded. The two most commonly used disease classification systems are the International Classification of Primary Care (Version 2) (ICPC-2)(15) and the International Classification of Disease (10th revision) (ICD-10).(16) ICPC-2 is used in primary care and its chapters, (with the exception of 'General & Unspecified' and 'Social' chapters), are body system-based, following the principle that localisation takes precedence over aetiology.(16) ICD-10 is primarily used in hospitals and its chapters axes include body systems, aetiology and "others".(16) ICD-10 lacks specificity for classification of undiagnosed problems or symptoms, both of which are

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commonly managed in primary care.(17) This has meant that data from primary health care records classified in the two systems have looked very different in the past. However, since most multimorbidity studies examine only chronic conditions this problem may be avoided when conditions are grouped at the chapter level. It is not known whether counting disease entities from different CIRS domains, ICPC-2 or ICD-10 chapters produces comparable multimorbidity prevalence estimates.

The third issue is the number of disease entities required to define multimorbidity. Originally, multimorbidity was defined as two or more (2+) disease entities, but recently there has been debate about whether three or more (3+) may be a better measure. Fortin et al argue that using 2+ disease entities identifies such a high proportion of patients as multimorbid that the measure lacks specificity.(11) They found that age-specific prevalence of multimorbidity using the 2+ definition produced an "S" shaped curve with a flat plateau for older ages. When using 3+, the increase in prevalence by age was more linear, with greater differentiation in older age groups. The authors further argued that using 3+ disease entities results in a lower prevalence estimate, is likely to identify patients with greater health needs, and is therefore more useful to clinicians.(11) They recommended further research to test the 3+ definition of multimorbidity.(11)

The current study was conducted in Australian general practice. Australia's universal medical insurance scheme, Medicare, fully or partially covers the individual's cost of visits to general practitioners (GPs). GPs provide the bulk of primary medical care and act as gate keepers to government-subsidised health care from other medical specialists. There are no patient lists and patients are free to visit multiple GPs and practices as they choose.

Our study examines the effect of the number of chronic conditions studied, how a disease entity is defined and the minimum number of disease entities required to define multimorbidity on prevalence estimates. We use a large Australian general practice based prospective multimorbidity study, which allows us to examine the effect of each of these

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variables on multimorbidity prevalence estimates while controlling for other confounding variables, an approach not possible in systematic reviews.

Method

The BEACH (Bettering the Evaluation And Care of Health) program is a continuous, national cross-sectional survey of general practice activity in Australia.(17) Each year an ever-changing sample of about 1,000 GPs is randomly selected, and each GP records information about encounters with 100 consecutive consenting patients, on structured paper forms.(17)

In sub-studies of BEACH, the GP records information additional to the encounter data, in discussion with the patient. The full methods for this sub-study are reported elsewhere.(18) In brief, it measured the prevalence of diagnosed chronic conditions in patients attending general practice in Australia. Over three five-week recording periods (August 2008 to May 2009) 375 sampled GPs were asked to record all diagnosed chronic conditions for each of 30 consecutive patients on 30 bespoke forms within their 100 BEACH records. A sample of the instruction sheet and recording form can be found at www.http://sydney.edu.au/medicine/fmrc/publications/sand-abstracts/132-Multimorbidity.pdf

GPs were asked, “Does the patient have any of the following chronic diseases/problems?” Common chronic conditions were listed (tick boxes) with additional free text fields to record other unlisted chronic conditions (Box 1). A “no chronic conditions” option was also provided. Listed chronic conditions were primarily those most frequently managed in Australian general practice(17) and were inclusions in O’Halloran et al’s definition of chronic conditions.(19) The free text options relied on GPs judgement of whether a condition was chronic in this patient. GPs were instructed to *“Use your own knowledge, patient knowledge and health records as you see fit, in order to answer these questions”.* Additional free text chronic conditions were coded using the ICPC-2 PLUS terminology,(20) which automatically classified them into ICPC-2.(15) All chronic conditions were classified to ICD-10

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chapters(16) (n=20), ICPC-2 chapters,(15) and CIRS domains(14) (Table 1). There were some chronic conditions (e.g. multisite cancer) that involved multiple systems. As these would usually be counted multiple times in different CIRS domains, we created an additional domain called “Whole system”, resulting in 15 CIRS domains instead of the usual 14. The ICPC-2 male and female genital system chapters (chapters Y and X) were combined as they referred to the same body system, resulting in 16 ICPC-2 chapters (rather than the usual 17).

Using this large prospective study we examined the effect of three different dimensions of measuring multimorbidity while controlling for other confounding variables.

Dimension One – Does the way disease entities are defined affect multimorbidity prevalence estimates?

To test this dimension we defined disease entity four different ways. First, each recorded/ticked chronic condition was treated as a separate disease entity. For the other three methods we considered a disease entity to be a chapter/domain that was affected by at least one chronic condition in each of the three classification systems. Comparing the resulting multimorbidity prevalence estimates we were able to test two research questions. Firstly, whether counting different body systems affected by chronic conditions produces prevalence estimates comparable to counting individual chronic conditions. Secondly, whether counting the number of different CIRS domains, ICPC-2 chapters or ICD-10 chapters affected produces comparable prevalence estimates.

Dimension 2 – Does the minimum number of disease entities required to define multimorbidity affect multimorbidity prevalence estimates?

We compared prevalence of multimorbidity using 2+ through to 6+ disease entities. We also compared the age-specific prevalence of multimorbidity when it was defined as 2+ and 3+ disease entities, to see whether we could reproduce the “S” shaped curve when using the 2+

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definition and test whether using 3+ provided greater differentiation among older patients, as found by Fortin et al.(11)

Dimension 3 – Does the number of chronic conditions included in the study affect multimorbidity estimates?

We reduced the number of chronic conditions used, in order to simulate studies that were based on fewer chronic conditions. We used the 11 minimum chronic conditions suggested by Diederichs et al (listed above, 'Diederich's list')(12), the 12 most prevalent chronic conditions in our study (hypertension, hyperlipidaemia, ischeamic heart disease, Type 2 diabetes, obesity, osteoarthritis, chronic back pain, asthma, depression, anxiety, GORD, malignant neoplasms) as suggested by Fortin et al(11) and the 24 listed chronic conditions with a tick box. We then compared these results with those generated using all diagnosed chronic conditions.

BEACH sub-studies have a single stage cluster design, with each GP having 30 patients clustered around them. The cluster effect was accounted for using SAS 9.3.

Ethics committees of the University of Sydney and Australian Institute of Health and Welfare approved BEACH and this sub-study.

Results

Completed research packs were returned by 290 GPs (77.3%) sampling 8,707 patients. In total 66.5% of patients (n= 5,777) had at least one chronic condition and 33.7% (n=2,930) had none.

Table 1 shows the proportion of patients with at least one chronic condition in each chapter/domain. For both ICPC-2 and ICD-10, the 11 most prevalent chapters were body-specific, with the non-body system specific chapters being relatively uncommon. Prevalence estimates of patients with at least one chronic condition within a body-system specific ICD-10 and ICPC-2 chapter were remarkably similar, the top six chapters being in the same

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order, with no significant differences in the prevalence estimates for these six chapters. There were larger differences between estimates using CIRS and those from both ICPC-2 and ICD-10. The major differences were due to CIRS splitting cardiovascular into vascular and cardiac domains, classifying cerebrovascular disease as neurological, and classifying hyperlipidaemia in the vascular domain. In all systems the most frequent chapters/domains were those relating to the: cardiac/vascular/circulatory; endocrine; musculoskeletal; psychological; digestive; and respiratory systems.

Figure 1 shows the prevalence of multimorbidity among patients in the sample (representing those in a GP's waiting room) using different definitions of multimorbidity. Estimated prevalence of multimorbidity ranged from 47.4% using 2+ individual chronic conditions to 2.8% when using 6+ ICPC-2 chapters. For all definitions using 3+ disease entities or more, counting individual chronic conditions resulted in significantly higher prevalence estimate than any of the grouped estimates. This difference increased proportionally as the minimum number of disease entities increased — the individual chronic conditions estimate was 23% higher than the ICPC-2 chapter estimate at 3+ disease entities, through to 268% higher at 6+ disease entities. Overall there was no significant difference found between prevalence estimates using ICD-10, ICPC-2 and CIRS, from 2+ through to 6+ disease entities.

Using the ICD-10 and ICPC-2 estimates, when multimorbidity was defined as two or more disease entities, about 44% of patients presenting to GP's were identified as multimorbid. This prevalence decreased with each increase in the number of disease entities required, with about 27% of patients being considered multimorbid for 3+, about 15% for 4+, 7% for 5+ and only 3% for 6+ disease entities. There was nearly perfect concordance between patients identified as having multimorbidity using the ICD-10 and ICPC-2 classifications systems. For example when using the minimum of three disease entities as the definition of multimorbidity, over 99% of patients identified using ICD-10 were also identified using ICPC-2 and visa-versa (Table 2) There was also high concordance between ICPC-2/ICD-10 and

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CIRS. For every 12 patients identified as having multimorbidity with CIRS, 11 were also identified using ICPC-2/ICD-10 and visa-versa.

Figure 2 shows multimorbidity prevalence estimates using the 2+ and the 3+ definitions across the different number of chronic conditions included. For all classification groups, the prevalence estimates derived when using Diederichs's 11 chronic conditions were significantly lower than those using the 12 most prevalent chronic conditions which in turn were significantly lower than estimates based on all chronic conditions. Prevalence estimates based on 12 most prevalent chronic conditions and on the 24 common chronic conditions (tick boxes) did not significantly differ except that 24 chronic conditions produced higher estimates when using 3+ individual chronic conditions or 3+ CIRS domains.

When using a restricted number of chronic conditions (ie. Diederichs's list or Fortin et al's 12) rather than all chronic conditions, the proportion of patients identified as having multimorbidity was significantly less when multimorbidity was defined as 3+ than when defined as 2+. For example, applying the 2+ definition to ICPC-2 chapters, using the 12 most prevalent chronic conditions, identified 79.4% of those identified as multimorbid using all chronic conditions. Using the 3+ ICPC-2 chapters definition, the 12 most prevalent conditions only identified 67.5%. Similarly, using Diederich's list with the 2+ definition identified 54.5% and the 3+ definition identified only 32.8% of those identified using all chronic conditions.

Figure 3 shows the age-specific multimorbidity prevalence estimates using the 2+ and 3+ definitions by individual chronic conditions and ICPC-2 chapters. Only the ICPC-2 chapters are presented as we have demonstrated there was no significant difference between estimates derived using ICPC-2 chapters, ICD-10 chapters or CIRS domains. The age-specific prevalence using both 2+ individual chronic conditions and 2+ ICPC-2 chapters increased rapidly up to the 70-79 years age group, and remained steady in the older age groups. Compared with 2+, the increase in prevalence started later for 3+ individual chronic

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conditions (between 20-29 and 30-39 years of age). For 3+ ICPC-2 chapters this increase started even later (between 30-39 and 40-49 years of age). For both the 3+ measures the prevalence did not plateau until 80-89 years of age, 10 years later than when using the 2+ definition.

Discussion

This study has shown that multimorbidity prevalence estimates are independently affected by the number of chronic conditions collected in a study, how a disease entity is defined, and the minimum number of disease entities used to define multimorbidity. It has also demonstrated that health data classified to ICPC-2 chapters, ICD-10 chapters, or CIRS domains produce similar multimorbidity prevalence estimates.

Dimension One – Does the way disease entities are defined affect multimorbidity prevalence estimates?

We found that when multimorbidity is defined as 2+ disease entities, prevalence estimates are similar no matter how a disease entity is defined, be it an individual chronic condition, or an ICPC-2 chapter, ICD-10 chapter or CIRS domain involving one or more chronic conditions. This means that studies that define multimorbidity as 2+ can be compared even if the morbidity is classified differently. However, when multimorbidity is defined as 3+ disease entities, using individual chronic conditions produces higher prevalence estimates than counting different domains/chapters affected. We conclude that researchers should not compare results from studies using the 3+ definition when one study has used grouped chronic conditions (classified) and the other individual chronic conditions.

Our finding that chronic conditions were predominantly classified to body system-specific chapters/domains for all three classifications suggests that chapters/domains could be used to represent body systems affected. We also found no difference between the prevalence estimates produced with any of the three classification systems. Together, these results

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suggest researchers may compare prevalence estimates from studies that count different ICPC-2 chapters, ICD-10 chapters or CIRS domains affected by chronic conditions. This allows researchers to draw data from primary care or hospital health records regardless of the classification system used (ICPC-2 or ICD-10) and know that results will be comparable to published studies that have used CIRS.(4;13)

Dimension 2 – Does the minimum number of disease entities required to define multimorbidity affect multimorbidity prevalence estimates?

We found that the higher the minimum number of different disease entities used to define multimorbidity, the lower the prevalence estimate. If multimorbidity is defined as 2+ disease entities, nearly every second person sitting in front of the GP would have multimorbidity, whereas using 3+ decreased the estimate to nearly one-in-four. Like Fortin et al, we found that the 3+ definition provided greater differentiation in the older age groups than the 2+ definition. These results support their argument that using 2+ disease entities identifies such a large proportion of patients as having multimorbidity that it lacks the specificity to be useful, with a minimum of three disease entities arguably a better measure of multimorbidity.

Dimension 3 – Does the number of chronic conditions included in the study affect multimorbidity estimates?

