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Prevalence of multimorbidity in general practice: a cross-sectional study within the Swiss Sentinel Surveillance System (Sentinella)

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Abstract:

Objectives: To estimate the prevalence of multimorbidity using a list of 75 chronic conditions derived from ICPC-2 and developed specifically to assess multimorbidity in primary care. Our aim was also to provide prevalence data for multimorbidity in primary care in a country in which GPs do not play a gatekeeping role in the health system.

Setting: A representative sample of GPs within the Swiss Sentinel surveillance network.

Participants: 118 GPs completed a paper-based questionnaire about 25 consecutive patients of all ages between September and November 2015. There were no patient exclusion criteria. Recorded data included date of birth, gender and the patients' chronic conditions.

Primary and secondary outcome measures: We estimated the prevalence of multimorbidity, defined as ≥ 2, and ≥ 3 chronic conditions stratified by gender and age group, and adjusted for clustering by GPs. We also computed the prevalence of each chronic condition individually and grouped by system.

Results: Data from 2904 patients were included (mean age (SD) = 56.5 (20.5) years; male= 43.7%). Prevalence was 52.1% (95%CI: 48.6-55.5%) for ≥ 2 and 35.0% (95%CI: 31.6-38.5%) for ≥ 3 chronic conditions, with no significant gender differences. Prevalence of two or more chronic conditions was low (6.2%, 95% CI:2.8-13.0%) in those below 20 but affected more than 85% (85.8%, 95%CI: 79.6-90.3%) of those above the age of 80. The most prevalent conditions were cardiovascular (42.7%, 95%CI: 39.7-45.7%), psychological (28.5%, 95%CI: 26.1-31.1%) and metabolic or endocrine disorders (24.1%, 95%CI:21.6-26.7%). Elevated blood pressure was the most prevalent cardiovascular and depression the most common psychological disorder.

Conclusion: In a country in which GPs do not play a gate-keeping role within the health system, the prevalence of multimorbidity, as assessed using a list of chronic conditions specifically relevant to primary care, is high and increases with age.

Strengths and limitations:

- This study provides estimates of the prevalence of multimorbidity based on a sample of patients of all ages from representative practices throughout an entire European country and using a scientifically established list of 75 chronic conditions relevant to multimorbidity in primary care.
- The list was based on codes from the International Classification for Primary Care (ICPC-2). As some common conditions (i.e. chronic renal failure) are missing from this classification, the reported prevalence estimates are somewhat conservative.
- Comparisons with previous studies is limited by the fact that this is the first time this newly established list of chronic conditions relevant to multimorbidity was used to provide prevalence estimates.

Introduction:

Multimorbidity (MM) is commonly defined as the co-occurrence of two, three or more chronic conditions (CCs) within one person.(1) Comorbidity in contrast refers to the development of conditions in addition to one main chronic condition.(2, 3) The prevalence of MM increases with age,(4) with an estimated prevalence ranging from 20-30% in the all-ages population to 55-98% in individuals over 65 years old.(1) This represents a significant challenge for current and future health care services. MM is most frequently managed in primary care (PC) and 70 to 80% of the population visits a general practitioner (GP) at least once a year.(5) (6) MM constitutes a growing problem in view of the aging population and is also associated with increased healthcare costs and threats to quality of care.(1) Estimates of the prevalence of MM vary significantly depending on various definitions of MM and selected lists with limited numbers of CCs, population settings and data collection methods.(1, 3, 4, 7-10) As a consequence, results between studies are difficult to compare.(11) This was highlighted in 2012 in a systematic review of the literature comparing studies in primary care settings and amongst the general population in different geographical regions. (7)

In PC, MM is becoming the norm rather than the exception and limited lists of CCs are not representative of daily practice. Yet the number and spread of high or low prevalent CCs is so important that for research purposes it is important to focus on the CCs that are most relevant to MM in PC. Academic investigators developed a list of 75 CCs relevant for MM in PC, based on the ICPC2 in a modified RAND method. We believe this is yet the best available list for this setting as the 20 participating experts where experienced and clinically active primary care providers. (12)

Furthermore, in the majority of the European countries, GPs act as gatekeepers to the healthcare system. In countries in which this is not the case, such as in Switzerland, Germany or Greece, where patients can directly access specialist care, the prevalence of MM in general practice may be lower. Only few studies conducted in such countries are reported in the literature. In a predominantly rural population in Greece the prevalence of MM (≥ 2 CCs) in primary care was 20.0%. (13) Yet there was potentially a participation bias since GPs participated on invitation and worked in specific rural and semi-rural populations. In a German study 58.9% of patients above the age of 65 seen in ambulatory settings had three or more CCs.(14) Yet these findings were based on insurance claims data and not limited to patients consulting in primary care. In Switzerland, one study used electronic data from general practices in a German-speaking region and identified a prevalence of MM (≥ 2 CCs) of 13-

15%. Yet there was a high probability of underreporting in this study since CCs that were not discussed during the consultation were not reported. (15)

In view of these limitations, our aim was to provide estimates of the prevalence of MM in primary care in Switzerland, based on the list of 75 CCs relevant for MM. We hypothesised that this prevalence may be lower in a setting in which GPs do not have a gatekeeper role within the healthcare system (as is the case in Switzerland), compared to a setting in which patients need to see a GP to be referred to a specialist. We also hypothesised that the use of a predefined list of CCs relevant to MM in primary care would provide us with a more precise estimate of the prevalence of MM in this setting.

Methods

Participants and procedure:

This cross-sectional study was conducted from 14th of September to 6th of November 2015 in general practices across Switzerland. We recruited a voluntary sample of 118 GPs from the Sentinella network, who collected data from 25 consecutive patients attending their practice during a two-week-period. Sentinella is a representative network involving 132 voluntary GPs (and approximately 30 general paediatricians, not included in this study) across Switzerland. The network was initially set up for the epidemiological monitoring of infectious diseases. The Sentinella network also participates in selected research projects. As partner of the network, the Federal Office of Population Health (FOPH) collects data from the GPs registered with the network and ensures they remain anonymous.

Data collection:

For our study participating GPs were asked to pre-select a day within the two-week study period on which they began data collection for our study. For each patient included in the study, participating GPs completed a paper Clinical Report Form (CRF), which included patients' age and gender and CCs, identified from the list of 75 CCs (described below).(12) The possibility to add relevant CCs in free text was left to the GPs, to overcome any limitations due to a selected list of CCs. The CRF was a double sided A4 sheet in which the list of CCs was grouped by main systems in order to facilitate GPs' quick identification of relevant CCs for each patient, thus limiting potential omissions.

All data were anonymised and recorded into a centralised database. All the written communications were made through official letters from the FOPH as per the usual communication of the Sentinella

network. This ensured the anonymity of data because there was no contact between the participating GPs and the investigators.

We used the list of 75 CCs developed by N'Goran et al. and recently used in the MMFM (Multimorbidity in Family Medicine) study.(12, 16) This list is based on ICPC-2 and is the result of a four-rounds modified RAND survey involving a panel of GPs throughout Switzerland to identify the CCs most relevant to MM.(17)

Sample size:

We calculated that a sample size of 2016 patients would be sufficient to measure a prevalence of MM of around 30% with a precision margin of 2%. Adapting for the clustering of patients within different practices, we used an intra-class coefficient of 0.01, based on the literature, and estimated a sample size adjusted to 2499, rounded off to 2500 for practical purposes.

Statistical analyses:

A double data entry followed by a reconciliation process was used to ensure the quality of the database. We performed descriptive analyses using Stata version 13 (StataCorp LP, College Station, TX, USA). Patients with missing data for age, gender and/or CCs were excluded. Continuous data (age) were summarized using means and standard deviations, whereas categorical data were summarized using proportions and confidence intervals (CI), adjusted for clustering within practices. We calculated the point prevalence of MM and estimated prevalence of MM by age groups (grouped by steps of 20 years) and by sex. We also computed the prevalence of each chronic condition individually as well as grouped by system.

Ethical aspects:

Since the study involved the analysis of completely anonymous data, it was granted a waiver from approval by the Human Research Ethics Committee of the Canton Vaud.

Results:

Descriptive statistics:

Participation rate was high with 118 of 132 eligible GPs (89.4%) in the Sentinella network participating in our study.

The GPs included 2966 patients. Gender information was missing for 54 patients (reported by 29 different GPs) and year of birth for 16 patients (from 13 GPs) including 8 patients for whom both gender and year of birth was missing. Furthermore, one patient was excluded because of missing data concerning CCs. As a result, 2904 patients were retained in the final sample and included in the statistical analysis. 43.7% were male and mean (SD) age was 56.5 (20.5) years.

The sex and age distribution in our sample was comparable to that of all doctor-patient contacts in the Sentinella network during a similar period (data not shown). We assumed that the minimal differences (‹2%) in the proportion of individuals in certain age subgroups did not have an influence on the results.

The prevalence of MM independently of age was 52.1% for two or more CCs and 35.0% for three or more CCs. Considering the total sample, 27% did not have any CCs and 1.5% had more than 8 CCs. Prevalence of MM was equally distributed between females and males. Table 1 shows details of the prevalence of two, three or more CCs by gender and age group. The prevalence of MM defined as two or more CCs was 6.2% in those below the age of 20 years, compared to 44.7%, 71.6% and 85.8% in the age groups 41-60 years, 61-80 years and above 80 years respectively (Table 1).

