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Supra-additive symptom burden in multimorbidity. A combined population-based questionnaire- and registry study.

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Supra-additive symptom burden in multimorbidity. A combined population-based questionnaire- and registry study.

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Abstract (250 words)

Introduction: Multimorbidity is associated with reduced quality of life. Patients with multimorbidity report high symptom burden and the symptoms, rather than the diagnoses, influence how patients rate their own health.

Objective: To explore symptom burden among people with different diagnoses and to explore how symptom burden is affected when diagnoses appear together vs. individually.

Design: A combined population-based questionnaire- and registry study.

Participants: In 2012, 47,452 participants from the Danish Symptom Cohort answered a questionnaire on symptom presence, interference with usual daily activities and concern of symptoms.

Setting: The Danish nationwide health registries were queried for these participants from 2002-2011 to see whether single diagnoses and multimorbidity occurred. Multimorbidity was defined as having diagnoses from at least two out of ten predefined groups of diagnoses. Multivariable models were used to estimate the association between symptom burden and diagnosis groups.

Main outcome measure: Symptom burden.

Results: Overall, 91.1% of the respondents reported one or more symptom(s) within the preceding four weeks, 36.3% of the study sample belonged to at least one diagnosis group and 11.9% had multimorbidity. Symptom burden was slightly higher for people with a diagnosis than for people not having the diagnosis in the registers. Mostly, symptom burden was increased for people with multimorbidity, and this increase was in excess of the sum of the increase attributable to the individual diagnosis groups.

Conclusion: Patients with multimorbidity reported higher symptom burden than the sum of burden from two persons with the individual diagnoses, indicating symptom burden being supra-additive in multimorbidity.

Strengths and limitations of this study.

- This study combines high quality data from Danish national registries and questionnaire data from the background population.
- The questionnaire used in this study contains a width of symptoms indicative of both serious and harmless diseases.
- The results are adjusted for several potential confounders believed to be of importance.
- The selection of symptoms in the questionnaire is not exhaustive which may induce artificial differences between diagnoses groups. Nevertheless, this does not bias the synergy estimates.
- In this study, multimorbidity is defined based on groups of diagnoses, instead of as single diagnoses, why multimorbidity may have a relatively higher severity.

Introduction

Multimorbidity, most often defined as the co-occurrence of two or more chronic diseases (1), affects mental health (2), quality of life (3), and survival (4), and patients with multimorbidity often struggle to manage their symptoms (5). Symptoms are central for how to rate own health (6), and factors like disability, duration, and feelings of vulnerability are important drivers for how a sensation gradually turns into a symptom (7), where interpretations of danger and intensiveness can be decisive for health care contact (8). Hence, symptoms are important for doctors to be able to make a diagnosis, and thereby the channel through which a person becomes a patient (9). However, symptoms can be difficult to explain, and doctors may stick to solely relieving symptoms (9, 10). Diagnoses, on the other hand, are not always helpful in explaining symptoms and experiences (11) and having diagnoses increases the risk of being diagnosed with other diseases (12). Patients with multimorbidity report considerable symptom burden (5, 13) and more focus on symptom management in multimorbidity has been suggested (14). In that light an understanding of the relation between diagnoses and symptom burden is warranted, especially an understanding of how symptom burden is experienced when diagnoses occur in multiples – as multimorbidity. The aim of this study was to explore how symptom burden is affected when diagnosis groups appear in combination (multimorbidity) compared to when they appear separately. We hypothesized that symptom burden in multimorbidity is additive i.e. that symptom burden in patients having multimorbidity is equivalent to the sum of symptom burden reported from two persons belonging to the diagnosis groups individually.

Methods

Study design and population

Participants were from the Danish Symptom Cohort (DaSK), a population-based study conducted in Denmark in June-December, 2012. People invited for the study lived in Denmark 1st January, 2012 (baseline). Of 100.000 persons randomly selected from the general Danish population aged 20 or older, 95.253 persons were eligible and invited (Figure 1). Of these, 49.706 (52.2%) answered the questionnaire (15).