As previous research suggests,(11;12) the number of chronic conditions studied affects the multimorbidity prevalence estimates – estimates based on a low number of chronic conditions being a fraction of those based on all chronic conditions. In our study, Diederichs's list identified only half the patients identified with multimorbidity using all chronic conditions when using 2+, and only a third using 3+. Including the 12 most prevalent chronic conditions (suggested by Fortin et al) four out of five multimorbid patients were identified using 2+ and two-thirds using 3+. While both used a similar number of chronic conditions, Diederichs's list included the most prevalent chronic conditions in patients aged 65 years and over whereas Fortin et al suggested the most prevalent overall.

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It is clear from these results that no matter how multimorbidity is defined, the list of chronic conditions suggested by Diederich et al as a minimum is not sufficient to reliably measure multimorbidity prevalence. Using the 12 most prevalent chronic conditions as suggested by Fortin et al, does provide prevalence estimates that are reasonably close to those gained with all chronic conditions when using the 2+ definition. However, when multimorbidity is defined as 3+, the twelve most prevalent chronic conditions are not sufficient to measure multimorbidity. For the 3+ definition, ideally researchers should include all chronic conditions in their study.

This study has some limitations. We only included chronic conditions, whereas some authors have recently included acute conditions in their definition of multimorbidity.(9;21) Including acute conditions is understandable in a clinical setting, as they will temporarily increase the patient's complexity of care. However, where the goal is to measure the prevalence of multimorbidity to inform planning to meet the health resource requirements of these high need patients, the use of only chronic conditions is logical.

Fortin et al suggest that when studying multimorbidity one should also include a measure of severity.(8) This study did not attempt to measure severity because of the limited space on the questionnaire and concerns that the additional burden on the GPs may reduce the response rate.

While our study was cross sectional, the variables tested are relevant to all types of multimorbidity studies, be they cross-sectional, longitudinal, interview-based or based on health record review.

Throughout this study we have found that multimorbidity behaves quite differently when defined as 2+ disease entities or 3+. With the 2+ definition, reasonable prevalence estimates could be obtained using only a dozen prevalent chronic conditions, regardless of how a disease entity was defined. With the 3+ definition, the way the disease entity was defined was important— counting individual chronic conditions produced significantly higher

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estimates than counting chapters/domains. The number of chronic conditions studied was also important as studying a restricted number of chronic conditions produced significantly lower estimates than studying all chronic conditions. However, the prevalence estimates gained using 2+ were so encompassing that they lacked specificity – especially in older patients, whereas 3+ provided greater specificity and more differentiation among the elderly patients.

These results suggest that the concept of 2+ and 3+ multimorbidity are quite different. Rather than having both these concepts included under the same label, we propose adding "complex" to those patients with 3+ chronic conditions from different body systems to clarify the meaning. "Multimorbidity' would be defined as the "co-occurrence of two or more chronic conditions within one person without defining an index chronic condition". "Complex-multimorbidity" would be defined as the "co-occurrence of three or more chronic conditions affecting three or more different body systems within one person without defining an index chronic condition". In this way we still have the more encompassing 2+ definition to compare with previous work, while also being able to identify patients requiring additional care.

For consistency, we also propose a similar concept for comorbidity. We suggest that "complex comorbidity" be defined as 'the existence of two or more additional chronic conditions from two or more body systems different to that of the index chronic condition under study'. This would mean that all patients with complex multimorbidity would also have complex comorbidity, the only difference being whether there is a chronic condition of interest.

There are advantages to using body systems affected (as represented by chapters/domains to which a chronic condition had been classified) rather than individual chronic conditions as 'disease entities'. Take for example two patients with three chronic conditions: patient A has peripheral vascular disease, hypertension and Type 2 diabetes; patient B has depression, osteoarthritis and Type 2 diabetes. The chronic conditions in patient A only affect two body

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systems while those in patient B, affect three. According to our definitions, both would have multimorbidity, but patient B would also have complex multimorbidity. Patients identified with chronic conditions in 3+ body systems (complex multimorbidity) may be those whose care is more complex, as chronic conditions in different body systems are likely to compete for treatment, while the treatments of chronic conditions within the same system are more likely to be complementary. This is a similar concept to Piette and Kerr's idea of concordant and discordant comorbidity.(22)

Counting the body systems affected also provides an estimate of the specialist types that may be involved in the care of the patient. This is important for healthcare planning as it reduces double counting of chronic conditions that may be referred to the same specialist type, e.g. a patient with depression and anxiety may be referred to one psychiatrist (not two). It also identifies patients who may need assistance with coordination of specialist care, as the health-care of patients with multimorbidity is more likely to be poorly coordinated.(23;24)

Conclusion

For the first time, a single large prospective study has been used to test the effect of the way multimorbidity is measured on prevalence estimates, while controlling for other variables, using the same data for all measures. This is not possible with systematic reviews. We have shown that multimorbidity behaves differently when defined as 2+ disease entities, and when it is defined as 3+ disease entities. To address this, we recommend that

- 'multimorbidity' be defined as the 'co-occurrence of two or more chronic conditions within one person without defining an index chronic condition' and
- 'complex multimorbidity' be defined as the "co-occurrence of three or more chronic conditions affecting three or more different body systems within one person without defining an index chronic condition".

This study provides some evidence that complex multimorbidity is a more useful measure of multimorbidity as it results in a lower prevalence estimate and shows greater differentiation

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among older patients. However, further research is needed to assess whether 'complex multimorbidity' is indeed better than alternative measures of multimorbidity (such as counting individual chronic conditions, measures of severity etc.) in identifying patients with greater health care resource use, lower quality of life and overall severity of illness.

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Data sharing statement: There are no additional data available.

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Table 1: Proportion of patients in GP waiting rooms that have at least one condition in each CIRS domain, ICPC 2 chapter or ICD 10 chapter

CIRS domain	n	Proportion of patients in waiting room (95% CIs)	ICPC 2 chapter	n	Proportion of patients in waiting room (95% CI)	ICD 10 chapter	n	Proportion of patients in waiting room (95% CI)
Vascular	2,934	33.7% (31.7%-35.7%)	**K (Circulatory)**	2,762	31.7% (29.8-33.6)	**9 (Circulatory)**	2,748	31.6% (29.7-33.5)
Musculoskeletal*	2,479	28.5% (26.6-30.4)	**T (Endocrine†)**	2,694	30.9% (29.2-32.7)	**4 (Endocrine~)**	2,688	30.9% (29.1-32.7)
Psychiatric	1,930	22.2% (20.6-23.7)	**L (Musculoskeletal)**	2,293	26.3% (24.5-28.2)	**13 (Musculoskeletal~)**	2,268	26.0% (24.2-27.9)
Endocrine*	1,840	21.1% (19.7-22.5)	**P (Psychological)**	1,953	22.4% (20.8-24.0)	**5 (Mental & behavioural disorders)**	1,910	21.9% (20.4-23.5)
Respiratory	1,195	13.7% (12.7-14.8)	**D (Digestive)**	1,387	15.9% (14.7-17.2)	**11 (Digestive)**	1,296	14.9% (13.7-16.1)
Cardiac	1,089	12.5% (11.3-13.7)	**R (Respiratory)**	1,227	14.1% (13.0-15.2)	**10 (Respiratory)**	1,211	13.9% (12.9-15.0)
Upper gastrointestinal	1,052	12.1% (11.0-13.2)	**X & Y (Genital)**	353	4.1% (3.5-4.6)	**2 (Neoplasms)**	474	5.4% (4.7-6.1)
Neurological	542	6.2% (5.4-7.0)	**U (Urology)**	312	3.6% (3.0-4.2)	**14 (Genitourinary)**	389	4.5% (3.8-5.2)
Opthalmological*	444	5.1% (4.4-5.8)	**N (Neurological)**	311	3.6% (3.1-4.1)	**6 (Nervous system)**	318	3.7% (3.1-4.2)
Lower gastrointestinal	377	4.3% (3.7-4.9)	**F (Eye)**	303	3.5% (2.9-4.1)	**7 (Eye & adnexa)**	292	3.4% (2.8-3.9)
Genitourinary	351	4.0% (3.4-4.6)	**S (Skin)**	294	3.4% (2.8-3.9)	**12 (Skin & subcutaneous tissue)**	179	2.1% (1.7-2.4)
Renal	232	2.7% (2.2-3.2)	**A (General & Unspecified)**	134	1.5% (1.2-1.8)	**18 (Symptoms~)**	105	1.2% (0.9-1.5)
Hematological	130	1.5% (1.0-2.0)	**B (Blood†)**	130	1.5% (1.0-2.0)	**1 (Infectious and parasitic~)**	80	0.9% (0.7-1.2)
Hepatic & pancreatic	90	1.0% (0.8-1.3)	**H (Ear†)**	47	0.5% (0.4-0.7)	**21 (Factors influencing health status~)**	68	0.8% (0.4-1.2)
Whole system	39	0.4% (0.3-0.6)	**W (Pregnancy†)**	8	0.1% (0.0-0.2)	**3 (Blood~)**	58	0.7% (0.5-0.9)
			Z (Social problems)	2	0.0% (0.0-0.1)	**19 (Injury, poisoning~)**	58	0.7% (0.5-0.8)
						8 (Ear and mastoid process)	47	0.5% (0.4-0.7)
						17 (Congenital~)	23	0.3% (0.2-0.4)
						15 (Pregnancy~)	3	0.0% (0.0-0.1)
						16 (Conditions - perinatal period~)	2	0.0% (0.0-0.1)

* = CIRS Musculoskeletal & tegumental; Endocrine, metabolic, breast; Opthalmological & otorhinolaryngology

† = ICPC 2 Endocrine, nutritional & metabolic; Blood, blood forming organs and immune mechanism; Ear & hearing; Pregnancy, child-bearing, family planning

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~ = ICD 10 2 Endocrine, nutritional & metabolic ; Musculoskeletal and connective tissue; Symptoms, signs and abnormal clinical and laboratory findings; Certain infectious and parasitic diseases; Factors influencing health status and contact with health services; Blood, blood forming organs and certain disorders involving the immune mechanism; Injury, poisoning and certain other consequences of external causes; Congenital malformations, deformations and chromosomal abnormalities; Pregnancy, childbirth & the puerperium; Certain conditions originating from the perinatal period

Table 2: Concordance of patients identified with multimorbidity (3+ definition) between ICPC-2, ICD-10 and CIRS

	Proportion identified for each classification system (horizontal) that were also identified using other classification systems (vertical) (95% CIs)		
	ICPC-2	ICD-10	CIRS
ICPC-2	100.0%	99.1% (98.7-99.5)	92.1% (90.9-93.3)
ICD-10	99.3% (98.9-99.6)	100.0%	91.9% (90.7-93.1)
CIRS	93.7% (92.6-94.7)	93.3% (92.2-94.4)	100.0%

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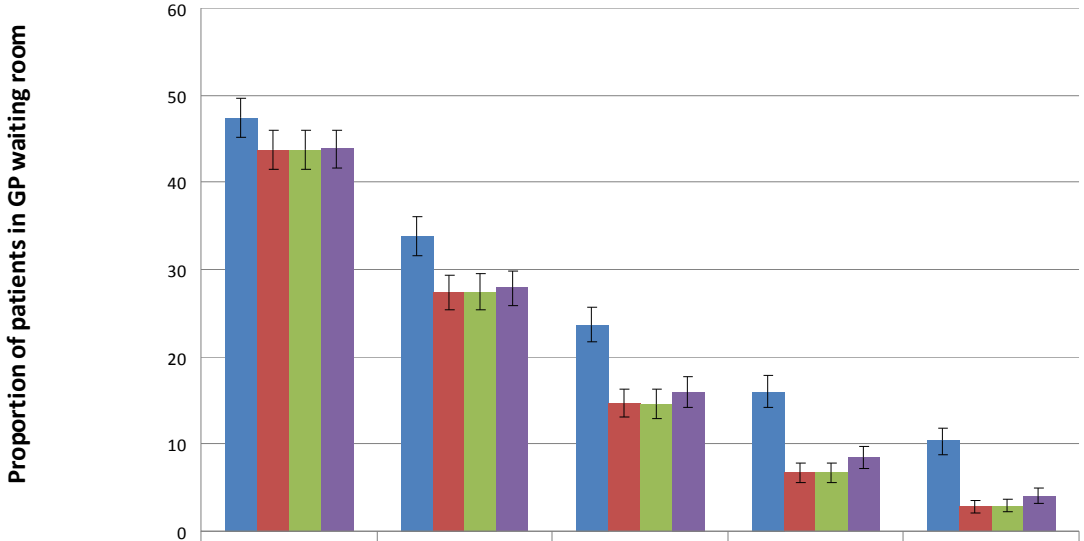
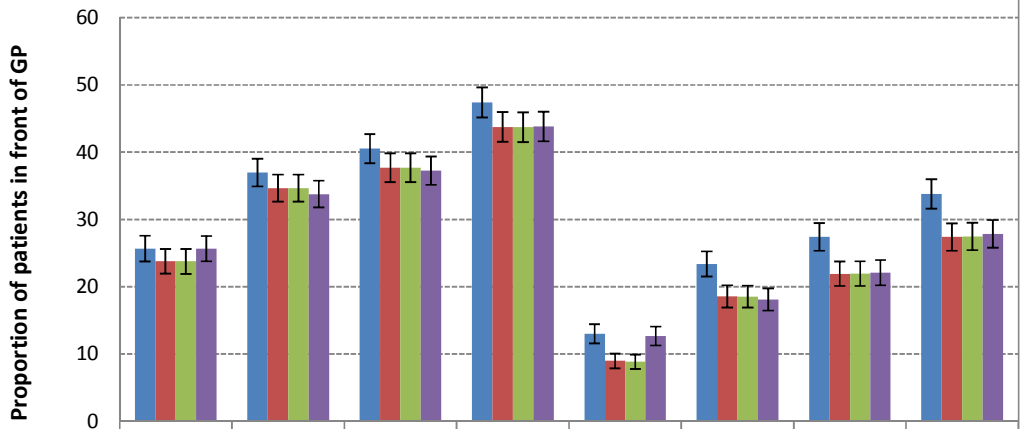
Figure 1: Multiple conditions within patients as defined by different classification systems