Table 1: prevalence of ≥ 2, and ≥ 3 chronic conditions by sex and age groups in the representative sample of 2904 patients recruited in 118 family practices throughout Switzerland

	Male (N=1268)				Female (N=1636)				Total (N=2904)			
	2 or more chronic conditions		3 or more chronic conditions		2 or more chronic conditions		3 or more chronic conditions		2 or more chronic conditions		3 or more chronic conditions	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
0-20 years	1.9	(0.2-12.5)	0.0	0.0	9.3	(4.4-18.7)	1.3	(0.2-9.2)	6.2	(2.8-13.0)	0.8	(0.1-5.4)
21-40 years	18.8	(13.8-25.2)	6.2	3.6-10.4	18.9	(14.6-24.0)	9.4	(6.1-14.3)	18.9	(15.3-23.1)	7.9	(5.5-11.3)
41-60 years	44.7	(39.0-50.7)	25.4	20.4-31.2	44.6	(39.4-50.0)	25.1	(21.0-29.7)	44.7	(40.3-49.1)	25.3	(21.7-29.2)
61-80 years	73.3	(68.4-77.6)	53.5	47.6-59.3	70.3	(64.9-75.2)	50.6	(45.0-56.2)	71.6	(67.4-75.5)	51.9	(47.0-56.8)
> 80 years	86.9	(79.5-91.9)	70.0	60.3-78.2	85.2	(77.9-90.4)	65.9	(57.6-73.3)	85.8	(79.6-90.3)	67.3	(60.2-73.6)

As expected, below the age of 20, only a minority of patients had a chronic condition (N=624, 21.5%). Between 40 and 60 years, about 70% had at least one chronic condition, and above the age of 80, the proportion of patients without any CCs was negligible (Figure 1).

Insert Figure 1 approximately here

Distribution by system:

The most commonly reported CCs concerned the cardiovascular system. Psychological disorders, metabolic and endocrine disorders were also common (Table 2). The detailed prevalence estimates for all conditions are presented in the supplementary table.

CCs which contributed most to MM in the age groups 0-20 and 20-40 were psychological conditions and metabolic diseases. Cardiovascular conditions were at the forefront in patients over the age of 40 even though psychological conditions also often contributed to MM in these age groups (Figure 2).

Insert Figure 2 approximately here

Table 2: Prevalence of chronic conditions in the representative sample of 2904 patients (presenting only chronic conditions with a prevalence ≥ 5% in one gender)

Chronic Conditions	*ICPC -2 Code*	Male (N=1268)		Female (N=1636)		Total (N=2904)	
		%	(95% CI)	%	(95% CI)	%	(95% CI)
Cardiovascular diseases							
Hypertension uncomplicated	K86	20.7	(17.8 - 23.9)	19.4	(16.9 - 22.3)	20.0	(17.6 - 22.6)
Elevated blood pressure	K85	14.0	(11.2 - 17.3)	10.8	(8.4 - 13.7)	12.2	(9.9 - 14.9)
Risk factor cardiovascular disease	K22	13.1	(10.3 - 16.5)	10.4	(7.9 - 13.6)	11.6	(9.2 - 14.5)
Atrial fibrillation/flutter	K78	7.0	(5.6 - 8.8)	6.3	(5.0 - 7.9)	6.6	(5.6 - 7.8)
Ischemic heart disease without angina	K76	6.9	(5.5 - 8.7)	3.7	(2.7 - 4.9)	5.1	(4.2 - 6.2)
Atherosclerosis	K92	6.4	(5.0 - 8.1)	3.7	(2.9 - 4.8)	4.9	(4.1 - 5.8)
Cerebrovascular disease	K91	5.1	(3.9 - 6.8)	3.0	(2.1 - 4.2)	3.9	(3.1 - 4.9)
Endocrine/Metabolic and Nutritional							
Obesity	T82	13.6	(11.2 - 16.5)	16.8	(14.1 - 19.9)	15.4	(13.3 - 17.9)
Diabetes non-insulin dependent	T90	13.0	(11.0 - 15.4)	8.3	(6.8 - 10.1)	10.4	(9.0 - 11.9)
Psychological							
Depressive disorder	P76	9.4	(7.6 - 11.5)	14.9	(13.0 - 17.1)	12.5	(10.9 - 14.3)
General and unspecified							
Pain general/multiple sites	A01	6.9	(5.3 - 9.0)	10.5	(8.7 - 12.7)	9.0	(7.5 - 10.7)
Musculoskeletal							
Osteoarthritis of knee	L90	6.1	(4.8 - 7.6)	9.4	(7.7 - 11.5)	8.0	(6.7 - 9.4)
Osteoarthritis of hip	L89	4.4	(3.2 - 6.1)	7.7	(6.2 - 9.5)	6.3	(5.1 - 7.7)
Osteoporosis	L95	0.9	(0.5 - 1.7)	7.6	(6.2 - 9.3)	4.7	(3.9 - 5.8)
Respiratory							
Chronic obstructive pulmonary disease	R95	5.0	(3.8 - 6.5)	3.6	(2.7 - 4.8)	4.2	(3.4 - 5.1)

Discussion:

Summary of main findings:

Our study highlights the high prevalence of MM in a nationwide cross-sectional study in primary care in Switzerland, based on a representative list of CCs relevant for MM. Prevalence of two or more CCs across all age-groups was 52.2%, and prevalence of 3 or more CCs was 35.0%. There were no significant gender differences. As expected, the prevalence of MM increases with age, with about 72% of patients above 60 years of age having at least two or more CCs, indicating that MM is common in GPs' daily practice, even in a country in which GPs do not have a gatekeeping role within the healthcare system. GPs in our study were more frequently in contact with patients with one or more CCs than without (73% vs 27%).

The distribution by organ chapter or system highlighted the predominance of cardiovascular diseases mainly due to elevated or high blood pressure with or without complications, which accounted for more than one third of the conditions. Psychological disorders were prevalent in all age groups and accounted for nearly 30% of all CCs.

Comparison with the existing literature:

Our prevalence estimates are much higher than that described in a previous study conducted in Switzerland, based on data extracted from electronic medical records, in which prevalence of MM was 15% (FIRE study).(15) Underreporting of CCs not actively treated in the consultation may possibly explain the low prevalence of MM in this study. Similar comments apply to a recent study based on electronic medical record data extraction from more than 300 practices in Scotland, in which prevalence of two or more CCs was 23.2%.(4) In addition, in the Scottish study, the CCs were identified within a list of 40 conditions established by the authors, and were not based on the ICPC-2. Thus these findings are not directly comparable with ours. Studies from the Netherlands used lists based on ICPC-2. In a Dutch study using a list of 28 CCs within this classification, prevalence of MM defined as two or more CCs in patients above the age of 55 years was 37%. (18) This is surprisingly low compared to our findings, particularly if one considers that younger patients were excluded. Again, underreporting due to extraction limited to active CCs within electronic medical files, may explain this low prevalence as well as the limited number of CCs to choose from within the list these authors used.

A reference group outside of Europe (Fortin et al.) reported prevalence estimates of two or more CCs of 98.7% in patients above the age of 65. (5) In this study, no pre-selected list of CCs was used. The practitioners had the possibility of reporting any conditions they considered chronic and this may have increased the spectrum of disorders potentially contributing to MM in this study. The same authors reported strong differences in estimated prevalence according to variations in the methodology of the study, particularly with regard to the number of CCs.(7) In a recent sub-study of the national survey BEACH (Bettering the Evaluation and Care of Health) in Australia a prevalence of around 50% for two or more CCs and 27% for three or more CCs in a family medicine sample was estimated, similar to our findings.(19)

Unlike in other health systems, GPs in Switzerland generally do not have a gatekeeper role and patients can have direct access to specialists. We hypothesize that a number of patients with only one chronic condition may tend to only see a specialist. However, as the complexity of managing CCs increases, we can expect that a more holistic management will require a GP. Therefore, we hypothesize that in the Swiss health care system, the more CCs a patient has, the more likely it is that they will be managed by a GP rather than a specialist. This could lead to a selection of patients, in turn resulting in a higher prevalence of MM in primary care, as observed in our study. Alternatively, patients with more CCs may more often require coordination of specialised care through the GP.

In our study, prevalence of two or more CCs in the 0-20 age group was 6.2% and above 90% in patients above 80 years old. Thus, MM is associated with age, but not gender, which is consistent with others studies.(1, 5, 20)

The main CCs reported in the literature are cardiovascular diseases, diabetes, chronic kidney disease, osteoarthritis, chronic lung diseases, mental disorders (depression, dementia).(21) Our results are consistent with a majority of conditions involving the cardiovascular system. However, our pre-specified list of chronic disorders did not include disorders such as back and cervical pain specifically. GPs could either report the latter as general pain or add a commentary at the end of the form. Thus the contribution of these disorders to the overall prevalence may have been under-estimated.

The prevalence of cardiovascular diseases and endocrine and metabolic diseases was 20 to 40 times higher in those above the age of 80 years compared to the youngest age group. Psychological disorders were only about three times more prevalent in older age groups, in line with previous studies reporting high prevalence of mental disorders in young persons.(22)

Strengths and limitations:

A main strength of the current study is that our data were collected from a representative sample of practices throughout an entire country and using a scientifically established list of 75 CCs relevant to MM in PC. This list is a result of a consensus process between experts in general practice to identify the CCs that are most relevant to MM in primary care.(12) It provides an estimate based on the daily reality of GPs, and adds strength to the validity of the selected list.

Our inclusion criteria did not exclude any age category, which enabled us to estimate prevalence among young people, contrary to the majority of other studies that have only been interested in patients above the age of 50 or 65 years.

There was no participation bias as every consecutive patient was included.

Our study has certain limitations. First, our estimate was rather conservative, as reported CCs were pre-selected. This may have led to an underestimation of MM, as it has been suggested that prevalence of MM is highly dependent on the number of CCs included in the definition.(11, 23) Some GPs added conditions at the end of the form if they had not found them in the pre-specified list. These were too heterogeneous to be counted in the MM prevalence estimates, which were thus based exclusively on the 75 pre-defined CCs. Second, some CCs (chronic renal failure) were missing from the ICPC-2, and thus from our selection. In addition, other CCs, such as thyroid diseases, degenerative diseases, chronic hepatitis, were not part of our selected list of CCs. Third, we used a newly created list of CCs.(12) This could compromise the external validity of our study, since no exact comparison with previous prevalence studies could be done. However this list was developed specifically for primary care following a rigorous methodology and its previous use to characterise a sample of multimorbid patients in primary care led to similar distributions of CCs (although as this previous study involved only multimorbid patients, no prevalence data could be extracted) .(16) Fourth, the definition of CCs such as elevated blood pressure was left to the appreciation of GPs and CCs such as cardiovascular risk factors may be redundant with obesity, high blood pressure or tobacco use. Fifth, we cannot differentiate whether reported CCs were active health problems or not. GPs may have reported important CCs which no longer had an impact on the patient's current health, such as cancer treated in the past. Finally, that no general paediatricians (who are primary care providers in Switzerland) participated in our study may have led to an underestimation of the prevalence of MM in the age group 0 to 20 years old.