All immigrated or live born individuals in Denmark receive a unique personal identification number stored in the Danish Civil Registration System (CRS) (16). CRS contains information on age, sex, vital status, etc., and CRS enables linking information from different Danish

registries. Information on diagnoses leading to either inpatient or outpatient care was collected from the Danish National Patient Register (NPR) (17), the Danish Cancer Registry (18), and the Danish Psychiatric Central Research Register (PCRR) (19). Information on education (20), work status (21), family income (22), assets (banks, stocks, bonds, and housing, within and outside Denmark) (22), degree of urbanization and cohabitation status derived from other nationwide registers stored in Statistics Denmark.

Symptoms and symptom burden

The survey consisted of a web-based questionnaire, with the opportunity to have it filled in during a telephone interview, if warranted. The participants were guided through the questionnaire depending on the answers given. The process of developing the questionnaire has been described elsewhere (23). The questionnaire consists of five domains: three dealing with experience of symptoms and actions taken on them, and two dealing with factors related to symptom experience and health care-seeking behaviour (Supplementary File 1). The questionnaire includes 38 general symptoms, as well as two specific symptoms for men and four for women (44 symptoms in total). The questionnaire introduced with the following sentence: “We are interested to hear if you have experienced any bodily sensations, symptoms or discomfort within the last four weeks”. For the general symptoms the following phrase is used: ‘Have you within the last 4 weeks experienced any of these?’ with the opportunity to tick more than one box in a list presenting the 38 symptoms (Supplementary File 1). Additionally, questions about how the symptoms interferes with usual daily activities and concern about the symptoms are included: ‘Within the last 4 weeks: To what extent did you experience that the following symptoms or discomfort interfered with your usual daily activities?’ and ‘Within the last 4 weeks: To what extent were you concerned about the following symptoms or discomfort?’.

Since the six gender-specific symptoms are treated differently in the questionnaire and since the symptoms “coughing up blood” and “blood in vomit” have low prevalence in the data, eight symptoms are excluded from the present analyses. Therefore, 36 symptoms are included (Supplementary File 2).

Hence, in this study symptom burden consists of three parts; number of symptoms, interference of the symptoms with usual daily activities and concern about the symptoms, defined as follows: 1) number of symptoms (0-36), 2) the burden from the symptom with the

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3 highest interference score (ranging 1-4 with 4 indicating the highest burden of interference
4 with usual daily activities), and 3) the concern from the symptom with the highest concern
5 score (ranging 1-4 with 4 indicating most concerns). The two latter definitions select the
6 symptom causing most problems to acknowledge because it is anticipated that more
7 burdensome symptoms affect quality of life more heavily than a number of minor symptoms
8 (24).
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14 *Multimorbidity*

16 Information on diagnoses is retrieved from the nationwide health registries in the ten years
17 period preceding baseline (1st January, 2002-31st December, 2011). Participants are excluded
18 if they have not been living continuously in Denmark during this 10-year period.
19

21 Multimorbidity is defined based on ten different groups of diagnoses: lung, musculoskeletal,
22 endocrine, mental, cancer, neurological, gastrointestinal, cardiovascular, genitourinary and
23 sensory. In each group several diagnoses, based on the International Classification of
24 Diseases, 10th edition (ICD-10) are included (Supplementary File 3). According to this
25 definition, to have multimorbidity, a patient must have a diagnosis from two or more different
26 groups of diagnoses, which rests on the assumption that it is more complex from an
27 organizational and physiological point of view if the patient suffers from diagnoses from
28 different areas in the body (4). Often two chronic diagnoses refer to the same disease entity
29 e.g. myocardial infarction and congestive heart failure. Therefore, this definition to a higher
30 extent than counting single diagnoses can relate to the way health care is organized and grasp
31 some aspects of complexity (Supplementary File 3).
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41 Information on all variables used for adjustments (see statistical analysis) is obtained from
42 the nationwide registries at baseline.
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45 *Statistical analysis*