	Two +	Three +	Four +	Five +	Six +
Individual conditions	47.4	33.8	23.7	16.0	10.3
ICPC 2 Chapters	43.7	27.4	14.7	6.7	2.8
ICD 10 Chapters	43.7	27.4	14.6	6.7	2.9
CIRS domains	43.8	27.9	16.0	8.4	4.0

Figure 2: Estimated prevalence of multimorbidity by different classification systems and by whether 2+ or 3+ minimum number of disease entities was used



	2+ Diederichs	2+ Fortin	2+ 24 conditions	2+ All chronic conditions	3+ Diederichs	3+ Fortin	3+ 24 conditions	3+ All chronic conditions
Individual diseases	25.7	37.0	40.5	47.4	13.0	23.4	27.4	33.8
ICPC-2 Chapters	23.8	34.7	37.7	43.7	9.0	18.5	21.9	27.4
ICD-10 Chapters	23.8	34.7	37.7	43.7	8.8	18.5	21.9	27.5
CIRS Domains	25.7	33.8	37.2	43.8	12.7	18.1	22.1	27.9

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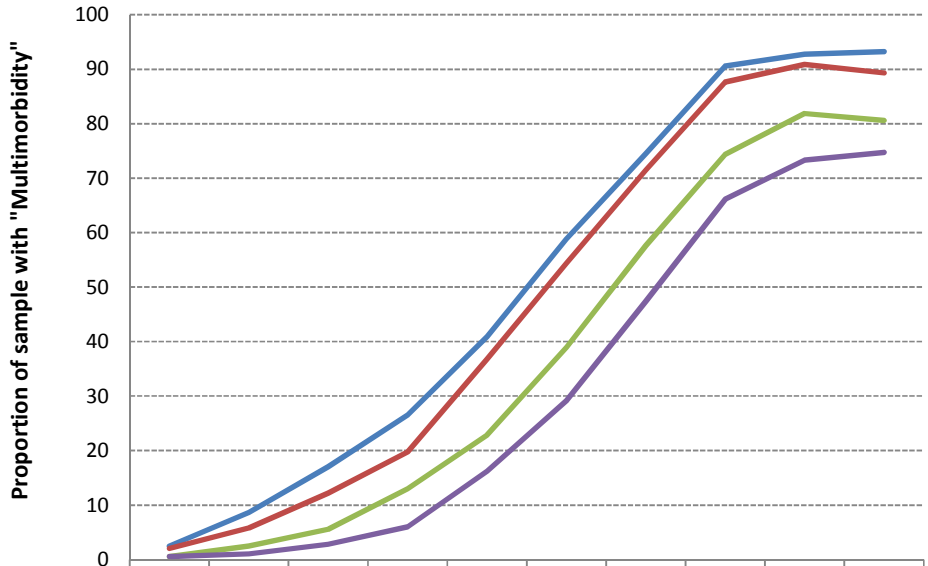
Figure 3: Patient age-specific prevalence of "multimorbidity"



	0-9 years	10-19 years	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	80-89 years	90+ years
2+ Individual diseases	2.4	8.7	17.1	26.6	40.9	58.8	74.5	90.6	92.7	93.2
2+ ICPC-2 chapters	2.0	5.8	12.2	19.7	36.8	54.3	71.5	87.7	90.8	89.3
3+ Individual diseases	0.5	2.5	5.5	13.0	22.8	39.0	57.6	74.3	81.8	80.6
3+ ICPC-2 chapters	0.5	1.0	2.8	6.0	16.2	29.1	47.4	66.1	73.3	74.8

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Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice

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Christopher Harrison – Senior research analyst, Helena Britt – Director, Graeme Miller – Medical Director, Joan Henderson – Deputy Director

Keywords: Multimorbidity, comorbidity, general practice, prevalence, ageing

Word Count: 4,069

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Abstract

Objectives – Prevalence estimates of multimorbidity vary widely due to inconsistent definitions and measurement methods. This study examines independent effect on prevalence estimates of how 'disease entity' is defined — as single chronic condition or chapters/domains in the International Classification of Primary Care (Version 2) (ICPC-2), International Classification of Disease (10th revision) (ICD-10) or the Cumulative Illness Rating Scale (CIRS), the number of disease entities required for multimorbidity, and the number of chronic conditions studied.

Design – National prospective cross sectional study

Setting – Australian general practice

Participants 8,707 random consenting de-identified patient encounters with 290 randomly selected general practitioners

Main outcome measures – Prevalence estimates of multimorbidity using different definitions

Results - Data classified to ICPC-2 chapters, ICD-10 chapters, or CIRS domains produce similar multimorbidity prevalence estimates. When multimorbidity was defined as two or more (2+) disease entities: counting individual chronic conditions and groups of chronic conditions produced similar estimates; twelve most prevalent chronic conditions identified about 80% of those identified using all chronic conditions. When multimorbidity was defined as 3+ disease entities: counting individual chronic conditions produced significantly higher estimates than counting groups of chronic conditions; twelve most prevalent chronic conditions identified only two-thirds of patients identified using all chronic conditions.

Conclusion - Multimorbidity defined as 2+ disease entities can be measured using different definitions of disease entity with as few as 12 prevalent chronic conditions, but lacks specificity to be useful, especially in older people. Multimorbidity, defined as 3+, requires more measurement conformity and inclusion of all chronic conditions, but provides greater specificity than 2+ definition. The proposed concept of "complex multimorbidity", the co-occurrence of three or more chronic conditions affecting three or more different body systems within one person without defining an index chronic condition, may be a useful in identifying high need individuals.

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ARTICLE SUMMARY

Strengths and limitations of the study

- A large, representative, prospective study of multimorbidity, involving 290 general practitioners and 8,707 patients, allowed testing of the independent effect of variables on prevalence estimates, something not possible with systematic reviews.
- This study investigated all chronic conditions, not a selection of conditions.
- This study used the general practitioner as an "expert interviewer", drawing upon the patient's knowledge, the patient's health record and their own knowledge to indicate the patient's current chronic conditions. Most multimorbidity studies rely on only one of these sources of data.
- This study only considered chronic conditions, whereas some authors now include acute conditions when defining multimorbidity.

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Introduction

Research into coexistence of multiple chronic health conditions in an individual was initially concerned with comorbidity, defined as 'the existence or occurrence of any distinct additional disease entity in a patient who has the index disease under study'.(1) However since the early nineties, interest has progressed to 'multimorbidity', commonly defined as the "co-occurrence of two or more diseases within one person without defining an index disease".(2)

Interest in multimorbidity is growing due to its expected increase resulting from the ageing of the world's population.(3;4) Studies have shown that multimorbidity is associated with increased patient mortality, demand on health resources, complexity of care, and with reduced patient quality of life.(5;6) However, prevalence estimates of multimorbidity have ranged from 3.5%(7) to 98.5%,(8) the wide variance thought to be due to the lack of standards defining multimorbidity, and how it is measured. A recent systematic review found 132 definitions involving 1,631 different criteria.(9) There have been many calls for standards and guidelines for research into multimorbidity.(10-12) Recent systematic reviews have raised specific issues regarding the way multimorbidity is defined and/or measured.(11;12)

The first issue is the number of conditions studied. Fortin et al(11) found this ranged from 5 to all conditions. Diederichs et al(12) reported a range of 4 to 102 conditions, (mean,18.5,median 14) and suggested that conditions may be chosen for pragmatic reasons (such as data availability), as the majority of authors did not give reasons for their selection. Where they did, the most common was those conditions with a high prevalence or high impact on patients.(12) Both Diederichs et al(12) and Fortin et al(11) suggested studies considering only a few conditions produced lower prevalence estimates than those examining many conditions. Diederichs et al(12) suggested a list of 11 chronic conditions prevalent in the elderly as a minimum (cancer, diabetes mellitus, depression, hypertension, myocardial infarction, chronic ischeamic heart disease, heart arrhythmias, heart insufficiency, stroke, CODP, arthritis). Fortin et al(11) suggested that any 12 prevalent conditions should suffice to measure multimorbidity accurately.

The second issue is how 'disease entity' was defined in multimorbidity studies. Ideally, morbidities being counted should be "distinct" disease entities. However, disease entities used across studies varied from very specific conditions to groups of conditions. Even Diederich et al's suggested list(12) (above), includes some disease entities that are groups of conditions (such as arthritis and cancer) and some very specific, closely related conditions (eg. myocardial infarction and chronic ischaemic heart disease). It is debatable whether

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both myocardial infarction and chronic ischaemic heart disease should be considered as two separate disease entities in measuring multimorbidity. Some multimorbidity studies have tried to overcome this problem by only counting chronic conditions that affect different body systems, to ensure the count was of distinct disease entities.(4;13) These studies used the Cumulative Illness Rating Scale (CIRS)(14) domains to group chronic conditions by body system.(4;13) Fortin et al suggested that while the use of the CIRS needed further research, this approach may simplify coding and data collection.(11) The impact of counting the different body systems affected by chronic conditions, on multimorbidity prevalence estimates is not known.

Most primary care based multimorbidity studies rely on health record review.(11) A disadvantage of using CIRS in such reviews is that it requires additional mapping of diagnoses from the classification system in which the health records were coded. The two most commonly used disease classification systems are the International Classification of Primary Care (Version 2) (ICPC-2)(15) and the International Classification of Disease (10th revision) (ICD-10).(16) ICPC-2 is used in primary care and its chapters, (with the exception of 'General & Unspecified' and 'Social' chapters), are body system-based, following the principle that localisation takes precedence over aetiology.(16) ICD-10 is primarily used in hospitals and its chapters axes include body systems, aetiology and "others".(16) ICD-10 lacks specificity for classification of undiagnosed problems or symptoms, both of which are commonly managed in primary care.(17) This has meant that data from primary health care records classified in the two systems have looked very different in the past. However, since most multimorbidity studies examine only chronic conditions this problem may be avoided when conditions are grouped at the chapter level. It is not known whether counting disease entities from different CIRS domains, ICPC-2 or ICD-10 chapters produces comparable multimorbidity prevalence estimates.

The third issue is the number of disease entities required to define multimorbidity. Originally, multimorbidity was defined as two or more (2+) disease entities, but recently there has been debate about whether three or more (3+) may be a better measure. Fortin et al argue that using 2+ disease entities identifies such a high proportion of patients as multimorbid that the measure lacks specificity.(11) They found that age-specific prevalence of multimorbidity using the 2+ definition produced an "S" shaped curve with a flat plateau for older ages. When using 3+, the increase in prevalence by age was more linear, with greater differentiation in older age groups. The authors further argued that using 3+ disease entities results in a lower prevalence estimate, is likely to identify patients with greater health needs, and is therefore more useful to clinicians.(11) They recommended further research to test the 3+ definition of multimorbidity.(11)

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The current study was conducted in Australian general practice. Australia's universal medical insurance scheme, Medicare, fully or partially covers the individual's cost of visits to general practitioners (GPs). GPs provide the bulk of primary medical care and act as gate keepers to government-subsidised health care from other medical specialists. There are no patient lists and patients are free to visit multiple GPs and practices as they choose.

Our study examines how multimorbidity prevalence estimates are effected by: the number of chronic conditions studied; how a disease entity is defined; and the minimum number of disease entities required to define multimorbidity. We use a large Australian general practice based prospective multimorbidity study, which allows us to examine the effect of each of these variables on multimorbidity prevalence estimates while controlling for other confounding variables, an approach not possible in systematic reviews.

Method

The BEACH (Bettering the Evaluation And Care of Health) program is a continuous, national cross-sectional survey of general practice activity in Australia.(17) Each year an ever-changing sample of about 1,000 GPs is randomly selected, and each GP records information about encounters with 100 consecutive consenting patients, on structured paper forms.(17)

In sub-studies of BEACH, the GP records information additional to the encounter data, in discussion with the patient. The full methods for this sub-study are reported elsewhere.(18) In brief, it measured the prevalence of diagnosed chronic conditions in patients attending general practice in Australia. Over three five-week recording periods (August 2008 to May 2009) 375 sampled GPs were asked to record all diagnosed chronic conditions for each of 30 consecutive patients on 30 bespoke forms within their 100 BEACH records. A sample of the instruction sheet and recording form can be found at www.http://sydney.edu.au/medicine/fmrc/publications/sand-abstracts/132-Multimorbidity.pdf

GPs were asked, "Does the patient have any of the following chronic diseases/problems?" Common chronic conditions were listed (tick boxes) with additional free text fields to record other unlisted chronic conditions. A "no chronic conditions" option was also provided. Listed chronic conditions were primarily those most frequently managed in Australian general practice(17) and were inclusions in O'Halloran et al's definition of chronic conditions.(19) The free text options relied on GPs judgement of whether a condition was chronic in this patient. GPs were instructed to *"Use your own knowledge, patient knowledge and health records as you see fit, in order to answer these questions".* Additional free text chronic conditions were coded using the ICPC-

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2 PLUS terminology,(20) which automatically classified them into ICPC-2.(15) All chronic conditions were classified to ICD-10 chapters(16) (n=20), ICPC-2 chapters,(15) and CIRS domains(14) (Table 1). There were some chronic conditions (e.g. multisite cancer) that involved multiple systems. As these would usually be counted multiple times in different CIRS domains, we created an additional domain called "Whole system", resulting in 15 CIRS domains instead of the usual 14. The ICPC-2 male and female genital system chapters (chapters Y and X) were combined as they referred to the same body system, resulting in 16 ICPC-2 chapters (rather than the usual 17). This sample was previously shown to be representative of the age-sex distribution of patients at all GP encounters claimed (as items of service) through Medicare in 2008–09(18).