Implications for practice and research:

Our findings highlight that even in a country in which GPs do not have a gate-keeping role, caring for patients with MM is at the forefront of their activity. In the context of a high prevalence of MM as estimated in our study, disease-based management is no longer possible and developing new models of care is essential. This has implications for service planning (including thoughts about pricing) and for pre- and postgraduate training.

A fundamental concept is the global impact of MM on the quality of care, and the complexity of care, that could be more accurately assessed by a validated morbidity index rather than by adding CCs together. Future studies need to specify which combination of CCs or patients' characteristics are associated with higher needs and impacts on quality of care, morbidity and mortality. This could help us identify subgroups of patients who could benefit the most from new models of care.

Conclusions

MM is highly prevalent among patients consulting GPs in Switzerland. These results have implications for training and the organization of health care in our country. The identification of the patients most likely to benefit from complex care within family practice, and the development of new models of care to address their needs are challenges for the future.

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Author contributions:

SE, DH, LH, ADL, ANG designed and elaborated the protocol, ANG, LH and ADL collected the data, SE and DH conducted the data analyses; all authors contributed to the interpretation of the data. SE provided the first draft of the manuscript, that was revised, read and approved by all authors.

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Competing interests:

The authors do not report any potential conflict of interest.

Data sharing statement:

Extra data is available by emailing dagmar.haller-hester@unige.ch

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Supplementary table: Prevalence of chronic conditions by system and by sex in the representative sample of 2904 patients recruited in 118 family practices throughout Switzerland

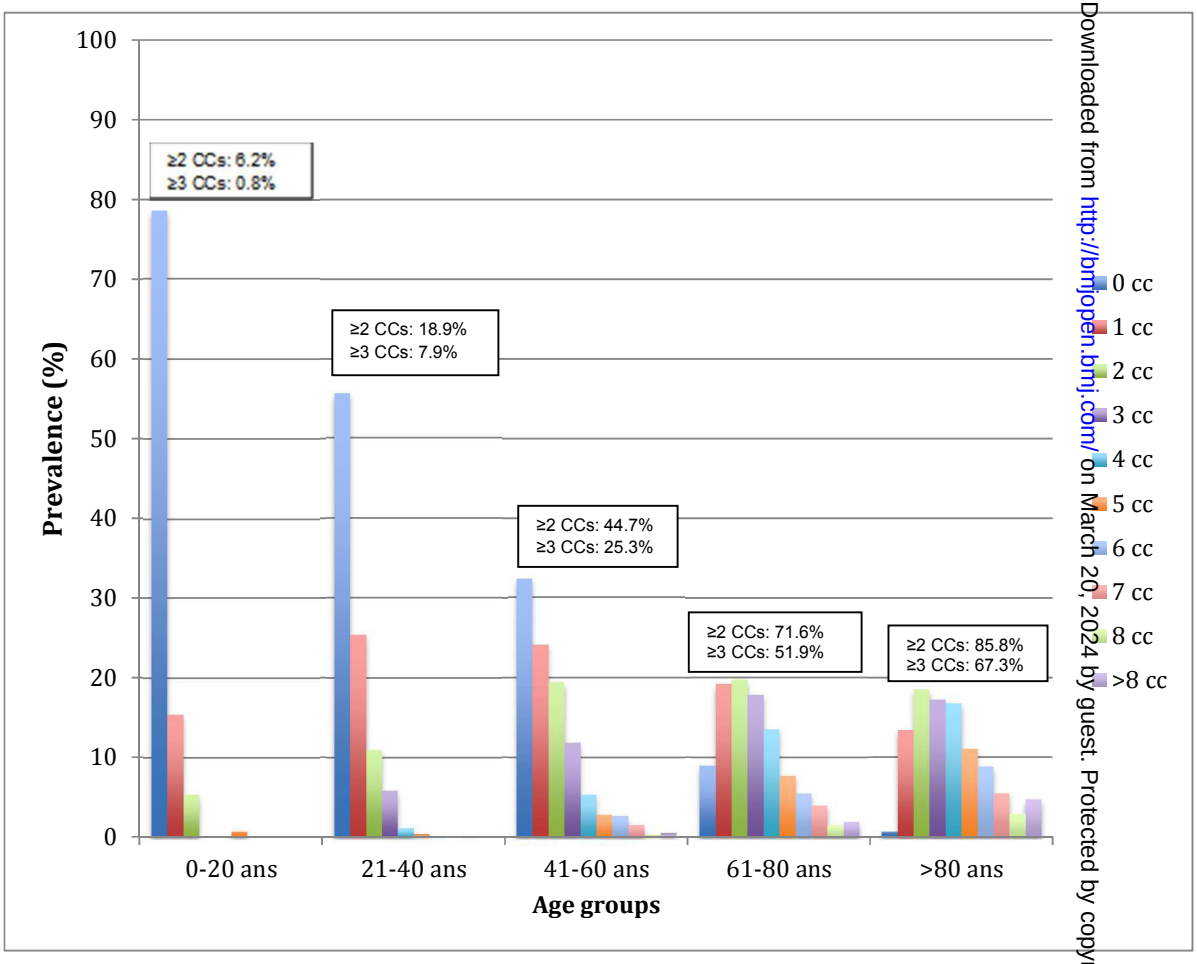
		Male (N=1268)			Female (N=1636)			Total (N=2904)		
Chronic conditions	**ICPC Code**	**%**	**(95% CI)**		**%**	**(95% CI)**		**%**	**(95% CI)**	
General and unspecified		**9.4**	**7.6**	**11.5**	**12.0**	**10.2**	**14.2**	**10.9**	**9.3**	**12.7**
Pain general/multiple sites	A01	6.9	5.3	9.0	10.5	8.7	12.7	9.0	7.5	10.7
Malignancy NOS	A79	0.8	0.4	1.5	0.7	0.4	1.3	0.8	0.5	1.2
Secondary effect of trauma	A82	1.8	1.1	2.9	0.9	0.5	1.6	1.3	0.9	1.9
Blood, blood forming organs and immune mechanisms		**1.1**	**0.6**	**2.0**	**1.5**	**1.0**	**2.2**	**1.3**	**0.9**	**1.9**
Infection HIV/AIDS	B90	0.5	0.2	1.2	0.3	0.1	0.7	0.4	0.2	0.8
Hodgkin's disease/lymphoma	B72	0.0	0.0	0.0	0.4	0.2	0.8	0.2	0.1	0.5
Malignant neoplasm blood other	B74	0.6	0.3	1.4	0.8	0.5	1.4	0.7	0.4	1.2
Digestive		**6.2**	**4.8**	**7.9**	**8.7**	**7.2**	**10.6**	**7.6**	**6.4**	**9.0**
Bowel Incontinence	D17	0.4	0.1	1.1	0.5	0.2	1.1	0.4	0.2	0.8
Malignant neoplasm stomach	D74	0.4	0.2	0.9	0.3	0.1	0.7	0.3	0.2	0.6
Malignant neoplasm colon/rectum	D75	0.8	0.4	1.5	1.0	0.7	1.6	0.9	0.7	1.3
Malignant neoplasm pancreas	D76	0.4	0.2	0.9	0.0	0.0	0.0	0.2	0.07	0.4
Malignant neoplasm digest other NOS	D77	0.7	0.4	1.3	0.1	<0.01	0.4	0.3	0.2	0.6
Irritable bowel syndrome	D93	2.7	1.9	3.8	5.7	4.4	7.4	4.4	3.5	5.6
Chronic enteritis/ulcerative colitis	D94	1.0	0.6	1.7	1.7	1.1	2.5	1.4	1.0	2.0
Endocrine/Metabolic and Nutritional		**25.1**	**22.1**	**28.3**	**23.3**	**20.3**	**26.7**	**24.1**	**21.6**	**26.7**