47 Excess symptom burden for persons having combinations of two diagnosis groups is assessed
48 in multivariable linear regression models. For each of the three measures of symptom burden
49 the $(10 \times 9) / 2 = 45$ regression coefficients pertaining to the two-way interactions between
50 diagnosis groups are retained from a multivariable linear regression on all combinations of
51 diagnosis groups, adjusted for age, sex, socioeconomic status (highest completed education,
52 income, assets, and work status), urbanization degree, cohabitation status, smoking and
53 alcohol consumption. These coefficients are directly interpreted as the synergy effect, i.e.
54 excess symptom burden associated with having diagnoses from both diagnosis groups
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3 relative to the sum of the symptom burden associated with having a diagnose from the
4 diagnosis groups individually. Analyses were performed using SAS, version 9.4 (SAS
5 Institute Inc., Cary, NC, USA).
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8 9 *Patient and public involvement*

10 No patients, or any other members of the public, were involved in designing, conducting, or
11 reporting this study.
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14 15 16 *Ethical approval*

17 The DaSK-study was approved by the Ethics Committee and the National Board of Health,
18 and informed consent was obtained from all participants. Administrative register data were
19 anonymized, why neither approval from the Ethics Committee, nor informed consent from
20 the participants was needed. The use of register data was approved by the Danish Data
21 Protection Agency, Statens Serum Institut and Statistics Denmark. Furthermore, the DaSK-
22 study was approved by the Danish Data Protection Agency (journal number 2011-41-6651)
23 and linkage between DaSK and registers was approved by the Danish Data Protection
24 Agency (journal number 2015-231-0149).
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33 **Results**

34 The study sample consisted of 47.452 persons aged ≥ 20 years (Figure 1) out of which 17.227
35 (36.3%) belonged to at least one diagnosis group and 5.652 (11.9%) had multimorbidity.
36 Overall, 43.228 (91.1%) reported symptoms (Supplementary File 4 and 5). Persons belonging
37 to at least one diagnosis group reported symptoms more often than those not belonging to any
38 of the diagnosis groups (92.8% vs. 90.2%), and the mean number of symptoms varied from
39 4.8-7.4 across the sample (Table 1).
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Table 1 Mean number of symptoms for each diagnosis groups with number of symptoms, interference with usual daily activities and concern of the symptoms.

	Number of symptoms (mean number)	Interference with usual daily activities (mean score) [□]	Concern about symptoms (mean score) [×]
LUNG	7.3	2.6	2.0
MUSCULO-SKELETAL	6.0	2.3	1.7
ENDO	6.1	2.3	1.7
MENTAL	7.4	2.8	2.2
CANCER	5.6	2.1	1.5
NEURO	6.8	2.4	1.8
GASTRO	7.4	2.5	1.9
HEART	5.9	2.2	1.7
KIDNEY	7.3	2.5	1.9
SENSORY	5.5	2.1	1.3
No diagnosis	4.8	1.7	1.2
Total	5.2	1.9	1.3

[□] Mean of the symptoms having highest interference on usual daily activities for each participant, asked in the questionnaire as: ‘within the last 4 weeks: to what extent did you experience that the following symptoms or discomfort interfered with your usual daily activities?’ with the following response categories: not at all, slightly, moderate, quite a bit, extremely. The response categories were transformed in to a numeric 4 digit scale where e.g. 4 is worse than 2.

[×] Mean of symptoms with the highest concern for each participant, asked in the questionnaire as: ‘within the last 4 weeks: to what extent were you concerned about the following symptoms or discomfort?’ with the following response categories: not at all, slightly, moderate, quite a bit, extremely. The response categories were transformed in to a numeric 4 digit scale where e.g. 4 is worse than 2.