Using this large prospective study we examined the effect of three different dimensions of measuring multimorbidity while controlling for other confounding variables. This is achieved through the structure of the study, by only changing one of the three variables at a time.

Dimension One – Does the way disease entities are defined affect multimorbidity prevalence estimates?

To test this dimension we defined disease entity four different ways. First, each recorded/ticked chronic condition was treated as a separate disease entity. For the other three methods we considered a disease entity to be a chapter/domain that was affected by at least one chronic condition in each of the three classification systems. Comparing the resulting multimorbidity prevalence estimates we were able to test two research questions. Firstly, whether counting different body systems affected by chronic conditions produces prevalence estimates comparable to counting individual chronic conditions. Secondly, whether counting the number of different CIRS domains, ICPC-2 chapters or ICD-10 chapters affected produces comparable prevalence estimates.

Dimension 2 – Does the minimum number of disease entities required to define multimorbidity affect multimorbidity prevalence estimates?

We compared prevalence of multimorbidity using 2+ through to 6+ disease entities. We also compared the age-specific prevalence of multimorbidity when it was defined as 2+ and 3+ disease entities, to see whether we could reproduce the "S" shaped curve when using the 2+ definition and test whether using 3+ provided greater differentiation among older patients, as found by Fortin et al.(11)

Dimension 3 – Does the number of chronic conditions included in the study affect multimorbidity estimates?

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We reduced the number of chronic conditions used, in order to simulate studies that were based on fewer chronic conditions. We used the 11 minimum chronic conditions suggested by Diederichs et al (listed above, 'Diederich's list')(12), the 12 most prevalent chronic conditions in our study (hypertension, hyperlipidaemia, ischeamic heart disease, Type 2 diabetes, obesity, osteoarthritis, chronic back pain, asthma, depression, anxiety, GORD, malignant neoplasms) as suggested by Fortin et al(11) and the 24 listed chronic conditions with a tick box. We then compared these results with those generated using all diagnosed chronic conditions.

BEACH sub-studies have a single stage cluster design, with each GP having 30 patients clustered around them. The cluster effect was accounted for using SAS 9.3.

Ethics committees of the University of Sydney and Australian Institute of Health and Welfare approved BEACH and this sub-study.

Results

Completed research packs were returned by 290 GPs (77.3%) sampling 8,707 patients. In total 66.5% of patients (n= 5,777) had at least one chronic condition and 33.7% (n=2,930) had none. The intracluster correlation coefficient was 0.121 for patients with at least one chronic condition.

Table 1 shows the proportion of patients with at least one chronic condition in each chapter/domain. For both ICPC-2 and ICD-10, the 11 most prevalent chapters were body-specific, with the non-body system specific chapters being relatively uncommon. Prevalence estimates of patients with at least one chronic condition within a body-system specific ICD-10 and ICPC-2 chapter were remarkably similar, the top six chapters being in the same order, with no significant differences in the prevalence estimates for these six chapters. There were larger differences between estimates using CIRS and those from both ICPC-2 and ICD-10. The major differences were due to CIRS splitting cardiovascular into vascular and cardiac domains, classifying cerebrovascular disease as neurological, and classifying hyperlipidaemia in the vascular domain. In all systems the most frequent chapters/domains were those relating to the: cardiac/vascular/circulatory; endocrine; musculoskeletal; psychological; digestive; and respiratory systems.

Figure 1 shows the prevalence of multimorbidity among patients in the sample (representing those in a GP's waiting room) using different definitions of multimorbidity. Estimated prevalence of multimorbidity ranged from 47.4% using 2+ individual chronic conditions to 2.8% when using 6+ ICPC-2 chapters. For all definitions using 3+ disease entities or more, counting individual chronic conditions resulted in significantly higher prevalence estimate than any of the grouped estimates. This difference increased proportionally as the minimum number

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of disease entities increased — the individual chronic conditions estimate was 23% higher than the ICPC-2 chapter estimate at 3+ disease entities, through to 268% higher at 6+ disease entities. Overall there was no significant difference found between prevalence estimates using ICD-10, ICPC-2 and CIRS, from 2+ through to 6+ disease entities.

Using the ICD-10 and ICPC-2 estimates, when multimorbidity was defined as two or more disease entities, about 44% of patients presenting to GP's were identified as multimorbid. This prevalence decreased with each increase in the number of disease entities required, with about 27% of patients being considered multimorbid for 3+, about 15% for 4+, 7% for 5+ and only 3% for 6+ disease entities. There was nearly perfect concordance between patients identified as having multimorbidity using the ICD-10 and ICPC-2 classifications systems. For example when using the minimum of three disease entities as the definition of multimorbidity, over 99% of patients identified using ICD-10 were also identified using ICPC-2 and visa-versa (Table 2) There was also high concordance between ICPC-2/ICD-10 and CIRS. For every 12 patients identified as having multimorbidity with CIRS, 11 were also identified using ICPC-2/ICD-10 and visa-versa.

Figure 2 shows multimorbidity prevalence estimates using the 2+ and the 3+ definitions across the different number of chronic conditions included. For all classification groups, the prevalence estimates derived when using Diederichs's 11 chronic conditions were significantly lower than those using the 12 most prevalent chronic conditions which in turn were significantly lower than estimates based on all chronic conditions. Prevalence estimates based on 12 most prevalent chronic conditions and on the 24 common chronic conditions (tick boxes) did not significantly differ except that 24 chronic conditions produced higher estimates when using 3+ individual chronic conditions or 3+ CIRS domains.

When using a restricted number of chronic conditions (ie. Diederichs's list or Fortin et al's 12) rather than all chronic conditions, the proportion of patients identified as having multimorbidity was significantly less when multimorbidity was defined as 3+ than when defined as 2+. For example, applying the 2+ definition to ICPC-2 chapters, using the 12 most prevalent chronic conditions, identified 79.4% of those identified as multimorbid using all chronic conditions. Using the 3+ ICPC-2 chapters definition, the 12 most prevalent conditions only identified 67.5%. Similarly, using Diederich's list with the 2+ definition identified 54.5% and the 3+ definition identified only 32.8% of those identified using all chronic conditions.

Figure 3 shows the age-specific multimorbidity prevalence estimates using the 2+ and 3+ definitions by individual chronic conditions and ICPC-2 chapters. Only the ICPC-2 chapters are presented as we have

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demonstrated there was no significant difference between estimates derived using ICPC-2 chapters, ICD-10 chapters or CIRS domains. The age-specific prevalence using both 2+ individual chronic conditions and 2+ ICPC-2 chapters increased rapidly up to the 70-79 years age group, and remained steady in the older age groups. Compared with 2+, the increase in prevalence started later for 3+ individual chronic conditions (between 20-29 and 30-39 years of age). For 3+ ICPC-2 chapters this increase started even later (between 30-39 and 40-49 years of age). For both the 3+ measures the prevalence did not plateau until 80-89 years of age, 10 years later than when using the 2+ definition.

Discussion

This study has shown that multimorbidity prevalence estimates are independently affected by the number of chronic conditions collected in a study, how a disease entity is defined, and the minimum number of disease entities used to define multimorbidity. It has also demonstrated that health data classified to ICPC-2 chapters, ICD-10 chapters, or CIRS domains produce similar multimorbidity prevalence estimates.

Dimension One – Does the way disease entities are defined affect multimorbidity prevalence estimates?

We found that when multimorbidity is defined as 2+ disease entities, prevalence estimates are similar no matter how a disease entity is defined, be it an individual chronic condition, or an ICPC-2 chapter, ICD-10 chapter or CIRS domain involving one or more chronic conditions. This means that studies that define multimorbidity as 2+ can be compared even if the morbidity is classified differently. However, when multimorbidity is defined as 3+ disease entities, using individual chronic conditions produces higher prevalence estimates than counting different domains/chapters affected. We conclude that researchers should not compare results from studies using the 3+ definition when one study has used grouped chronic conditions (classified) and the other individual chronic conditions.

Our finding that chronic conditions were predominantly classified to body system-specific chapters/domains for all three classifications suggests that chapters/domains could be used to represent body systems affected. We also found no difference between the prevalence estimates produced with any of the three classification systems. Together, these results suggest researchers may compare prevalence estimates from studies that count different ICPC-2 chapters, ICD-10 chapters or CIRS domains affected by chronic conditions. This allows researchers to draw data from primary care or hospital health records regardless of the classification system

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used (ICPC-2 or ICD-10) and know that results will be comparable to published studies that have used CIRS.(4;13)

Dimension 2 – Does the minimum number of disease entities required to define multimorbidity affect multimorbidity prevalence estimates?

We found that the higher the minimum number of different disease entities used to define multimorbidity, the lower the prevalence estimate. If multimorbidity is defined as 2+ disease entities, nearly every second person sitting in front of the GP would have multimorbidity, whereas using 3+ decreased the estimate to nearly one-in-four. Like Fortin et al, we found that the 3+ definition provided greater differentiation in the older age groups than the 2+ definition. These results support their argument that using 2+ disease entities identifies such a large proportion of patients as having multimorbidity that it lacks the specificity to be useful, with a minimum of three disease entities arguably a better measure of multimorbidity.

Dimension 3 – Does the number of chronic conditions included in the study affect multimorbidity estimates?

As previous research suggests,(11;12) the number of chronic conditions studied affects the multimorbidity prevalence estimates – estimates based on a low number of chronic conditions being a fraction of those based on all chronic conditions. In our study, Diederichs's list identified only half the patients identified with multimorbidity using all chronic conditions when using 2+, and only a third using 3+. Including the 12 most prevalent chronic conditions (suggested by Fortin et al) four out of five multimorbid patients were identified using 2+ and two-thirds using 3+. While both used a similar number of chronic conditions, Diederichs's list included the most prevalent chronic conditions in patients aged 65 years and over whereas Fortin et al suggested the most prevalent overall.

It is clear from these results that no matter how multimorbidity is defined, the list of chronic conditions suggested by Diederich et al as a minimum is not sufficient to reliably measure multimorbidity prevalence. Using the 12 most prevalent chronic conditions as suggested by Fortin et al, does provide prevalence estimates that are reasonably close to those gained with all chronic conditions when using the 2+ definition. However, when multimorbidity is defined as 3+, the twelve most prevalent chronic conditions are not sufficient to measure multimorbidity. For the 3+ definition, ideally researchers should include all chronic conditions in their study.

This study has some limitations. We only included chronic conditions, whereas some authors have recently included acute conditions in their definition of multimorbidity.(9;21) Including acute conditions is

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understandable in a clinical setting, as they will temporarily increase the patient's complexity of care. However, where the goal is to measure the prevalence of multimorbidity to inform planning to meet the health resource requirements of these high need patients, the use of only chronic conditions is logical.

Fortin et al suggest that when studying multimorbidity one should also include a measure of severity.(8) This study did not attempt to measure severity because of the limited space on the questionnaire and concerns that the additional burden on the GPs may reduce the response rate.

While our study was representative of patients at GP encounters, it should be remembered that patients are not representative of population. Patients at GP encounters are generally older and therefore more likely to have a chronic condition(18).

While our study was cross sectional, the variables tested are relevant to all types of multimorbidity studies, be they cross-sectional, longitudinal, interview-based or based on health record review.

Throughout this study we have found that multimorbidity behaves quite differently when defined as 2+ disease entities or 3+. With the 2+ definition, reasonable prevalence estimates could be obtained using only a dozen prevalent chronic conditions, regardless of how a disease entity was defined. With the 3+ definition, the way the disease entity was defined was important— counting individual chronic conditions produced significantly higher estimates than counting chapters/domains. The number of chronic conditions studied was also important as studying a restricted number of chronic conditions produced significantly lower estimates than studying all chronic conditions. However, the prevalence estimates gained using 2+ were so encompassing that they lacked specificity – especially in older patients, whereas 3+ provided greater specificity and more differentiation among the elderly patients.

These results suggest that the concept of 2+ and 3+ multimorbidity are quite different. Rather than having both these concepts included under the same label, we propose adding "complex" to those patients with 3+ chronic conditions from different body systems to clarify the meaning. "Multimorbidity' would be defined as the "co-occurrence of two or more chronic conditions within one person without defining an index chronic condition". "Complex-multimorbidity" would be defined as the "co-occurrence of three or more chronic conditions affecting three or more different body systems within one person without defining an index chronic condition". In this way we still have the more encompassing 2+ definition to compare with previous work, while also being able to identify patients requiring additional care.

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For consistency, we also propose a similar concept for comorbidity. We suggest that "complex comorbidity" be defined as 'the existence of two or more additional chronic conditions from two or more body systems different to that of the index chronic condition under study'. This would mean that all patients with complex multimorbidity would also have complex comorbidity, the only difference being whether there is a chronic condition of interest.