Obesity	T82	13.6	11.2	16.5	16.8	14.1	19.9	15.4	13.3	17.9
Diabetes insulin-dependent	T89	2.4	1.7	3.6	1.4	0.9	2.2	1.9	1.3	2.6
Diabetes non-insulin dependent	T90	13.0	11.0	15.4	8.3	6.8	10.1	10.4	9.0	11.9
Gout	T92	4.1	3.0	5.5	1.7	1.1	2.6	2.7	2.1	3.5
Malignant neoplasm thyroid	T71	0.08	0.01	0.6	0.4	0.2	1.0	0.3	0.1	0.6
Respiratory		**9.4**	**7.7**	**11.6**	**9.8**	**8.2**	**11.6**	**9.6**	**8.3**	**11.1**
Chronic bronchitis	R79	2.4	1.5	3.8	1.8	1.2	2.9	2.1	1.4	3.0
Malignant neoplasm bronchi/lung	R84	0.2	0.1	0.7	0.6	0.3	1.0	0.4	0.2	0.7
Chronic obstructive pulmonary disease	R95	5.0	3.8	6.5	3.6	2.7	4.8	4.2	3.4	5.1
Asthma	R96	2.3	1.5	3.4	4.3	3.4	5.4	3.4	2.7	4.2
Eye		**1.5**	**1.0**	**2.3**	**2.8**	**2.0**	**3.9**	**2.2**	**1.7**	**2.9**
Retinopathy	F83	0.7	0.4	1.3	1.0	0.5	1.9	0.9	0.5	1.4
Macular degeneration	F84	0.8	0.4	1.4	1.8	1.3	2.6	1.4	1.0	1.9
Blindness	F94	0.0	0.0	0.0	0.2	0.06	0.6	0.1	0.03	0.3
Ear		**4.1**	**3.1**	**5.4**	**3.5**	**2.5**	**4.8**	**3.8**	**2.9**	**4.8**
Hearing complaints	H02	2.7	1.9	3.8	2.3	1.6	3.3	2.5	1.9	3.3
Deafness	H86	1.4	0.9	2.3	1.3	0.8	2.0	1.3	0.9	1.9
Cardiovascular diseases		**45.6**	**41.9**	**49.3**	**40.4**	**36.8**	**44.1**	**42.7**	**39.7**	**45.7**
risk factor cardiovascular disease	K22	13.1	10.3	16.5	10.4	7.9	13.6	11.6	9.2	14.5
Ischemic heart disease with angina	K74	4.3	3.2	5.7	2.1	1.4	3.3	3.1	2.3	4.0
Ischemic heart disease without angina	K76	6.9	5.5	8.7	3.7	2.7	4.9	5.1	4.2	6.2
Atrial fibrillation/flutter	K78	7.0	5.6	8.8	6.3	5.0	7.9	6.6	5.6	7.8
Pulmonary heart diseases	K82	0.7	0.3	1.4	0.4	0.2	0.8	0.5	0.3	0.9
Elevated blood pressure	K85	14.0	11.2	17.3	10.8	8.4	13.7	12.2	9.9	14.9
Hypertension uncomplicated	K86	20.7	17.8	23.9	19.4	16.9	22.3	20.0	17.6	22.6
Hypertension complicated	K87	4.6	3.4	6.2	4.9	3.6	6.7	4.8	3.7	6.1
Cerebrovascular disease	K91	5.1	3.9	6.8	3.0	2.1	4.2	3.9	3.1	4.9
Atherosclerosis	K92	6.4	5.0	8.1	3.7	2.9	4.8	4.9	4.1	5.8

Neurological diseases		**6.6**	**5.3**	**8.2**	**7.8**	**6.6**	**9.2**	**7.3**	**6.3**	**8.4**
Poliomyelitis	N70	0.2	0.07	0.7	0.0	0.0	0.0	0.1	0.03	0.3
Malignant neoplasm nervous system	N74	0.0	0.0	0.0	0.2	0.06	0.6	0.1	0.03	0.3
Multiple sclerosis	N86	0.4	0.2	0.9	0.9	0.5	1.5	0.7	0.4	1.0
Parkinsonism	N87	0.6	0.3	1.2	0.6	0.3	1.1	0.6	0.4	1.0
Epilepsy	N88	1.1	0.7	1.8	1.1	0.7	1.7	1.1	0.8	1.5
Migraine	N89	0.9	0.5	1.6	2.5	1.9	3.4	1.8	1.3	2.4
Trigeminal neuralgia	N92	0.2	0.08	0.7	0.4	0.2	1.0	0.3	0.2	0.7
Abnormal involuntary movements	N08	0.8	0.4	1.4	0.4	0.2	0.9	0.6	0.4	0.9
Peripheral neuritis/neuropathy	N94	2.6	1.8	3.8	1.9	1.3	2.7	2.2	1.6	3.0
Pain face	N03	0.08	0.01	0.6	0.4	0.2	0.8	0.2	0.1	0.5
Skin		**1.8**	**1.0**	**3.1**	**1.2**	**0.7**	**2.1**	**1.5**	**0.9**	**2.3**
Chronic ulcer skin	S97	1.8	1.0	3.1	1.2	0.7	2.1	1.5	0.9	2.3
Musculoskeletal		**11.0**	**9.0**	**13.2**	**20.4**	**18.0**	**23.1**	**16.3**	**14.4**	**18.3**
Rheumatoid/seropositive arthritis	L88	1.4	0.9	2.3	2.9	2.1	3.9	2.2	1.7	3.0
Hip osteoarthritis	L89	4.4	3.2	6.1	7.7	6.2	9.5	6.3	5.1	7.7
Knee osteoarthritis	L90	6.1	4.8	7.6	9.4	7.7	11.5	8.0	6.7	9.4
Osteoporosis	L95	0.9	0.5	1.7	7.6	6.2	9.3	4.7	3.9	5.8
Urological		**2.0**	**1.3**	**3.1**	**2.9**	**2.1**	**4.0**	**2.5**	**1.9**	**3.3**
Urinary incontinence	U04	1.2	0.7	2.0	2.7	1.9	3.7	2.0	1.5	2.7
Malignant neoplasm bladder	U76	0.6	0.2	1.3	0.2	0.09	0.6	0.4	0.2	0.7
Malignant neoplasm kidney	U75	0.2	0.05	1.0	0.1	0.03	0.5	0.2	0.06	0.5
Psychological		**26.5**	**23.3**	**30.0**	**30.1**	**27.5**	**32.9**	**28.5**	**26.1**	**31.1**
Chronic alcohol abuse	P15	4.6	3.5	6.0	1.7	1.1	2.5	2.9	2.3	3.7
Tobacco abuse	P17	5.8	4.2	8.0	4.8	3.5	6.7	5.3	4.0	6.9
Drug abuse	P19	1.7	1.1	2.6	1.0	0.6	1.7	1.3	0.9	1.8
Dementia	P70	2.2	1.5	3.2	2.6	1.9	3.5	2.4	1.9	3.2
Organic psychosis other	P71	0.6	0.3	1.2	0.5	0.2	1.0	0.6	0.3	0.9

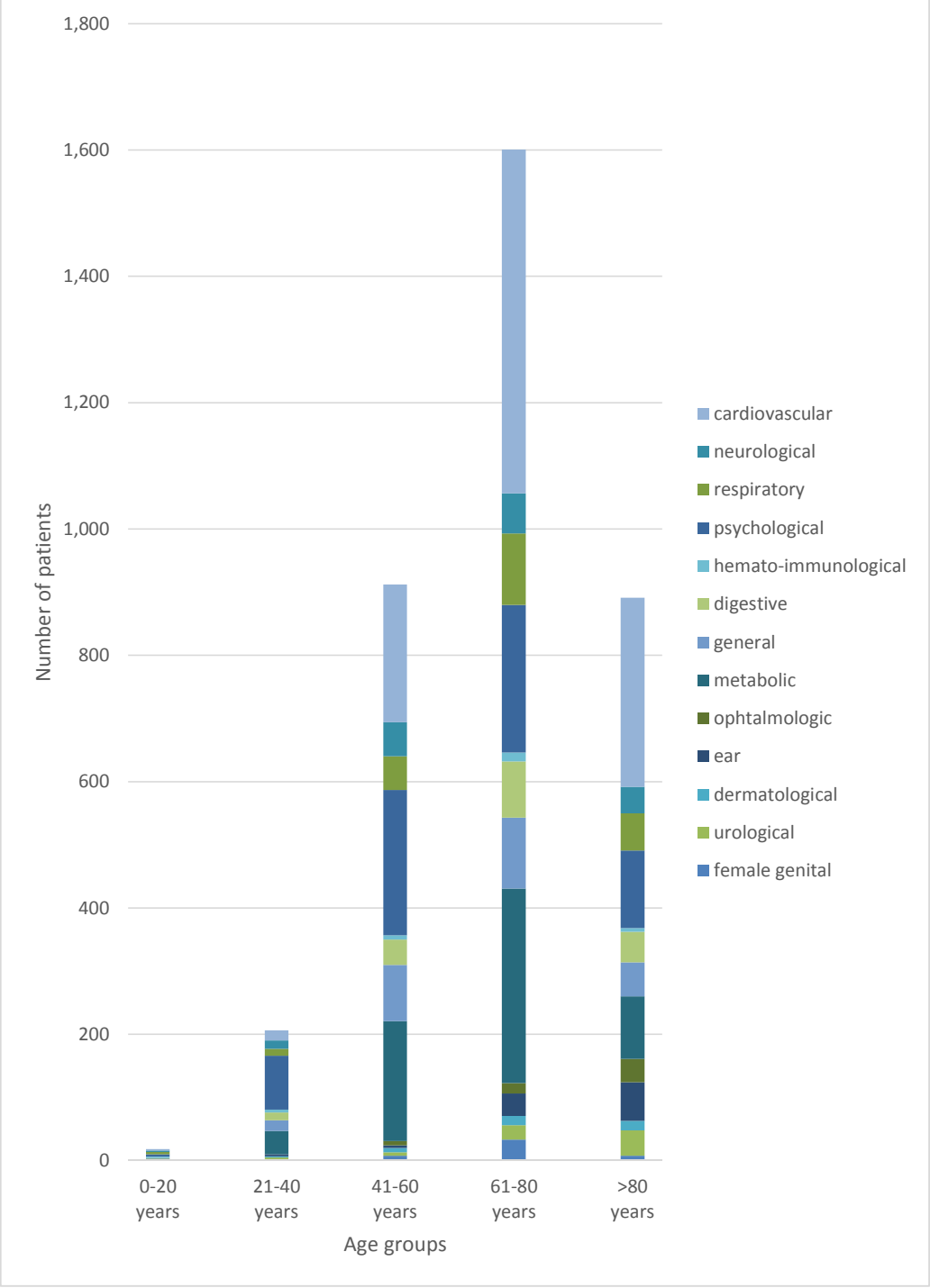
Schizophrenia	P72	0.9	0.6	1.6	1.2	0.8	1.9	1.1	0.8	1.6
Affective psychosis	P73	0.9	0.5	1.7	0.7	0.3	1.3	0.8	0.5	1.3
Somatization disorder	P75	2.3	1.6	3.3	4.3	3.3	5.5	3.4	2.7	4.3
Depressive disorder	P76	9.4	7.6	11.5	14.9	13.0	17.1	12.5	10.9	14.3
Phobia/compulsive disorder	P79	0.9	0.5	1.7	1.4	0.9	2.2	1.2	0.8	1.7
Personality disorder	P80	2.7	1.9	3.8	2.8	2.1	3.8	2.8	2.2	3.5
Post-traumatic disorder	P82	1.1	0.7	1.8	1.2	0.7	2.0	1.2	0.8	1.8
Mental retardation	P85	0.8	0.4	1.5	0.6	0.3	1.1	0.7	0.4	1.1
Anorexia nervosa/bulimia	P86	0.08	0.01	0.6	0.4	0.1	0.9	0.2	0.1	0.6
Psychological disorders, other	P98	0.2	0.04	0.6	0.4	0.2	0.9	0.3	0.2	0.6
Medication abuse	P18	0.7	0.4	1.3	1.4	0.9	2.3	1.1	0.7	1.6
Memory disturbance	P20	1.7	1.0	2.7	1.4	0.8	2.4	1.5	1.0	2.2
Female genital		**0.0**	**0.0**	**0.0**	**3.7**	**2.8**	**5.0**	**2.1**	**1.6**	**2.8**
Malignant neoplasm cervix	X75	0.0	0.0	0.0	0.4	0.2	0.8	0.2	0.09	0.5
Malignant neoplasm breast female	X76	0.0	0.0	0.0	3.4	2.5	4.6	1.9	1.4	2.6
Male genital		**3.2**	**2.4**	**4.4**	**0.0**	**0.0**	**0.0**	**1.4**	**1.1**	**1.9**
Malignant neoplasm prostate	Y77	3.2	2.4	4.4	0.0	0.0	0.0	1.4	1.1	1.9

Figure 1: Number of chronic conditions by age-group in a representative sample of 2904 patients recruited in 118 family practices throughout Switzerland, and prevalence of multimorbidity in each age-group.