LUNG = lung diagnoses, MUSCULOSKELETAL = musculoskeletal diagnoses, ENDO = endocrine diagnoses, MENTAL = mental diagnoses, CANCER = cancer diagnoses, NEURO = neurological diagnoses, GASTRO = gastrointestinal diagnoses, HEART = cardiovascular diagnoses, KIDNEY = genitourinary diagnoses, SENSORY = sensory organ diagnoses

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Multimorbidity combinations including heart, musculoskeletal or sensory diagnosis groups (as one of the two groups) were most prevalent (Figure 2-4). Persons belonging to the combinations lung-mental, kidney-gastro and mental-cancer reported the highest number of symptoms (Figure 2). The co-occurrence of two diagnosis groups in one person resulted generally in a higher number of reported symptoms than the sum of symptoms from two persons having the two diagnosis groups individually i.e. the number of reported symptoms in relation to multimorbidity was supra-additive as witnessed by the large amount of red halos in Figure 2. The lung-mental combination was most supra-additive, with approximately 5 symptoms more than the sum of the individual diagnosis groups (Figure 2). Only three combinations showed a discernable lower number of symptoms for the combination compared to the sum of the symptoms from the two diagnosis groups: lung-cancer, mental-neurological and cancer-kidney (Figure 2).

Persons belonging to the mental-sensory, mental-kidney, and the mental-musculoskeletal combinations reported a relatively high interference with daily activities (Figure 3). Almost all combinations were supra-additive, except for the cancer-kidney combination (Figure 3).

The combination mental-cancer and mental-kidney reported the most concerns about their symptoms, followed by mental-musculoskeletal (Figure 4). Furthermore, the majority of the combinations were supra-additive, highest for the mental-cancer combination. Only few combinations were infra-additive, with all combinations except one including the kidney group (Figure 4).

Median age of the participants in DaSK was 52 years (IQR 40-64) and 50 years (IQR 36-67) for non-participants. The non-participants were more often men, unmarried, had lower education, lower income level and generally had a looser attachment to the labour market (25).

Discussion

Summary

In this study, we explored the burden of symptoms in persons belonging to none, one and two (multimorbidity) different diagnosis groups in the Danish background population. We found that persons belonging to a diagnosis group had only slightly higher symptom burden than

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3 persons not belonging to a diagnosis group. Furthermore, we found that symptom burden in
4 multimorbidity in general is supra-additive i.e. the number of symptoms, interference with
5 usual daily activities and concern about symptoms were higher for the combination of two
6 diagnosis groups in one person than the sum of these measures in two persons belonging to
7 one of the separate diagnosis groups.
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10 11 12 13 *Strengths and limitations*

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15 The population-based cohort with high response rate is a strength (26), as well as the
16 questionnaire containing a width of symptoms indicative of both serious and harmless
17 diseases, and the adjustments for several important factors. The relatively low prevalence of
18 multimorbidity in this study compared to other studies can be explained by the definition
19 based on ten groups of diagnoses from secondary care (2, 27). The nationwide registers are
20 highly valid, and because it requires a referral to secondary care to be included in the
21 registers the diagnoses have certain seriousness (18, 17). In Denmark, primary care data on
22 diagnoses are not available. However, we believe our broader definition, in contrast to simple
23 disease counts (28, 29), better grasp the burden and complexity of multimorbidity.
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32 The selection of symptoms in the questionnaire is not exhaustive and may show preference to
33 certain diseases, e.g. there are many urinary tract related symptoms relative to only few
34 kidney diagnoses. This may induce artificial differences between diagnoses groups. However,
35 this does not bias the synergy estimates. Furthermore, the identification of the presence of
36 diagnoses from secondary care contacts does not allow us to obtain adequate data on
37 diagnosis duration which could be of importance for symptom experience (30). However, the
38 time limit of four weeks in the questionnaire was used to focus on relevant symptoms, while
39 they can still be recalled (15).
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48 *Comparisons with existing literature*