There are advantages to using body systems affected (as represented by chapters/domains to which a chronic condition had been classified) rather than individual chronic conditions as 'disease entities'. Take for example two patients with three chronic conditions: patient A has peripheral vascular disease, hypertension and Type 2 diabetes; patient B has depression, osteoarthritis and Type 2 diabetes. The chronic conditions in patient A only affect two body systems while those in patient B, affect three. According to our definitions, both would have multimorbidity, but patient B would also have complex multimorbidity. Patients identified with chronic conditions in 3+ body systems (complex multimorbidity) may be those whose care is more complex, as chronic conditions in different body systems are likely to compete for treatment, while the treatments of chronic conditions within the same system are more likely to be complementary. This is a similar concept to Piette and Kerr's idea of concordant and discordant comorbidity.(22)

Counting the body systems affected also provides an estimate of the specialist types that may be involved in the care of the patient. This is important for healthcare planning as it reduces double counting of chronic conditions that may be referred to the same specialist type, e.g. a patient with depression and anxiety may be referred to one psychiatrist (not two). It also identifies patients who may need assistance with coordination of specialist care, as the health-care of patients with multimorbidity is more likely to be poorly coordinated.(23;24)

Conclusion

For the first time, a single large prospective study has been used to test the effect of the way multimorbidity is measured on prevalence estimates, while controlling for other variables, using the same data for all measures. This is not possible with systematic reviews. We have shown that multimorbidity behaves differently when defined as 2+ disease entities, and when it is defined as 3+ disease entities. To address this, we recommend that

- 'multimorbidity' be defined as the 'co-occurrence of two or more chronic conditions within one person without defining an index chronic condition' and

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- ‘complex multimorbidity’ be defined as the “co-occurrence of three or more chronic conditions affecting three or more different body systems within one person without defining an index chronic condition”.

This study provides some evidence that complex multimorbidity is a more useful measure of multimorbidity as it results in a lower prevalence estimate and shows greater differentiation among older patients. However, further research is needed to assess whether ‘complex multimorbidity’ is indeed better than alternative measures of multimorbidity (such as counting individual chronic conditions, measures of severity etc.) in identifying patients with greater health care resource use, complexity of care, lower quality of life and overall severity of illness.

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Ethical approval: The BEACH program and this sub-study were approved by the Human Research Ethics Committee of the University of Sydney (Reference No. 11428) and the Ethics Committee of the Australian Institute of Health and Welfare.

Data sharing statement: No additional data available.

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Figure Legends:

Figure 1: Multiple conditions within patients as defined by different classification systems

Figure 2: Estimated prevalence of multimorbidity by different classification systems and by whether 2+ or 3+ minimum number of disease entities was used

Figure 3: Patient age-specific prevalence of "multimorbidity"

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Table 1: Proportion of patients in GP waiting rooms that have at least one condition in each CIRS domain, ICPC 2 chapter or ICD 10 chapter

* = CIRS Musculoskeletal & tegumental; Endocrine, metabolic, breast; Opthalmological & otorhinolaryngology

† = ICPC 2 Endocrine, nutritional & metabolic; Blood, blood forming organs and immune mechanism; Ear & hearing; Pregnancy, child-bearing, family planning

~ = ICD 10 2 Endocrine, nutritional & metabolic ; Musculoskeletal and connective tissue; Symptoms, signs and abnormal clinical and laboratory findings; Certain infectious and parasitic diseases; Factors influencing health status and contact with health services; Blood, blood forming organs and certain disorders involving the immune mechanism; Injury, poisoning and certain other consequences of external causes; Congenital malformations, deformations and chromosomal abnormalities; Pregnancy, childbirth & the puerperium; Certain conditions originating from

CIRS domain	n	Proportion of patients in waiting room (95% CIs)	ICPC 2 chapter	n	Proportion of patients in waiting room (95% CI)	ICD 10 chapter	n	Proportion of patients in waiting room (95% CI)
Vascular	2,934	33.7% (31.7%-35.7%)	**K (Circulatory)**	2,762	31.7% (29.8-33.6)	**9 (Circulatory)**	2,748	31.6% (29.7-33.5)
Musculoskeletal*	2,479	28.5% (26.6-30.4)	**T (Endocrine†)**	2,694	30.9% (29.2-32.7)	**4 (Endocrine~)**	2,688	30.9% (29.1-32.7)
Psychiatric	1,930	22.2% (20.6-23.7)	**L (Musculoskeletal)**	2,293	26.3% (24.5-28.2)	**13 (Musculoskeletal~)**	2,268	26.0% (24.2-27.9)
Endocrine*	1,840	21.1% (19.7-22.5)	**P (Psychological)**	1,953	22.4% (20.8-24.0)	**5 (Mental & behavioural disorders)**	1,910	21.9% (20.4-23.5)
Respiratory	1,195	13.7% (12.7-14.8)	**D (Digestive)**	1,387	15.9% (14.7-17.2)	**11 (Digestive)**	1,296	14.9% (13.7-16.1)
Cardiac	1,089	12.5% (11.3-13.7)	**R (Respiratory)**	1,227	14.1% (13.0-15.2)	**10 (Respiratory)**	1,211	13.9% (12.9-15.0)
Upper gastrointestinal	1,052	12.1% (11.0-13.2)	**X & Y (Genital)**	353	4.1% (3.5-4.6)	**2 (Neoplasms)**	474	5.4% (4.7-6.1)
Neurological	542	6.2% (5.4-7.0)	**U (Urology)**	312	3.6% (3.0-4.2)	**14 (Genitourinary)**	389	4.5% (3.8-5.2)
Opthalmological*	444	5.1% (4.4-5.8)	**N (Neurological)**	311	3.6% (3.1-4.1)	**6 (Nervous system)**	318	3.7% (3.1-4.2)
Lower gastrointestinal	377	4.3% (3.7-4.9)	**F (Eye)**	303	3.5% (2.9-4.1)	**7 (Eye & adnexa)**	292	3.4% (2.8-3.9)
Genitourinary	351	4.0% (3.4-4.6)	**S (Skin)**	294	3.4% (2.8-3.9)	**12 (Skin & subcutaneous tissue)**	179	2.1% (1.7-2.4)
Renal	232	2.7% (2.2-3.2)	**A (General & Unspecified)**	134	1.5% (1.2-1.8)	**18 (Symptoms~)**	105	1.2% (0.9-1.5)
Hematological	130	1.5% (1.0-2.0)	**B (Blood†)**	130	1.5% (1.0-2.0)	**1 (Infectious and parasitic~)**	80	0.9% (0.7-1.2)
Hepatic & pancreatic	90	1.0% (0.8-1.3)	**H (Ear†)**	47	0.5% (0.4-0.7)	**21 (Factors influencing health status~)**	68	0.8% (0.4-1.2)
Whole system	39	0.4% (0.3-0.6)	**W (Pregnancy†)**	8	0.1% (0.0-0.2)	**3 (Blood~)**	58	0.7% (0.5-0.9)
			Z (Social problems)	2	0.0% (0.0-0.1)	**19 (Injury, poisoning~)**	58	0.7% (0.5-0.8)
						8 (Ear and mastoid process)	47	0.5% (0.4-0.7)
						17 (Congenital~)	23	0.3% (0.2-0.4)
						15 (Pregnancy~)	3	0.0% (0.0-0.1)
						16 (Conditions - perinatal period~)	2	0.0% (0.0-0.1)

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the perinatal period

Table 2: Concordance of patients identified with multimorbidity (3+ definition) between ICPC-2, ICD-10 and CIRS

	Proportion identified for each classification system (horizontal) that were also identified using other classification systems (vertical) (95% CIs)		
	ICPC-2	ICD-10	CIRS
ICPC-2	100.0%	99.1% (98.7-99.5)	92.1% (90.9-93.3)
ICD-10	99.3% (98.9-99.6)	100.0%	91.9% (90.7-93.1)
CIRS	93.7% (92.6-94.7)	93.3% (92.2-94.4)	100.0%

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Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice

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The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Abstract

Objectives – Prevalence estimates of multimorbidity vary widely due to inconsistent definitions and measurement methods. This study examines independent effect on prevalence estimates of ~~the number of chronic conditions studied, number of disease entities required for multimorbidity, and~~ how 'disease entity' is defined — as single chronic condition or chapters/domains in the International Classification of Primary Care (Version 2) (ICPC-2), International Classification of Disease (10th revision) (ICD-10) or the Cumulative Illness Rating Scale (CIRS), the number of disease entities required for multimorbidity, and the number of chronic conditions studied.~~)~~.

Design – National prospective cross sectional study

Setting – Australian general practice

Participants 8,707 random consenting de-identified patient~~patients sampled from~~ encounters with 290 randomly selected general practitioners

Main outcome measures – Prevalence estimates of multimorbidity ~~measured~~ using different definitions

Results - Data~~Health data~~ classified to ICPC-2 chapters, ICD-10 chapters, or CIRS domains produce similar multimorbidity prevalence estimates. When multimorbidity was defined as two or more (2+) disease entities: counting individual chronic conditions and groups of chronic conditions produced similar estimates; twelve most prevalent chronic conditions identified about 80% of those identified using all chronic conditions.~~; age-specific prevalence plateaued in patients aged 70+ years.~~ When multimorbidity was defined as 3+ disease entities: counting individual chronic conditions produced significantly higher estimates than counting groups of chronic conditions; twelve most prevalent chronic

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conditions identified only two-thirds of patients identified using all chronic conditions~~; age-specific prevalence of multimorbidity had greater differentiation among older patients~~.

Conclusion ~~**Conclusion** - For the first time, a large prospective study has tested the independent effect of multimorbidity measurement methods on prevalence estimates.~~ Multimorbidity defined as 2+ disease entities can be measured using different definitions of disease entity with as few as 12 prevalent chronic conditions, but lacks specificity to be useful, especially in older people. Multimorbidity, defined as 3+, requires more measurement conformity and inclusion of all chronic conditions, but provides greater specificity than 2+ definition. The proposed concept of "complex multimorbidity", the co-occurrence of three or more chronic conditions affecting three or more different body systems within one person without defining an index chronic condition, may be a useful in identifying high need individuals.

ARTICLE SUMMARY

Strengths and limitations of the study

- A large, representative, prospective study of multimorbidity, involving 290 general practitioners and 8,707 patients, allowed testing of the independent effect of variables on prevalence estimates, something not possible with systematic reviews.
- This study investigated all chronic conditions, not a selection of conditions.
- This study used the general practitioner as an "expert interviewer", drawing upon the patient's knowledge, the patient's health record and their own knowledge to indicate the patient's current chronic conditions. Most multimorbidity studies rely on only one of these sources of data.

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- This study only considered chronic conditions, whereas some authors now include acute conditions when defining multimorbidity.

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Introduction

Research into coexistence of multiple chronic health conditions in an individual was initially concerned with comorbidity, defined as 'the existence or occurrence of any distinct additional disease entity in a patient who has the index disease under study'.(1) However since the early nineties, interest has progressed to 'multimorbidity', commonly defined as the "co-occurrence of two or more diseases within one person without defining an index disease".(2)

Interest in multimorbidity is growing due to its expected increase resulting from the ageing of the world's population.(3;4) Studies have shown that multimorbidity is associated with increased patient mortality, demand on health resources, complexity of care, and with reduced patient quality of life.(5;6) However, prevalence estimates of multimorbidity have ranged from 3.5%(7) to 98.5%,(8) the wide variance thought to be due to the lack of standards defining multimorbidity, and how it is measured. A recent systematic review found 132 definitions involving 1,631 different criteria.(9) There have been many calls for standards and guidelines for research into multimorbidity.(10-12) Recent systematic reviews have raised specific issues regarding the way multimorbidity is defined and/or measured.(11;12)

The first issue is the number of conditions studied. Fortin et al(11) found this ranged from 5 to all conditions. Diederichs et al(12) reported a range of 4 to 102 conditions, (mean,18.5,median 14) and suggested that conditions may be chosen for pragmatic reasons (such as data availability), as the majority of authors did not give reasons for their selection. Where they did, the most common was those conditions with a high prevalence or high impact on patients.(12) Both Diederichs et al(12) and Fortin et al(11) suggested studies considering only a few conditions produced lower prevalence estimates than those examining many conditions. Diederichs et al(12) suggested a list of 11 chronic conditions prevalent in the elderly as a minimum (cancer, diabetes mellitus, depression, hypertension, myocardial infarction, chronic ischeamic heart disease, heart arrhythmias, heart

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insufficiency, stroke, CODP, arthritis). Fortin et al(11) suggested that any 12 prevalent conditions should suffice to measure multimorbidity accurately.

The second issue is how 'disease entity' was defined in multimorbidity studies. Ideally, morbidities being counted should be "distinct" disease entities. However, disease entities used across studies varied from very specific conditions to groups of conditions. Even Diederich et al's suggested list(12) (above), includes some disease entities that are groups of conditions (such as arthritis and cancer) and some very specific, closely related conditions (eg. myocardial infarction and chronic ischaemic heart disease). It is debatable whether both myocardial infarction and chronic ischaemic heart disease should be considered as two separate disease entities in measuring multimorbidity. Some multimorbidity studies have tried to overcome this problem by only counting chronic conditions that affect different body systems, to ensure the count was of distinct disease entities.(4;13) These studies used the Cumulative Illness Rating Scale (CIRS)(14) domains to group chronic conditions by body system.(4;13) Fortin et al suggested that while the use of the CIRS needed further research, this approach may simplify coding and data collection.(11) The impact of counting the different body systems affected by chronic conditions, on multimorbidity prevalence estimates is not known.