CCs : chronic conditions

Figure 2: Spread across systems of chronic conditions contributing to multimorbidity, by age group, in 2904 primary care patients



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	4	Last paragraph of introduction
Methods				
Study design	4	Present key elements of study design early in the paper	4	Methods section
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	Participants and procedure
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	Participants and procedure
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4	Data collection
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4	Data collection
Bias	9	Describe any efforts to address potential sources of bias	4	Data collection
Study size	10	Explain how the study size was arrived at	5	Sample size

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5	Statistical analysis
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5	Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions		
		(*c*) Explain how missing data were addressed	5	Statistical analysis
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5	Analyses were adjusted for clustering
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6	First paragraph of results
		(b) Give reasons for non-participation at each stage	6	Results
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6	Results
		(b) Indicate number of participants with missing data for each variable of interest	6	Results
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures	6-8	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7	Table 1
		(*b*) Report category boundaries when continuous variables were categorized	5	Methods
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8	
Discussion				
Key results	18	Summarise key results with reference to study objectives	10	First section of discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12	Strengths and limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13	Implications
Generalisability	21	Discuss the generalisability (external validity) of the study results	12	Strengths and limitations
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14	Fuding

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Prevalence of multimorbidity in general practice: a cross-sectional study within the Swiss Sentinel Surveillance System (Sentinella)

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Keywords:	PRIMARY CARE, family medicine, chronic conditions, multimoribdity

Prevalence of multimorbidity in general practice: a cross-sectional study within the Swiss Sentinel Surveillance System (Sentinella)

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Tables: 2, supplementary table:1. Figures: 2.

Keywords: general practice, primary care, multimorbidity, chronic conditions

Abstract:

Objectives: To estimate the prevalence of multimorbidity using a list of 75 chronic conditions derived from ICPC-2 and developed specifically to assess multimorbidity in primary care. Our aim was also to provide prevalence data for multimorbidity in primary care in a country in which GPs do not play a gatekeeping role in the health system.

Setting: A representative sample of GPs within the Swiss Sentinel surveillance network.

Participants: 118 GPs completed a paper-based questionnaire about 25 consecutive patients of all ages between September and November 2015. There were no patient exclusion criteria. Recorded data included date of birth, gender and the patients' chronic conditions.

Primary and secondary outcome measures: We estimated the prevalence of multimorbidity, defined as ≥ 2, and ≥ 3 chronic conditions stratified by gender and age group, and adjusted for clustering by GPs. We also computed the prevalence of each chronic condition individually and grouped by system.

Results: Data from 2904 patients were included (mean age (SD) = 56.5 (20.5) years; male= 43.7%). Prevalence was 52.1% (95%CI: 48.6-55.5%) for ≥ 2 and 35.0% (95%CI: 31.6-38.5%) for ≥ 3 chronic conditions, with no significant gender differences. Prevalence of two or more chronic conditions was low (6.2%, 95% CI:2.8-13.0%) in those below 20 but affected more than 85% (85.8%, 95%CI: 79.6-90.3%) of those above the age of 80. The most prevalent conditions were cardiovascular (42.7%, 95%CI: 39.7-45.7%), psychological (28.5%, 95%CI: 26.1-31.1%) and metabolic or endocrine disorders (24.1%, 95%CI:21.6-26.7%). Elevated blood pressure was the most prevalent cardiovascular and depression the most common psychological disorder.

Conclusion: In a country in which GPs do not play a gate-keeping role within the health system, the prevalence of multimorbidity, as assessed using a list of chronic conditions specifically relevant to primary care, is high and increases with age.

Strengths and limitations:

- This study provides estimates of the prevalence of multimorbidity based on a sample of patients of all ages from representative practices throughout an entire European country and using a scientifically established list of 75 chronic conditions relevant to multimorbidity in primary care.
- The list was based on codes from the International Classification for Primary Care (ICPC-2). As some common conditions (i.e. chronic renal failure) are missing from this classification, the reported prevalence estimates are somewhat conservative.
- Comparisons with previous studies is limited by the fact that this is the first time this newly established list of chronic conditions relevant to multimorbidity was used to provide prevalence estimates.

Introduction:

Multimorbidity (MM) is commonly defined as the co-occurrence of two, three or more chronic conditions (CCs) within one person.(1) Comorbidity in contrast refers to the development of conditions in addition to one main chronic condition.(2, 3) The prevalence of MM increases with age,(4) with an estimated prevalence ranging from 20-30% in the all-ages population to 55-98% in individuals over 65 years old.(1) This represents a significant challenge for current and future health care services. MM is most frequently managed in primary care (PC) and 70 to 80% of the population visits a general practitioner (GP) at least once a year.(5) (6) MM constitutes a growing problem in view of the aging population and is also associated with increased healthcare costs and threats to quality of care.(1) Estimates of the prevalence of MM vary significantly depending on various definitions of MM and selected lists with limited numbers of CCs, population settings and data collection methods.(1, 3, 4, 7-10) As a consequence, results between studies are difficult to compare.(11) This was highlighted in 2012 in a systematic review of the literature comparing studies in primary care settings and amongst the general population in different geographical regions. (7)

In PC, MM is becoming the norm rather than the exception and limited lists of CCs are not representative of daily practice. Yet the number and spread of high or low prevalent CCs is so important that for research purposes it is important to focus on the CCs that are most relevant to MM in PC. Academic investigators developed a list of 75 CCs relevant for MM in PC, based on the ICPC2 in a modified RAND method. We believe this is yet the best available list for this setting as the 20 participating experts where experienced and clinically active primary care providers. (12)

Furthermore, in the majority of the European countries, GPs act as gatekeepers to the healthcare system. In countries in which this is not the case, such as in Switzerland, Germany or Greece, where patients can directly access specialist care, the prevalence of MM in general practice may be lower. Only few studies conducted in such countries are reported in the literature. In a predominantly rural population in Greece the prevalence of MM (≥ 2 CCs) in primary care was 20.0%. (13) Yet there was potentially a participation bias since GPs participated on invitation and worked in specific rural and semi-rural populations. In a German study 58.9% of patients above the age of 65 seen in ambulatory settings had three or more CCs.(14) Yet these findings were based on insurance claims data and not limited to patients consulting in primary care. In Switzerland, one study used electronic data from general practices in a German-speaking region and identified a prevalence of MM (≥ 2 CCs) of 13-

15%. Yet there was a high probability of underreporting in this study since CCs that were not discussed during the consultation were not reported. (15)

In view of these limitations, our aim was to provide estimates of the prevalence of MM in primary care in Switzerland, based on the list of 75 CCs relevant for MM. We hypothesised that this prevalence may be lower in a setting in which GPs do not have a gatekeeper role within the healthcare system (as is the case in Switzerland), compared to a setting in which patients need to see a GP to be referred to a specialist. We also hypothesised that the use of a predefined list of CCs relevant to MM in primary care would provide us with a more precise estimate of the prevalence of MM in this setting.

Methods

Participants and procedure:

This cross-sectional study was conducted from 14th of September to 6th of November 2015 in general practices across Switzerland. We recruited a voluntary sample of 118 GPs from the Sentinella network, who collected data from 25 consecutive patients attending their practice during a two-week-period. Sentinella is a representative network involving 132 voluntary GPs (and approximately 30 general paediatricians, not included in this study) across Switzerland. The network was initially set up for the epidemiological monitoring of infectious diseases. The Swiss Federal Office of Public Health (FOPH) runs the administrative part of the program and ensures that GPs are included to be overall representative of all GPs working in Switzerland and thus also of 75 to 80% of the population who visits a GP at least once a year.The Sentinella network also participates in selected research projects. As partner of the network, the FOPH collects data from the GPs registered with the network and ensures they remain anonymous.

Data collection:

For our study, participating GPs were asked to pre-select a day within the two-week study period on which they began data collection for our study. For each patient included in the study, participating GPs completed a paper Clinical Report Form (CRF), which included patients' age and gender and CCs, identified from the list of 75 CCs (described below).(12) The possibility to add relevant CCs in free text was left to the GPs, to overcome any limitations due to a selected list of CCs. The CRF was a

double-sided A4 sheet in which the list of CCs was grouped by main systems in order to facilitate GPs' quick identification of relevant CCs for each patient, thus limiting potential omissions.

All data were anonymised and recorded into a centralised database. All the written communications were made through official letters from the FOPH as per the usual communication of the Sentinella network. This ensured the anonymity of data because there was no contact between the participating GPs and the investigators.