Most primary care based multimorbidity studies rely on health record review.(11) A disadvantage of using CIRS in such reviews is that it requires additional mapping of diagnoses from the classification system in which the health records were coded. The two most commonly used disease classification systems are the International Classification of Primary Care (Version 2) (ICPC-2)(15) and the International Classification of Disease (10th revision) (ICD-10).(16) ICPC-2 is used in primary care and its chapters, (with the exception of 'General & Unspecified' and 'Social' chapters), are body system-based, following the principle that localisation takes precedence over aetiology.(16) ICD-10 is primarily used in hospitals and its chapters axes include body systems, aetiology and "others".(16) ICD-10 lacks specificity for classification of undiagnosed problems or symptoms, both of which are

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commonly managed in primary care.(17) This has meant that data from primary health care records classified in the two systems have looked very different in the past. However, since most multimorbidity studies examine only chronic conditions this problem may be avoided when conditions are grouped at the chapter level. It is not known whether counting disease entities from different CIRS domains, ICPC-2 or ICD-10 chapters produces comparable multimorbidity prevalence estimates.

The third issue is the number of disease entities required to define multimorbidity. Originally, multimorbidity was defined as two or more (2+) disease entities, but recently there has been debate about whether three or more (3+) may be a better measure. Fortin et al argue that using 2+ disease entities identifies such a high proportion of patients as multimorbid that the measure lacks specificity.(11) They found that age-specific prevalence of multimorbidity using the 2+ definition produced an "S" shaped curve with a flat plateau for older ages. When using 3+, the increase in prevalence by age was more linear, with greater differentiation in older age groups. The authors further argued that using 3+ disease entities results in a lower prevalence estimate, is likely to identify patients with greater health needs, and is therefore more useful to clinicians.(11) They recommended further research to test the 3+ definition of multimorbidity.(11)

The current study was conducted in Australian general practice. Australia's universal medical insurance scheme, Medicare, fully or partially covers the individual's cost of visits to general practitioners (GPs). GPs provide the bulk of primary medical care and act as gate keepers to government-subsidised health care from other medical specialists. There are no patient lists and patients are free to visit multiple GPs and practices as they choose.

Our study examines how multimorbidity prevalence estimates are effected by:~~the effect of~~ the number of chronic conditions studied;~~,~~ how a disease entity is defined; and the minimum number of disease entities required to define multimorbidity~~ on prevalence estimates~~. We use a large Australian general practice based prospective multimorbidity study, which allows

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us to examine the effect of each of these variables on multimorbidity prevalence estimates while controlling for other confounding variables, an approach not possible in systematic reviews.

Method

The BEACH (Bettering the Evaluation And Care of Health) program is a continuous, national cross-sectional survey of general practice activity in Australia.(17) Each year an ever-changing sample of about 1,000 GPs is randomly selected, and each GP records information about encounters with 100 consecutive consenting patients, on structured paper forms.(17)

In sub-studies of BEACH, the GP records information additional to the encounter data, in discussion with the patient. The full methods for this sub-study are reported elsewhere.(18) In brief, it measured the prevalence of diagnosed chronic conditions in patients attending general practice in Australia. Over three five-week recording periods (August 2008 to May 2009) 375 sampled GPs were asked to record all diagnosed chronic conditions for each of 30 consecutive patients on 30 bespoke forms within their 100 BEACH records. A sample of the instruction sheet and recording form can be found at www.http://sydney.edu.au/medicine/fmrc/publications/sand-abstracts/132-Multimorbidity.pdf

GPs were asked, "Does the patient have any of the following chronic diseases/problems?" Common chronic conditions were listed (tick boxes) with additional free text fields to record other unlisted chronic conditions ~~(Box 1)~~. A "no chronic conditions" option was also provided. Listed chronic conditions were primarily those most frequently managed in Australian general practice(17) and were inclusions in O'Halloran et al's definition of chronic conditions.(19) The free text options relied on GPs judgement of whether a condition was chronic in this patient. GPs were instructed to *"Use your own knowledge, patient knowledge and health records as you see fit, in order to answer these questions".* Additional free text chronic conditions were coded using the ICPC-2 PLUS terminology,(20) which automatically

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classified them into ICPC-2.(15) All chronic conditions were classified to ICD-10 chapters(16) (n=20), ICPC-2 chapters,(15) and CIRS domains(14) (Table 1). There were some chronic conditions (e.g. multisite cancer) that involved multiple systems. As these would usually be counted multiple times in different CIRS domains, we created an additional domain called "Whole system", resulting in 15 CIRS domains instead of the usual 14. The ICPC-2 male and female genital system chapters (chapters Y and X) were combined as they referred to the same body system, resulting in 16 ICPC-2 chapters (rather than the usual 17). This sample was previously shown to be representative of the age-sex distribution of patients at all GP encounters claimed (as items of service) through Medicare in 2008–09(18).

Using this large prospective study we examined the effect of three different dimensions of measuring multimorbidity while controlling for other confounding variables. This is achieved through the structure of the study, by only changing one of the three variables at a time.

Dimension One – Does the way disease entities are defined affect multimorbidity prevalence estimates?

To test this dimension we defined disease entity four different ways. First, each recorded/ticked chronic condition was treated as a separate disease entity. For the other three methods we considered a disease entity to be a chapter/domain that was affected by at least one chronic condition in each of the three classification systems. Comparing the resulting multimorbidity prevalence estimates we were able to test two research questions. Firstly, whether counting different body systems affected by chronic conditions produces prevalence estimates comparable to counting individual chronic conditions. Secondly, whether counting the number of different CIRS domains, ICPC-2 chapters or ICD-10 chapters affected produces comparable prevalence estimates.

Dimension 2 – Does the minimum number of disease entities required to define multimorbidity affect multimorbidity prevalence estimates?

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We compared prevalence of multimorbidity using 2+ through to 6+ disease entities. We also compared the age-specific prevalence of multimorbidity when it was defined as 2+ and 3+ disease entities, to see whether we could reproduce the "S" shaped curve when using the 2+ definition and test whether using 3+ provided greater differentiation among older patients, as found by Fortin et al.(11)

Dimension 3 – Does the number of chronic conditions included in the study affect multimorbidity estimates?

We reduced the number of chronic conditions used, in order to simulate studies that were based on fewer chronic conditions. We used the 11 minimum chronic conditions suggested by Diederichs et al (listed above, 'Diederich's list')(12), the 12 most prevalent chronic conditions in our study (hypertension, hyperlipidaemia, ischeamic heart disease, Type 2 diabetes, obesity, osteoarthritis, chronic back pain, asthma, depression, anxiety, GORD, malignant neoplasms) as suggested by Fortin et al(11) and the 24 listed chronic conditions with a tick box. We then compared these results with those generated using all diagnosed chronic conditions.

BEACH sub-studies have a single stage cluster design, with each GP having 30 patients clustered around them. The cluster effect was accounted for using SAS 9.3.

Ethics committees of the University of Sydney and Australian Institute of Health and Welfare approved BEACH and this sub-study.

Results

Completed research packs were returned by 290 GPs (77.3%) sampling 8,707 patients. In total 66.5% of patients (n= 5,777) had at least one chronic condition and 33.7% (n=2,930) had none. The intracluster correlation coefficient was 0.121 for patients with at least one chronic condition.

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Table 1 shows the proportion of patients with at least one chronic condition in each chapter/domain. For both ICPC-2 and ICD-10, the 11 most prevalent chapters were body-specific, with the non-body system specific chapters being relatively uncommon. Prevalence estimates of patients with at least one chronic condition within a body-system specific ICD-10 and ICPC-2 chapter were remarkably similar, the top six chapters being in the same order, with no significant differences in the prevalence estimates for these six chapters. There were larger differences between estimates using CIRS and those from both ICPC-2 and ICD-10. The major differences were due to CIRS splitting cardiovascular into vascular and cardiac domains, classifying cerebrovascular disease as neurological, and classifying hyperlipidaemia in the vascular domain. In all systems the most frequent chapters/domains were those relating to the: cardiac/vascular/circulatory; endocrine; musculoskeletal; psychological; digestive; and respiratory systems.

Figure 1 shows the prevalence of multimorbidity among patients in the sample (representing those in a GP's waiting room) using different definitions of multimorbidity. Estimated prevalence of multimorbidity ranged from 47.4% using 2+ individual chronic conditions to 2.8% when using 6+ ICPC-2 chapters. For all definitions using 3+ disease entities or more, counting individual chronic conditions resulted in significantly higher prevalence estimate than any of the grouped estimates. This difference increased proportionally as the minimum number of disease entities increased — the individual chronic conditions estimate was 23% higher than the ICPC-2 chapter estimate at 3+ disease entities, through to 268% higher at 6+ disease entities. Overall there was no significant difference found between prevalence estimates using ICD-10, ICPC-2 and CIRS, from 2+ through to 6+ disease entities.

Using the ICD-10 and ICPC-2 estimates, when multimorbidity was defined as two or more disease entities, about 44% of patients presenting to GP's were identified as multimorbid. This prevalence decreased with each increase in the number of disease entities required, with about 27% of patients being considered multimorbid for 3+, about 15% for 4+, 7% for 5+ and only 3% for 6+ disease entities. There was nearly perfect concordance between patients

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identified as having multimorbidity using the ICD-10 and ICPC-2 classifications systems. For example when using the minimum of three disease entities as the definition of multimorbidity, over 99% of patients identified using ICD-10 were also identified using ICPC-2 and visa-versa (Table 2) There was also high concordance between ICPC-2/ICD-10 and CIRS. For every 12 patients identified as having multimorbidity with CIRS, 11 were also identified using ICPC-2/ICD-10 and visa-versa.

Figure 2 shows multimorbidity prevalence estimates using the 2+ and the 3+ definitions across the different number of chronic conditions included. For all classification groups, the prevalence estimates derived when using Diederichs's 11 chronic conditions were significantly lower than those using the 12 most prevalent chronic conditions which in turn were significantly lower than estimates based on all chronic conditions. Prevalence estimates based on 12 most prevalent chronic conditions and on the 24 common chronic conditions (tick boxes) did not significantly differ except that 24 chronic conditions produced higher estimates when using 3+ individual chronic conditions or 3+ CIRS domains.

When using a restricted number of chronic conditions (ie. Diederichs's list or Fortin et al's 12) rather than all chronic conditions, the proportion of patients identified as having multimorbidity was significantly less when multimorbidity was defined as 3+ than when defined as 2+. For example, applying the 2+ definition to ICPC-2 chapters, using the 12 most prevalent chronic conditions, identified 79.4% of those identified as multimorbid using all chronic conditions. Using the 3+ ICPC-2 chapters definition, the 12 most prevalent conditions only identified 67.5%. Similarly, using Diederich's list with the 2+ definition identified 54.5% and the 3+ definition identified only 32.8% of those identified using all chronic conditions.

Figure 3 shows the age-specific multimorbidity prevalence estimates using the 2+ and 3+ definitions by individual chronic conditions and ICPC-2 chapters. Only the ICPC-2 chapters are presented as we have demonstrated there was no significant difference between

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estimates derived using ICPC-2 chapters, ICD-10 chapters or CIRS domains. The age-specific prevalence using both 2+ individual chronic conditions and 2+ ICPC-2 chapters increased rapidly up to the 70-79 years age group, and remained steady in the older age groups. Compared with 2+, the increase in prevalence started later for 3+ individual chronic conditions (between 20-29 and 30-39 years of age). For 3+ ICPC-2 chapters this increase started even later (between 30-39 and 40-49 years of age). For both the 3+ measures the prevalence did not plateau until 80-89 years of age, 10 years later than when using the 2+ definition.

Discussion

This study has shown that multimorbidity prevalence estimates are independently affected by the number of chronic conditions collected in a study, how a disease entity is defined, and the minimum number of disease entities used to define multimorbidity. It has also demonstrated that health data classified to ICPC-2 chapters, ICD-10 chapters, or CIRS domains produce similar multimorbidity prevalence estimates.

Dimension One – Does the way disease entities are defined affect multimorbidity prevalence estimates?

We found that when multimorbidity is defined as 2+ disease entities, prevalence estimates are similar no matter how a disease entity is defined, be it an individual chronic condition, or an ICPC-2 chapter, ICD-10 chapter or CIRS domain involving one or more chronic conditions. This means that studies that define multimorbidity as 2+ can be compared even if the morbidity is classified differently. However, when multimorbidity is defined as 3+ disease entities, using individual chronic conditions produces higher prevalence estimates than counting different domains/chapters affected. We conclude that researchers should not compare results from studies using the 3+ definition when one study has used grouped chronic conditions (classified) and the other individual chronic conditions.

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Our finding that chronic conditions were predominantly classified to body system-specific chapters/domains for all three classifications suggests that chapters/domains could be used to represent body systems affected. We also found no difference between the prevalence estimates produced with any of the three classification systems. Together, these results suggest researchers may compare prevalence estimates from studies that count different ICPC-2 chapters, ICD-10 chapters or CIRS domains affected by chronic conditions. This allows researchers to draw data from primary care or hospital health records regardless of the classification system used (ICPC-2 or ICD-10) and know that results will be comparable to published studies that have used CIRS.(4;13)

Dimension 2 – Does the minimum number of disease entities required to define multimorbidity affect multimorbidity prevalence estimates?

We found that the higher the minimum number of different disease entities used to define multimorbidity, the lower the prevalence estimate. If multimorbidity is defined as 2+ disease entities, nearly every second person sitting in front of the GP would have multimorbidity, whereas using 3+ decreased the estimate to nearly one-in-four. Like Fortin et al, we found that the 3+ definition provided greater differentiation in the older age groups than the 2+ definition. These results support their argument that using 2+ disease entities identifies such a large proportion of patients as having multimorbidity that it lacks the specificity to be useful, with a minimum of three disease entities arguably a better measure of multimorbidity.

Dimension 3 – Does the number of chronic conditions included in the study affect multimorbidity estimates?

As previous research suggests,(11;12) the number of chronic conditions studied affects the multimorbidity prevalence estimates – estimates based on a low number of chronic conditions being a fraction of those based on all chronic conditions. In our study, Diederichs's list identified only half the patients identified with multimorbidity using all chronic conditions when using 2+, and only a third using 3+. Including the 12 most prevalent chronic

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conditions (suggested by Fortin et al) four out of five multimorbid patients were identified using 2+ and two-thirds using 3+. While both used a similar number of chronic conditions, Diederichs's list included the most prevalent chronic conditions in patients aged 65 years and over whereas Fortin et al suggested the most prevalent overall.

It is clear from these results that no matter how multimorbidity is defined, the list of chronic conditions suggested by Diederich et al as a minimum is not sufficient to reliably measure multimorbidity prevalence. Using the 12 most prevalent chronic conditions as suggested by Fortin et al, does provide prevalence estimates that are reasonably close to those gained with all chronic conditions when using the 2+ definition. However, when multimorbidity is defined as 3+, the twelve most prevalent chronic conditions are not sufficient to measure multimorbidity. For the 3+ definition, ideally researchers should include all chronic conditions in their study.

This study has some limitations. We only included chronic conditions, whereas some authors have recently included acute conditions in their definition of multimorbidity.(9;21) Including acute conditions is understandable in a clinical setting, as they will temporarily increase the patient's complexity of care. However, where the goal is to measure the prevalence of multimorbidity to inform planning to meet the health resource requirements of these high need patients, the use of only chronic conditions is logical.

Fortin et al suggest that when studying multimorbidity one should also include a measure of severity.(8) This study did not attempt to measure severity because of the limited space on the questionnaire and concerns that the additional burden on the GPs may reduce the response rate.

While our study was representative of patients at GP encounters, it should be remembered that patients are not representative of population. Patients at GP encounters are generally older and therefore more likely to have a chronic condition(18).

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While our study was cross sectional, the variables tested are relevant to all types of multimorbidity studies, be they cross-sectional, longitudinal, interview-based or based on health record review.

Throughout this study we have found that multimorbidity behaves quite differently when defined as 2+ disease entities or 3+. With the 2+ definition, reasonable prevalence estimates could be obtained using only a dozen prevalent chronic conditions, regardless of how a disease entity was defined. With the 3+ definition, the way the disease entity was defined was important— counting individual chronic conditions produced significantly higher estimates than counting chapters/domains. The number of chronic conditions studied was also important as studying a restricted number of chronic conditions produced significantly lower estimates than studying all chronic conditions. However, the prevalence estimates gained using 2+ were so encompassing that they lacked specificity – especially in older patients, whereas 3+ provided greater specificity and more differentiation among the elderly patients.

These results suggest that the concept of 2+ and 3+ multimorbidity are quite different. Rather than having both these concepts included under the same label, we propose adding “complex” to those patients with 3+ chronic conditions from different body systems to clarify the meaning. “Multimorbidity’ would be defined as the “co-occurrence of two or more chronic conditions within one person without defining an index chronic condition”. “Complex-multimorbidity” would be defined as the “co-occurrence of three or more chronic conditions affecting three or more different body systems within one person without defining an index chronic condition”. In this way we still have the more encompassing 2+ definition to compare with previous work, while also being able to identify patients requiring additional care.

For consistency, we also propose a similar concept for comorbidity. We suggest that “complex comorbidity” be defined as ‘the existence of two or more additional chronic conditions from two or more body systems different to that of the index chronic condition

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under study'. This would mean that all patients with complex multimorbidity would also have complex comorbidity, the only difference being whether there is a chronic condition of interest.

There are advantages to using body systems affected (as represented by chapters/domains to which a chronic condition had been classified) rather than individual chronic conditions as 'disease entities'. Take for example two patients with three chronic conditions: patient A has peripheral vascular disease, hypertension and Type 2 diabetes; patient B has depression, osteoarthritis and Type 2 diabetes. The chronic conditions in patient A only affect two body systems while those in patient B, affect three. According to our definitions, both would have multimorbidity, but patient B would also have complex multimorbidity. Patients identified with chronic conditions in 3+ body systems (complex multimorbidity) may be those whose care is more complex, as chronic conditions in different body systems are likely to compete for treatment, while the treatments of chronic conditions within the same system are more likely to be complementary. This is a similar concept to Piette and Kerr's idea of concordant and discordant comorbidity.(22)

Counting the body systems affected also provides an estimate of the specialist types that may be involved in the care of the patient. This is important for healthcare planning as it reduces double counting of chronic conditions that may be referred to the same specialist type, e.g. a patient with depression and anxiety may be referred to one psychiatrist (not two). It also identifies patients who may need assistance with coordination of specialist care, as the health-care of patients with multimorbidity is more likely to be poorly coordinated.(23;24)

Conclusion

For the first time, a single large prospective study has been used to test the effect of the way multimorbidity is measured on prevalence estimates, while controlling for other variables, using the same data for all measures. This is not possible with systematic reviews. We have

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shown that multimorbidity behaves differently when defined as 2+ disease entities, and when it is defined as 3+ disease entities. To address this, we recommend that

- 'multimorbidity' be defined as the 'co-occurrence of two or more chronic conditions within one person without defining an index chronic condition' and
- 'complex multimorbidity' be defined as the "co-occurrence of three or more chronic conditions affecting three or more different body systems within one person without defining an index chronic condition".

This study provides some evidence that complex multimorbidity is a more useful measure of multimorbidity as it results in a lower prevalence estimate and shows greater differentiation among older patients. However, further research is needed to assess whether 'complex multimorbidity' is indeed better than alternative measures of multimorbidity (such as counting individual chronic conditions, measures of severity etc.) in identifying patients with greater health care resource use, complexity of care, lower quality of life and overall severity of illness.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Ethical approval: The BEACH program and this sub-study were approved by the Human Research Ethics Committee of the University of Sydney (Reference No. 11428) and the Ethics Committee of the Australian Institute of Health and Welfare.

Data sharing statement: There are no additional data available.

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Table 1: Proportion of patients in GP waiting rooms that have at least one condition in each CIRS domain, ICPC 2 chapter or ICD 10 chapter

CIRS domain	n	Proportion of patients in waiting room (95% CIs)	ICPC 2 chapter	n	Proportion of patients in waiting room (95% CI)	ICD 10 chapter	n	Proportion of patients in waiting room (95% CI)
Vascular	2,934	33.7% (31.7%-35.7%)	K (Circulatory)	2,762	31.7% (29.8-33.6)	9 (Circulatory)	2,748	31.6% (29.7-33.5)
Musculoskeletal*	2,479	28.5% (26.6-30.4)	T (Endocrine†)	2,694	30.9% (29.2-32.7)	4 (Endocrine~)	2,688	30.9% (29.1-32.7)
Psychiatric	1,930	22.2% (20.6-23.7)	L (Musculoskeletal)	2,293	26.3% (24.5-28.2)	13 (Musculoskeletal~)	2,268	26.0% (24.2-27.9)
Endocrine*	1,840	21.1% (19.7-22.5)	P (Psychological)	1,953	22.4% (20.8-24.0)	5 (Mental & behavioural disorders)	1,910	21.9% (20.4-23.5)
Respiratory	1,195	13.7% (12.7-14.8)	D (Digestive)	1,387	15.9% (14.7-17.2)	11 (Digestive)	1,296	14.9% (13.7-16.1)
Cardiac	1,089	12.5% (11.3-13.7)	R (Respiratory)	1,227	14.1% (13.0-15.2)	10 (Respiratory)	1,211	13.9% (12.9-15.0)
Upper gastrointestinal	1,052	12.1% (11.0-13.2)	X & Y (Genital)	353	4.1% (3.5-4.6)	2 (Neoplasms)	474	5.4% (4.7-6.1)
Neurological	542	6.2% (5.4-7.0)	U (Urology)	312	3.6% (3.0-4.2)	14 (Genitourinary)	389	4.5% (3.8-5.2)
Opthalmological*	444	5.1% (4.4-5.8)	N (Neurological)	311	3.6% (3.1-4.1)	6 (Nervous system)	318	3.7% (3.1-4.2)
Lower gastrointestinal	377	4.3% (3.7-4.9)	F (Eye)	303	3.5% (2.9-4.1)	7 (Eye & adnexa)	292	3.4% (2.8-3.9)
Genitourinary	351	4.0% (3.4-4.6)	S (Skin)	294	3.4% (2.8-3.9)	12 (Skin & subcutaneous tissue)	179	2.1% (1.7-2.4)
Renal	232	2.7% (2.2-3.2)	A (General & Unspecified)	134	1.5% (1.2-1.8)	18 (Symptoms~)	105	1.2% (0.9-1.5)
Hematological	130	1.5% (1.0-2.0)	B (Blood†)	130	1.5% (1.0-2.0)	1 (Infectious and parasitic~)	80	0.9% (0.7-1.2)
Hepatic & pancreatic	90	1.0% (0.8-1.3)	H (Ear†)	47	0.5% (0.4-0.7)	21 (Factors influencing health status~)	68	0.8% (0.4-1.2)
Whole system	39	0.4% (0.3-0.6)	W (Pregnancy†)	8	0.1% (0.0-0.2)	3 (Blood~)	58	0.7% (0.5-0.9)
			Z (Social problems)	2	0.0% (0.0-0.1)	19 (Injury, poisoning~)	58	0.7% (0.5-0.8)
						8 (Ear and mastoid process)	47	0.5% (0.4-0.7)
						17 (Congenital~)	23	0.3% (0.2-0.4)
						15 (Pregnancy~)	3	0.0% (0.0-0.1)
						16 (Conditions - perinatal period~)	2	0.0% (0.0-0.1)

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* = CIRS Musculoskeletal & tegumental; Endocrine, metabolic, breast; Opthalmological & otorhinolaryngology
† = ICPC 2 Endocrine, nutritional & metabolic; Blood, blood forming organs and immune mechanism; Ear & hearing; Pregnancy, child-bearing, family planning
~ = ICD 10 2 Endocrine, nutritional & metabolic ; Musculoskeletal and connective tissue; Symptoms, signs and abnormal clinical and laboratory findings; Certain infectious and parasitic diseases; Factors influencing health status and contact with health services; Blood, blood forming organs and certain disorders involving the immune mechanism; Injury, poisoning and certain other consequences of external causes; Congenital malformations, deformations and chromosomal abnormalities; Pregnancy, childbirth & the puerperium; Certain conditions originating from the perinatal period

Table 2: Concordance of patients identified with multimorbidity (3+ definition) between ICPC-2, ICD-10 and CIRS

	Proportion identified for each classification system (horizontal) that were also identified using other classification systems (vertical) (95% CIs)		
	ICPC-2	ICD-10	CIRS
ICPC-2	100.0%	99.1% (98.7-99.5)	92.1% (90.9-93.3)
ICD-10	99.3% (98.9-99.6)	100.0%	91.9% (90.7-93.1)
CIRS	93.7% (92.6-94.7)	93.3% (92.2-94.4)	100.0%

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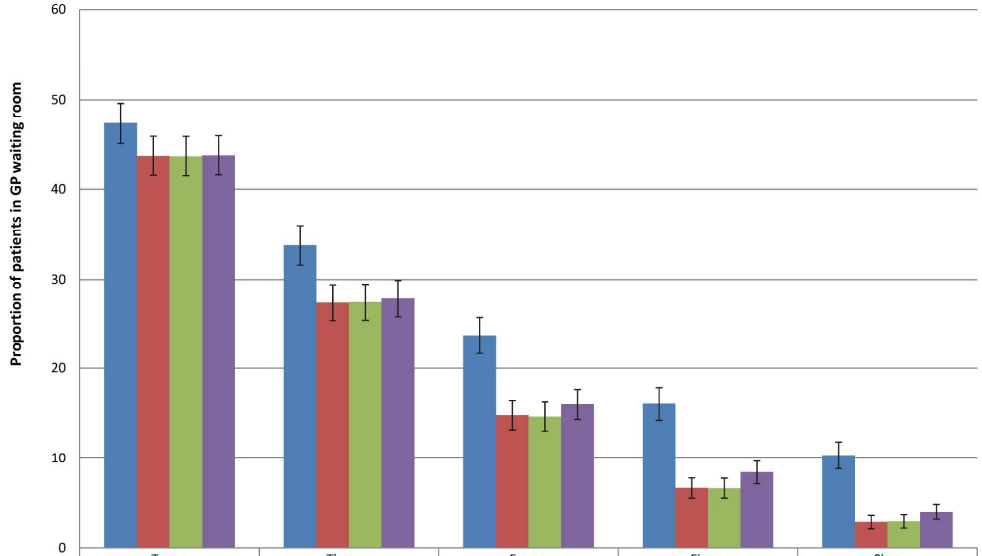
Figure 1: Multiple conditions within patients as defined by different classification systems