We used the list of 75 CCs developed by N'Goran et al. and recently used in the MMFM (Multimorbidity in Family Medicine) study.(12, 16) This list is based on ICPC-2 and is the result of a four-rounds modified RAND survey involving a panel of GPs throughout Switzerland to identify the CCs most relevant to MM.(17)

Sample size:

We calculated that a sample size of 2016 patients would be sufficient to measure a prevalence of MM of around 30% with a precision margin of 2%. Adapting for the clustering of patients within different practices, we used an intra-class coefficient of 0.01, based on the literature, and estimated a sample size adjusted to 2499, rounded off to 2500 for practical purposes.

Statistical analyses:

A double data entry followed by a reconciliation process was used to ensure the quality of the database. We performed descriptive analyses using Stata version 13 (StataCorp LP, College Station, TX, USA). Patients with missing data for age, gender and/or CCs were excluded. Continuous data (age) were summarized using means and standard deviations, whereas categorical data were summarized using proportions and confidence intervals (CI), adjusted for clustering within practices. We calculated the point prevalence of MM and estimated prevalence of MM by age groups (grouped by steps of 20 years) and by sex. We also computed the prevalence of each chronic condition individually as well as grouped by system.

Ethical aspects:

Since the study involved the analysis of completely anonymous data, it was granted a waiver from approval by the Human Research Ethics Committee of the Canton Vaud.

Results:

Descriptive statistics:

Participation rate was high with 118 of 132 eligible GPs (89.4%) in the Sentinella network participating in our study.

The GPs included 2966 patients. Gender information was missing for 54 patients (reported by 29 different GPs) and year of birth for 16 patients (from 13 GPs) including 8 patients for whom both gender and year of birth was missing. Furthermore, one patient was excluded because of missing data concerning CCs. As a result, 2904 patients were retained in the final sample and included in the statistical analysis. 43.7% were male and mean (SD) age was 56.5 (20.5) years.

The sex and age distribution in our sample was comparable to that of all doctor-patient contacts in the Sentinella network during a similar period (data not shown). We assumed that the minimal differences (‹2%) in the proportion of individuals in certain age subgroups did not have an influence on the results.

The prevalence of MM independently of age was 52.1% for two or more CCs and 35.0% for three or more CCs. Considering the total sample, 27% did not have any CCs and 1.5% had more than 8 CCs. Prevalence of MM was equally distributed between females and males. Table 1 shows details of the prevalence of two, three or more CCs by gender and age group. The prevalence of MM defined as two or more CCs was 6.2% in those below the age of 20 years, compared to 44.7%, 71.6% and 85.8% in the age groups 41-60 years, 61-80 years and above 80 years respectively (Table 1).

Table 1: prevalence of ≥ 2, and ≥ 3 chronic conditions by sex and age groups in the representative sample of 2904 patients reported by 118 GPs throughout Switzerland

	Male (N=1268)				Female (N=1636)				Total (N=2904)			
	2 or more chronic conditions		3 or more chronic conditions		2 or more chronic conditions		3 or more chronic conditions		2 or more chronic conditions		3 or more chronic conditions	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
0-20 years	1.9	(0.2-12.5)	0.0	0.0	9.3	(4.4-18.7)	1.3	(0.2-9.2)	6.2	(2.8-13.0)	0.8	(0.1-5.4)
21-40 years	18.8	(13.8-25.2)	6.2	3.6-10.4	18.9	(14.6-24.0)	9.4	(6.1-14.3)	18.9	(15.3-23.1)	7.9	(5.5-11.3)
41-60 years	44.7	(39.0-50.7)	25.4	20.4-31.2	44.6	(39.4-50.0)	25.1	(21.0-29.7)	44.7	(40.3-49.1)	25.3	(21.7-29.2)
61-80 years	73.3	(68.4-77.6)	53.5	47.6-59.3	70.3	(64.9-75.2)	50.6	(45.0-56.2)	71.6	(67.4-75.5)	51.9	(47.0-56.8)
> 80 years	86.9	(79.5-91.9)	70.0	60.3-78.2	85.2	(77.9-90.4)	65.9	(57.6-73.3)	85.8	(79.6-90.3)	67.3	(60.2-73.6)

As expected, below the age of 20, only a minority of patients had a chronic condition (N=624, 21.5%). Between 40 and 60 years, about 70% had at least one chronic condition, and above the age of 80, the proportion of patients without any CCs was negligible (Figure 1).

Insert Figure 1 approximately here

Distribution by system:

The most commonly reported CCs concerned the cardiovascular system. Psychological disorders, metabolic and endocrine disorders were also common (Table 2). The detailed prevalence estimates for all conditions are presented in the supplementary table.

CCs which contributed most to MM in the age groups 0-20 and 20-40 were psychological conditions and metabolic diseases. Cardiovascular conditions were at the forefront in patients over the age of 40 even though psychological conditions also often contributed to MM in these age groups (Figure 2).

Insert Figure 2 approximately here

Table 2: Prevalence of chronic conditions in the representative sample of 2904 patients (presenting only chronic conditions with a prevalence ≥ 5% in one gender)

Chronic Conditions	*ICPC -2 Code*	Male (N=1268)		Female (N=1636)		Total (N=2904)	
		%	(95% CI)	%	(95% CI)	%	(95% CI)
Cardiovascular diseases							
Hypertension uncomplicated	K86	20.7	(17.8 - 23.9)	19.4	(16.9 - 22.3)	20.0	(17.6 - 22.6)
Elevated blood pressure	K85	14.0	(11.2 - 17.3)	10.8	(8.4 - 13.7)	12.2	(9.9 - 14.9)
Risk factor cardiovascular disease	K22	13.1	(10.3 - 16.5)	10.4	(7.9 - 13.6)	11.6	(9.2 - 14.5)
Atrial fibrillation/flutter	K78	7.0	(5.6 - 8.8)	6.3	(5.0 - 7.9)	6.6	(5.6 - 7.8)
Ischemic heart disease without angina	K76	6.9	(5.5 - 8.7)	3.7	(2.7 - 4.9)	5.1	(4.2 - 6.2)
Atherosclerosis	K92	6.4	(5.0 - 8.1)	3.7	(2.9 - 4.8)	4.9	(4.1 - 5.8)
Cerebrovascular disease	K91	5.1	(3.9 - 6.8)	3.0	(2.1 - 4.2)	3.9	(3.1 - 4.9)
Endocrine/Metabolic and Nutritional							
Obesity	T82	13.6	(11.2 - 16.5)	16.8	(14.1 - 19.9)	15.4	(13.3 - 17.9)
Diabetes non-insulin dependent	T90	13.0	(11.0 - 15.4)	8.3	(6.8 - 10.1)	10.4	(9.0 - 11.9)
Psychological							
Depressive disorder	P76	9.4	(7.6 - 11.5)	14.9	(13.0 - 17.1)	12.5	(10.9 - 14.3)
General and unspecified							
Pain general/multiple sites	A01	6.9	(5.3 - 9.0)	10.5	(8.7 - 12.7)	9.0	(7.5 - 10.7)
Musculoskeletal							
Osteoarthritis of knee	L90	6.1	(4.8 - 7.6)	9.4	(7.7 - 11.5)	8.0	(6.7 - 9.4)
Osteoarthritis of hip	L89	4.4	(3.2 - 6.1)	7.7	(6.2 - 9.5)	6.3	(5.1 - 7.7)
Osteoporosis	L95	0.9	(0.5 - 1.7)	7.6	(6.2 - 9.3)	4.7	(3.9 - 5.8)
Respiratory							
Chronic obstructive pulmonary disease	R95	5.0	(3.8 - 6.5)	3.6	(2.7 - 4.8)	4.2	(3.4 - 5.1)

Discussion:

Summary of main findings:

Our study highlights the high prevalence of MM in a nationwide cross-sectional study in primary care in Switzerland, based on a representative list of CCs relevant for MM. Prevalence of two or more CCs across all age-groups was 52.2%, and prevalence of 3 or more CCs was 35.0%. There were no significant gender differences. As expected, the prevalence of MM increases with age, with about 72% of patients above 60 years of age having at least two or more CCs, indicating that MM is common in GPs' daily practice, even in a country in which GPs do not have a gatekeeping role within the healthcare system. GPs in our study were more frequently in contact with patients with one or more CCs than without (73% vs 27%).

The distribution by organ chapter or system highlighted the predominance of cardiovascular diseases mainly due to elevated or high blood pressure with or without complications, which accounted for more than one third of the conditions. Psychological disorders were prevalent in all age groups and accounted for nearly 30% of all CCs.

Comparison with the existing literature:

Our prevalence estimates are much higher than that described in a previous study conducted in Switzerland, based on data extracted from electronic medical records, in which prevalence of MM was 15% (FIRE study).(15) Underreporting of CCs not actively treated in the consultation may possibly explain the low prevalence of MM in this study. Similarly, under-recording in electronic medical records may explain the lower prevalence of MM measured as two or more CCs (23.2%) in another study involving more than 300 practices in Scotland.(4) In addition, in the Scottish study, the CCs were identified within a list of 40 conditions established by the authors, and were not based on the ICPC-2. Thus, these findings are not directly comparable with ours. Studies from the Netherlands used lists based on ICPC-2. In a Dutch study using a list of 28 CCs within this classification, prevalence of MM defined as two or more CCs in patients above the age of 55 years was 37%. (18) This is surprisingly low compared to our findings, particularly if one considers that younger patients were excluded. Again, underreporting due to extraction limited to active CCs within electronic medical files, may explain this low prevalence as well as the limited number of CCs to choose from within the list these authors used.