	Two +	Three +	Four +	Five +	Six +
Individual conditions	47.4	33.8	23.7	16.0	10.3
ICPC 2 Chapters	43.7	27.4	14.7	6.7	2.8
ICD 10 Chapters	43.7	27.4	14.6	6.7	2.9
CIRS domains	43.8	27.9	16.0	8.4	4.0

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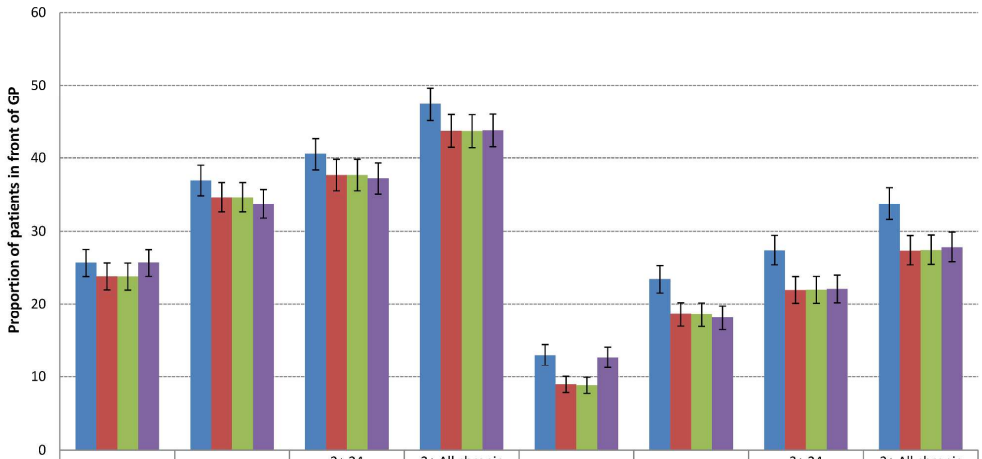
Figure 2: Estimated prevalence of multimorbidity by different classification systems and by whether 2+ or 3+ minimum number of disease entities was used



	2+ Diederichs	2+ Fortin	2+ 24 conditions	2+ All chronic conditions	3+ Diederichs	3+ Fortin	3+ 24 conditions	3+ All chronic conditions
Individual diseases	25.7	37.0	40.5	47.4	13.0	23.4	27.4	33.8
ICPC 2 Chapters	23.8	34.7	37.7	43.7	9.0	18.5	21.9	27.4
ICD-10 Chapters	23.8	34.7	37.7	43.7	8.8	18.5	21.9	27.5
CIRS Domains	25.7	33.8	37.2	43.8	12.7	18.1	22.1	27.9

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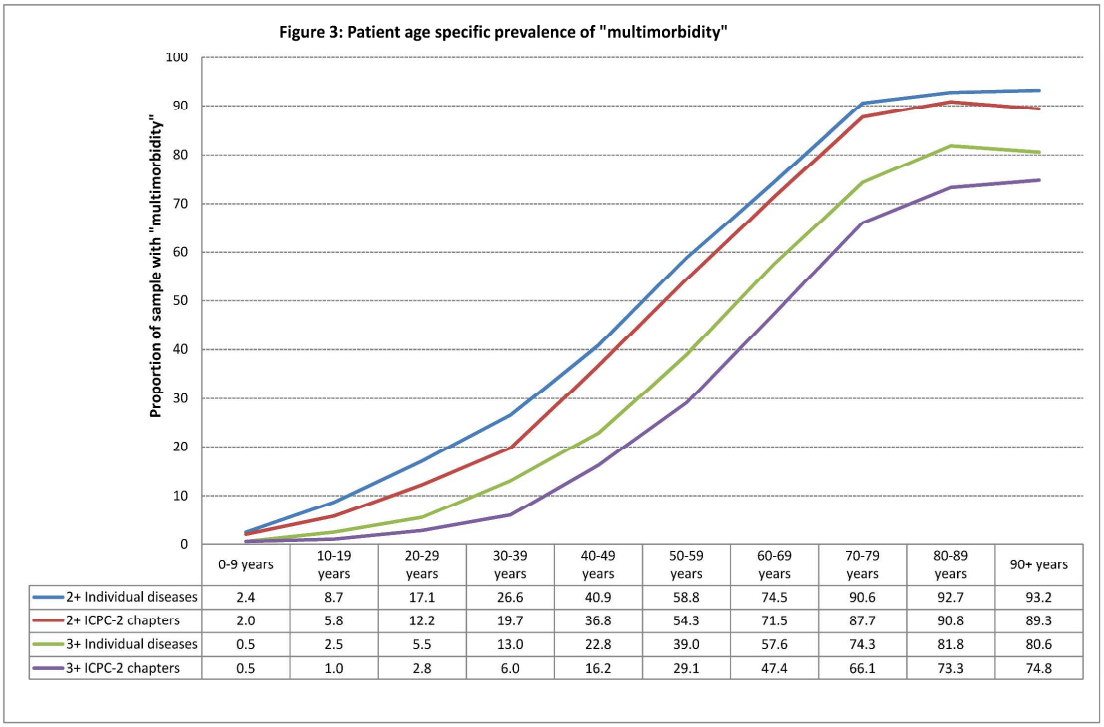

	0-9 years	10-19 years	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	80-89 years	90+ years
2+ Individual diseases	2.4	8.7	17.1	26.6	40.9	58.8	74.5	90.6	92.7	93.2
2+ ICPC-2 chapters	2.0	5.8	12.2	19.7	36.8	54.3	71.5	87.7	90.8	89.3
3+ Individual diseases	0.5	2.5	5.5	13.0	22.8	39.0	57.6	74.3	81.8	80.6
3+ ICPC-2 chapters	0.5	1.0	2.8	6.0	16.2	29.1	47.4	66.1	73.3	74.8

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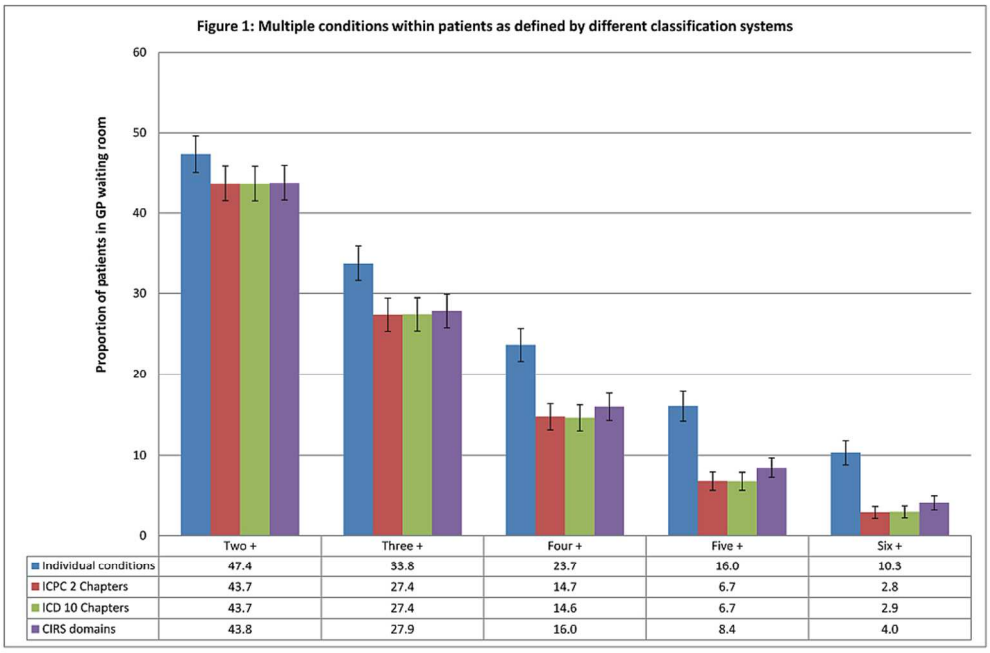

	Two +	Three +	Four +	Five +	Six +
Individual conditions	47.4	33.8	23.7	16.0	10.3
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CIRS domains	43.8	27.9	16.0	8.4	4.0

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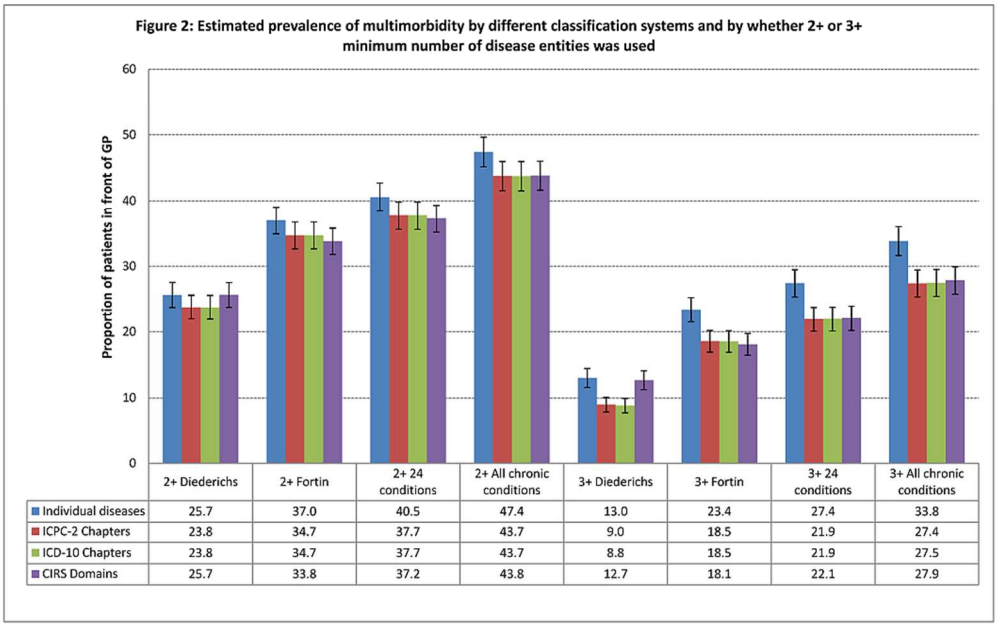

	2+ Diederichs	2+ Fortin	2+ 24 conditions	2+ All chronic conditions	3+ Diederichs	3+ Fortin	3+ 24 conditions	3+ All chronic conditions
Individual diseases	25.7	37.0	40.5	47.4	13.0	23.4	27.4	33.8
ICPC-2 Chapters	23.8	34.7	37.7	43.7	9.0	18.5	21.9	27.4
ICD-10 Chapters	23.8	34.7	37.7	43.7	8.8	18.5	21.9	27.5
CIRS Domains	25.7	33.8	37.2	43.8	12.7	18.1	22.1	27.9

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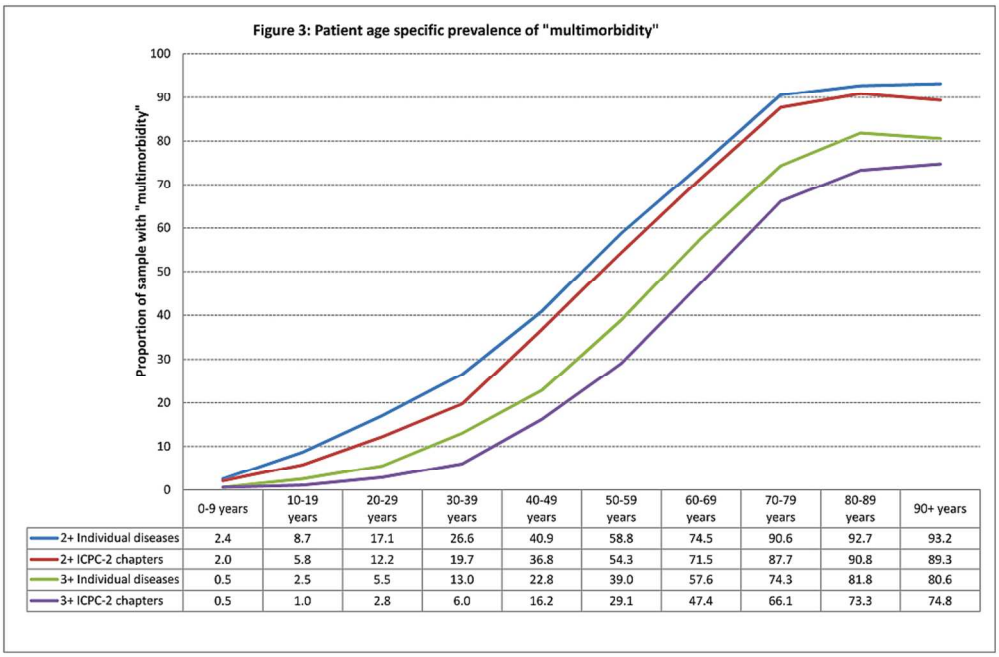

	0-9 years	10-19 years	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	80-89 years	90+ years
2+ Individual diseases	2.4	8.7	17.1	26.6	40.9	58.8	74.5	90.6	92.7	93.2
2+ ICPC-2 chapters	2.0	5.8	12.2	19.7	36.8	54.3	71.5	87.7	90.8	89.3
3+ Individual diseases	0.5	2.5	5.5	13.0	22.8	39.0	57.6	74.3	81.8	80.6
3+ ICPC-2 chapters	0.5	1.0	2.8	6.0	16.2	29.1	47.4	66.1	73.3	74.8

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