A reference group outside of Europe (Fortin et al.) reported prevalence estimates of two or more CCs of 98.7% in patients above the age of 65. (5) In this study, no pre-selected list of CCs was used. The practitioners had the possibility of reporting any conditions they considered chronic and this may have increased the spectrum of disorders potentially contributing to MM in this study. The same authors reported strong differences in estimated prevalence according to variations in the methodology of the study, particularly with regard to the number of CCs.(7) In a recent sub-study of the national survey BEACH (Bettering the Evaluation and Care of Health) in Australia a prevalence of around 50% for two or more CCs and 27% for three or more CCs in a family medicine sample was estimated, similar to our findings.(19)

Unlike in other health systems, GPs in Switzerland generally do not have a gatekeeper role and patients can have direct access to specialists. We hypothesize that a number of patients with only one chronic condition may tend to only see a specialist. However, as the complexity of managing CCs increases, we can expect that a more holistic management will require a GP. Therefore, we hypothesize that in the Swiss health care system, the more CCs a patient has, the more likely it is that they will be managed by a GP rather than a specialist. This could lead to a selection of patients, in turn resulting in a higher prevalence of MM in primary care, as observed in our study. Alternatively, patients with more CCs may more often require coordination of specialised care through the GP.

In our study, prevalence of two or more CCs in the 0-20 age group was 6.2% and above 90% in patients above 80 years old. Thus, MM is associated with age, but not gender, which is consistent with others studies.(1, 5, 20)

The main CCs reported in the literature are cardiovascular diseases, diabetes, chronic kidney disease, osteoarthritis, chronic lung diseases, mental disorders (depression, dementia).(21) Our results are consistent with a majority of conditions involving the cardiovascular system. However, our pre-specified list of chronic disorders did not include disorders such as back and cervical pain specifically. GPs could either report the latter as general pain or add a commentary at the end of the form. Thus, the contribution of these disorders to the overall prevalence may have been under-estimated.

The prevalence of cardiovascular diseases and endocrine and metabolic diseases was 20 to 40 times higher in those above the age of 80 years compared to the youngest age group. Psychological disorders were only about three times more prevalent in older age groups, in line with previous studies reporting high prevalence of mental disorders in young persons.(22)

Strengths and limitations:

A main strength of the current study is that our data were collected from a representative sample of practices throughout an entire country and using a scientifically established list of 75 CCs relevant to MM in PC. This list is a result of a consensus process between experts in general practice to identify the CCs that are most relevant to MM in primary care.(12) It provides an estimate based on the daily reality of GPs, and adds strength to the validity of the selected list.

Our inclusion criteria did not exclude any age category, which enabled us to estimate prevalence among young people, contrary to the majority of other studies that have only been interested in patients above the age of 50 or 65 years.

There was no participation bias as every consecutive patient was included.

Our study has certain limitations. First, our estimate was rather conservative, as reported CCs were pre-selected. This may have led to an underestimation of MM, as it has been suggested that prevalence of MM is highly dependent on the number of CCs included in the definition.(11, 23) Some GPs added conditions at the end of the form if they had not found them in the pre-specified list. These were too heterogeneous to be counted in the MM prevalence estimates, which were thus based exclusively on the 75 pre-defined CCs. Second, some CCs (chronic renal failure) were missing from the ICPC-2, and thus from our selection. In addition, other CCs, such as thyroid diseases, degenerative diseases, chronic hepatitis, were not part of our selected list of CCs. Third, we used a newly created list of CCs.(12) This could compromise the external validity of our study, since no exact comparison with previous prevalence studies could be done. However this list was developed specifically for primary care following a rigorous methodology. Its previous use to characterise a sample of multimorbid patients in primary care led to similar distributions of CCs (although as this previous study involved only multimorbid patients, no prevalence data could be extracted).(16) GPs from all parts of Switzerland, practicing in three culturally diverse regions of the country, were involved in the development of this list. Since the epidemiological profile of MM is likely to be similar in other high-income countries, the list is likely to be relevant for studies in most other high-income countries.

Fourth, the definition of CCs such as elevated blood pressure was left to the appreciation of GPs and CCs such as cardiovascular risk factors may be redundant with obesity, high blood pressure or tobacco use. In addition, GPs who were not familiar with ICPC2 codes may have miscoded some items thus leading to reporting bias. In particular, we cannot exclude that some GPs may have recorded family history, or age, as a cardiovascular risk factor. Fifth, we cannot differentiate whether reported CCs were active health problems or not. GPs may have reported important CCs which no longer had an impact on the patient's current health, such as cancer treated in the past. Finally, that no general paediatricians (who are primary care providers in Switzerland) participated in our study may have led to an underestimation of the prevalence of MM in the age group 0 to 20 years old.

Implications for practice and research:

Our findings highlight that even in a country in which GPs do not have a gate-keeping role, caring for patients with MM is at the forefront of their activity. In the context of a high prevalence of MM as estimated in our study, disease-based management is no longer possible and developing new models of care is essential. This has implications for service planning (including thoughts about pricing) and for pre- and postgraduate training.

A fundamental concept is the global impact of MM on quality of care, and complexity of care, that could be more accurately assessed by a validated morbidity index rather than by adding CCs together. Future studies need to specify which combination of CCs or patients' characteristics are associated with higher needs and impacts on quality of care, morbidity and mortality. This could help us identify subgroups of patients who could benefit the most from new models of care.

Conclusions

MM is highly prevalent among patients consulting GPs in Switzerland. These results have implications for training and the organization of health care in our country. The identification of the patients most likely to benefit from complex care within family practice, and the development of new models of care to address their needs are challenges for the future.

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Author contributions:

SE, DH, LH, ADL, ANG designed and elaborated the protocol, ANG, LH and ADL collected the data, SE and DH conducted the data analyses; all authors contributed to the interpretation of the data. SE provided the first draft of the manuscript, that was revised, read and approved by all authors.

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Competing interests:

The authors do not report any potential conflict of interest.

Data sharing statement:

Extra data is available by emailing dagmar.haller-hester@unige.ch

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Figure Legends:

Figure 1: Number of chronic conditions by age group in a representative sample of 2904 patients reported by 118 GPs throughout Switzerland, and prevalence of multimorbidity in each age-group.

Figure 2: Spread across systems of chronic conditions contributing to multimorbidity, by age group, in 2904 primary care patients

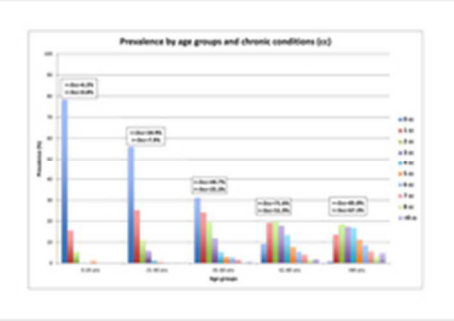

Figure 1: Number of chronic conditions by age group in a representative sample of 2904 patients reported by 118 GPs throughout Switzerland, and prevalence of multimorbidity in each age group

19x13mm (300 x 300 DPI)

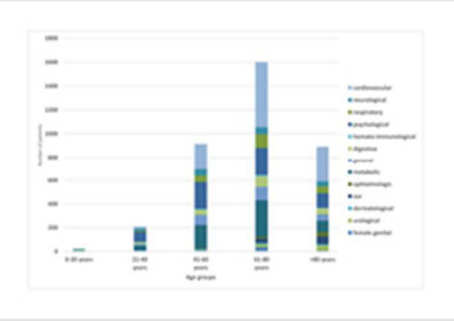

Figure 2: Spread across systems of chronic conditions contributing to multimorbidity, by age group, in 2904 primary care patients

19x13mm (300 x 300 DPI)

Supplementary table: Prevalence of chronic conditions by system and by sex in the representative sample of 2904 patients recruited in 118 family practices throughout Switzerland

		Male (N=1268)			Female (N=1636)			Total (N=2904)		
Chronic conditions	**ICPC Code**	**%**	**(95% CI)**		**%**	**(95% CI)**		**%**	**(95% CI)**	
General and unspecified		**9.4**	**7.6**	**11.5**	**12.0**	**10.2**	**14.2**	**10.9**	**9.3**	**12.7**
Pain general/multiple sites	A01	6.9	5.3	9.0	10.5	8.7	12.7	9.0	7.5	10.7
Malignancy NOS	A79	0.8	0.4	1.5	0.7	0.4	1.3	0.8	0.5	1.2
Secondary effect of trauma	A82	1.8	1.1	2.9	0.9	0.5	1.6	1.3	0.9	1.9
Blood, blood forming organs and immune mechanisms		**1.1**	**0.6**	**2.0**	**1.5**	**1.0**	**2.2**	**1.3**	**0.9**	**1.9**
Infection HIV/AIDS	B90	0.5	0.2	1.2	0.3	0.1	0.7	0.4	0.2	0.8
Hodgkin's disease/lymphoma	B72	0.0	0.0	0.0	0.4	0.2	0.8	0.2	0.1	0.5
Malignant neoplasm blood other	B74	0.6	0.3	1.4	0.8	0.5	1.4	0.7	0.4	1.2
Digestive		**6.2**	**4.8**	**7.9**	**8.7**	**7.2**	**10.6**	**7.6**	**6.4**	**9.0**
Bowel Incontinence	D17	0.4	0.1	1.1	0.5	0.2	1.1	0.4	0.2	0.8
Malignant neoplasm stomach	D74	0.4	0.2	0.9	0.3	0.1	0.7	0.3	0.2	0.6
Malignant neoplasm colon/rectum	D75	0.8	0.4	1.5	1.0	0.7	1.6	0.9	0.7	1.3
Malignant neoplasm pancreas	D76	0.4	0.2	0.9	0.0	0.0	0.0	0.2	0.07	0.4
Malignant neoplasm digest other NOS	D77	0.7	0.4	1.3	0.1	<0.01	0.4	0.3	0.2	0.6
Irritable bowel syndrome	D93	2.7	1.9	3.8	5.7	4.4	7.4	4.4	3.5	5.6
Chronic enteritis/ulcerative colitis	D94	1.0	0.6	1.7	1.7	1.1	2.5	1.4	1.0	2.0
Endocrine/Metabolic and Nutritional		**25.1**	**22.1**	**28.3**	**23.3**	**20.3**	**26.7**	**24.1**	**21.6**	**26.7**

Obesity	T82	13.6	11.2	16.5	16.8	14.1	19.9	15.4	13.3	17.9
Diabetes insulin-dependent	T89	2.4	1.7	3.6	1.4	0.9	2.2	1.9	1.3	2.6
Diabetes non-insulin dependent	T90	13.0	11.0	15.4	8.3	6.8	10.1	10.4	9.0	11.9
Gout	T92	4.1	3.0	5.5	1.7	1.1	2.6	2.7	2.1	3.5
Malignant neoplasm thyroid	T71	0.08	0.01	0.6	0.4	0.2	1.0	0.3	0.1	0.6
Respiratory		**9.4**	**7.7**	**11.6**	**9.8**	**8.2**	**11.6**	**9.6**	**8.3**	**11.1**
Chronic bronchitis	R79	2.4	1.5	3.8	1.8	1.2	2.9	2.1	1.4	3.0
Malignant neoplasm bronchi/lung	R84	0.2	0.1	0.7	0.6	0.3	1.0	0.4	0.2	0.7
Chronic obstructive pulmonary disease	R95	5.0	3.8	6.5	3.6	2.7	4.8	4.2	3.4	5.1
Asthma	R96	2.3	1.5	3.4	4.3	3.4	5.4	3.4	2.7	4.2
Eye		**1.5**	**1.0**	**2.3**	**2.8**	**2.0**	**3.9**	**2.2**	**1.7**	**2.9**
Retinopathy	F83	0.7	0.4	1.3	1.0	0.5	1.9	0.9	0.5	1.4
Macular degeneration	F84	0.8	0.4	1.4	1.8	1.3	2.6	1.4	1.0	1.9
Blindness	F94	0.0	0.0	0.0	0.2	0.06	0.6	0.1	0.03	0.3
Ear		**4.1**	**3.1**	**5.4**	**3.5**	**2.5**	**4.8**	**3.8**	**2.9**	**4.8**
Hearing complaints	H02	2.7	1.9	3.8	2.3	1.6	3.3	2.5	1.9	3.3
Deafness	H86	1.4	0.9	2.3	1.3	0.8	2.0	1.3	0.9	1.9
Cardiovascular diseases		**45.6**	**41.9**	**49.3**	**40.4**	**36.8**	**44.1**	**42.7**	**39.7**	**45.7**
risk factor cardiovascular disease	K22	13.1	10.3	16.5	10.4	7.9	13.6	11.6	9.2	14.5
Ischemic heart disease with angina	K74	4.3	3.2	5.7	2.1	1.4	3.3	3.1	2.3	4.0
Ischemic heart disease without angina	K76	6.9	5.5	8.7	3.7	2.7	4.9	5.1	4.2	6.2
Atrial fibrillation/flutter	K78	7.0	5.6	8.8	6.3	5.0	7.9	6.6	5.6	7.8
Pulmonary heart diseases	K82	0.7	0.3	1.4	0.4	0.2	0.8	0.5	0.3	0.9
Elevated blood pressure	K85	14.0	11.2	17.3	10.8	8.4	13.7	12.2	9.9	14.9
Hypertension uncomplicated	K86	20.7	17.8	23.9	19.4	16.9	22.3	20.0	17.6	22.6
Hypertension complicated	K87	4.6	3.4	6.2	4.9	3.6	6.7	4.8	3.7	6.1
Cerebrovascular disease	K91	5.1	3.9	6.8	3.0	2.1	4.2	3.9	3.1	4.9
Atherosclerosis	K92	6.4	5.0	8.1	3.7	2.9	4.8	4.9	4.1	5.8

Neurological diseases		**6.6**	**5.3**	**8.2**	**7.8**	**6.6**	**9.2**	**7.3**	**6.3**	**8.4**
Poliomyelitis	N70	0.2	0.07	0.7	0.0	0.0	0.0	0.1	0.03	0.3
Malignant neoplasm nervous system	N74	0.0	0.0	0.0	0.2	0.06	0.6	0.1	0.03	0.3
Multiple sclerosis	N86	0.4	0.2	0.9	0.9	0.5	1.5	0.7	0.4	1.0
Parkinsonism	N87	0.6	0.3	1.2	0.6	0.3	1.1	0.6	0.4	1.0
Epilepsy	N88	1.1	0.7	1.8	1.1	0.7	1.7	1.1	0.8	1.5
Migraine	N89	0.9	0.5	1.6	2.5	1.9	3.4	1.8	1.3	2.4
Trigeminal neuralgia	N92	0.2	0.08	0.7	0.4	0.2	1.0	0.3	0.2	0.7
Abnormal involuntary movements	N08	0.8	0.4	1.4	0.4	0.2	0.9	0.6	0.4	0.9
Peripheral neuritis/neuropathy	N94	2.6	1.8	3.8	1.9	1.3	2.7	2.2	1.6	3.0
Pain face	N03	0.08	0.01	0.6	0.4	0.2	0.8	0.2	0.1	0.5
Skin		**1.8**	**1.0**	**3.1**	**1.2**	**0.7**	**2.1**	**1.5**	**0.9**	**2.3**
Chronic ulcer skin	S97	1.8	1.0	3.1	1.2	0.7	2.1	1.5	0.9	2.3
Musculoskeletal		**11.0**	**9.0**	**13.2**	**20.4**	**18.0**	**23.1**	**16.3**	**14.4**	**18.3**
Rheumatoid/seropositive arthritis	L88	1.4	0.9	2.3	2.9	2.1	3.9	2.2	1.7	3.0
Hip osteoarthritis	L89	4.4	3.2	6.1	7.7	6.2	9.5	6.3	5.1	7.7
Knee osteoarthritis	L90	6.1	4.8	7.6	9.4	7.7	11.5	8.0	6.7	9.4
Osteoporosis	L95	0.9	0.5	1.7	7.6	6.2	9.3	4.7	3.9	5.8
Urological		**2.0**	**1.3**	**3.1**	**2.9**	**2.1**	**4.0**	**2.5**	**1.9**	**3.3**
Urinary incontinence	U04	1.2	0.7	2.0	2.7	1.9	3.7	2.0	1.5	2.7
Malignant neoplasm bladder	U76	0.6	0.2	1.3	0.2	0.09	0.6	0.4	0.2	0.7
Malignant neoplasm kidney	U75	0.2	0.05	1.0	0.1	0.03	0.5	0.2	0.06	0.5
Psychological		**26.5**	**23.3**	**30.0**	**30.1**	**27.5**	**32.9**	**28.5**	**26.1**	**31.1**
Chronic alcohol abuse	P15	4.6	3.5	6.0	1.7	1.1	2.5	2.9	2.3	3.7
Tobacco abuse	P17	5.8	4.2	8.0	4.8	3.5	6.7	5.3	4.0	6.9
Drug abuse	P19	1.7	1.1	2.6	1.0	0.6	1.7	1.3	0.9	1.8
Dementia	P70	2.2	1.5	3.2	2.6	1.9	3.5	2.4	1.9	3.2
Organic psychosis other	P71	0.6	0.3	1.2	0.5	0.2	1.0	0.6	0.3	0.9

Schizophrenia	P72	0.9	0.6	1.6	1.2	0.8	1.9	1.1	0.8	1.6
Affective psychosis	P73	0.9	0.5	1.7	0.7	0.3	1.3	0.8	0.5	1.3
Somatization disorder	P75	2.3	1.6	3.3	4.3	3.3	5.5	3.4	2.7	4.3
Depressive disorder	P76	9.4	7.6	11.5	14.9	13.0	17.1	12.5	10.9	14.3
Phobia/compulsive disorder	P79	0.9	0.5	1.7	1.4	0.9	2.2	1.2	0.8	1.7
Personality disorder	P80	2.7	1.9	3.8	2.8	2.1	3.8	2.8	2.2	3.5
Post-traumatic disorder	P82	1.1	0.7	1.8	1.2	0.7	2.0	1.2	0.8	1.8
Mental retardation	P85	0.8	0.4	1.5	0.6	0.3	1.1	0.7	0.4	1.1
Anorexia nervosa/bulimia	P86	0.08	0.01	0.6	0.4	0.1	0.9	0.2	0.1	0.6
Psychological disorders, other	P98	0.2	0.04	0.6	0.4	0.2	0.9	0.3	0.2	0.6
Medication abuse	P18	0.7	0.4	1.3	1.4	0.9	2.3	1.1	0.7	1.6
Memory disturbance	P20	1.7	1.0	2.7	1.4	0.8	2.4	1.5	1.0	2.2
Female genital		**0.0**	**0.0**	**0.0**	**3.7**	**2.8**	**5.0**	**2.1**	**1.6**	**2.8**
Malignant neoplasm cervix	X75	0.0	0.0	0.0	0.4	0.2	0.8	0.2	0.09	0.5
Malignant neoplasm breast female	X76	0.0	0.0	0.0	3.4	2.5	4.6	1.9	1.4	2.6
Male genital		**3.2**	**2.4**	**4.4**	**0.0**	**0.0**	**0.0**	**1.4**	**1.1**	**1.9**
Malignant neoplasm prostate	Y77	3.2	2.4	4.4	0.0	0.0	0.0	1.4	1.1	1.9

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	4	Last paragraph of introduction
Methods				
Study design	4	Present key elements of study design early in the paper	4	Methods section
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	Participants and procedure
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	Participants and procedure
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4	Data collection
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4	Data collection
Bias	9	Describe any efforts to address potential sources of bias	4	Data collection
Study size	10	Explain how the study size was arrived at	5	Sample size

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5	Statistical analysis
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5	Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions		
		(*c*) Explain how missing data were addressed	5	Statistical analysis
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5	Analyses were adjusted for clustering
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6	First paragraph of results
		(b) Give reasons for non-participation at each stage	6	Results
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6	Results
		(b) Indicate number of participants with missing data for each variable of interest	6	Results
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures	6-8	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7	Table 1
		(*b*) Report category boundaries when continuous variables were categorized	5	Methods
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8	
Discussion				
Key results	18	Summarise key results with reference to study objectives	10	First section of discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12	Strengths and limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13	Implications
Generalisability	21	Discuss the generalisability (external validity) of the study results	12	Strengths and limitations
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14	Fuding

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.