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50 In this study, 92.8% of those belonging to a diagnosis group reported symptoms compared to
51 90.2% among those not belonging to any of the groups. Since symptoms are a main source of
52 information when a doctor establishes a diagnosis (9, 10) and symptoms are important
53 mediators for health care seeking (31) the small difference between the groups was rather
54 surprising and underline the unclear relation between symptoms and diagnoses. It also
55 highlights the fact that symptoms to some degree are prerequisites of the human nature (7)
56 apart from diagnoses that are created by humans (10).
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3 Since one diagnosis will increase the probability for a second diagnosis, through increased
4 contact with health care professionals (12), and these second diagnoses are tentatively found
5 earlier in the natural course of the disease, we find the results in this study, with the majority
6 of the multimorbidity combinations being supra-additive in relation to symptom burden,
7 rather surprising. Maybe this may help us to understand why especially patients with
8 multimorbidity struggle to recognize what symptoms to focus on (32). But also help us to
9 understand, why patients with multimorbidity are overwhelmed by the symptom burden (5,
10 13), experience complexity (2), organisational challenges (33), and demands from everyday
11 life (34).
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20 Participants having multimorbidity including a mental diagnosis generally reported high
21 symptom burden and supra-additivity. For mental diagnoses both anxiety (35) and feelings of
22 depression have been related to lower quality of life and low self-rated health (36) and
23 depression can modify how self-rated health is affected by symptoms (6). Even though many
24 of the mentioned symptoms deteriorate own ratings of health, evidence points to that it is not
25 the symptom itself, rather limitations on daily activities, worries and treatment burden related
26 to the symptom that affect patients most (34). Moreover, hypothetically some multimorbidity
27 combinations can veil specific explanations e.g. mental-sensory may include patients not
28 being offered or having received helping devices because of their underlying mental disease
29 and many patients with chronic illness gradually become “problem patients” because of the
30 demanding task to manage them optimally (37). Furthermore, patients with multimorbidity
31 progressively lose confidence in their bodies and constantly have to scan the body for signs
32 of worsening (38). In addition, patients with mental diagnoses like anxiety and depression
33 may be more concerned about their symptoms and the signs of them. Finally, even though
34 patients, especially in older age groups, adapt to chronic conditions as time passes (39), the
35 high prevalence of multimorbidity also in the younger age groups (2) may be indicative for a
36 lack of such an adaptation.
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51 The relatively low rating of symptom burden for the cancer group was surprising, since
52 cancer alarm symptoms are a mediator for doctor contact (31). However, in our definition of
53 multimorbidity severity is not included, and for the cancer group, a low stage of the cancer
54 and thereof a potential higher degree of radical treatment may be an explanation.
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58 Furthermore, among patients with other chronic conditions in combination with cancer i.e.
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3 multimorbidity, they describe an ended cancer treatment not being the focus of concern
4 anymore (40).
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8 *Implications*

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10 Multimorbidity does not only consist of diagnoses and their medical consequences (28), but
11 also, as shown by this study, of a considerable symptom burden embedded in the diagnosis
12 coexistence itself. This, in combination with weak evidence of optimal symptom
13 management among patients with multimorbidity (14), underlines the need for increased
14 attention to symptom burden among patients with multimorbidity entering the health care
15 system. In doing so, patient dairies, describing quality of disease management , attention to
16 how patients explain illness in order to understand their stories and life themes (38), and
17 patient involvement in deciding the agenda and achieving realistic goals (34), is probably
18 valuable for optimal management.
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27 In conclusion, patients with multimorbidity reported higher symptom burden than the sum of
28 burden from to persons with the individual diagnoses, indicating symptom burden being
29 supra-additive in multimorbidity.
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43 contributed to the discussion and reviewed/edited the manuscript. RKR researched the data,
44 contributed to the discussion and reviewed/edited the manuscript. ADG, DJ, SR made
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46 All authors approved the final version of the manuscript. TGW, VS and DN have full access
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8 **Competing interests**
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10 None
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13 **Patient consent for publication**
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15 Not required
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18 **Data availability statement**
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20 Data may be obtained from a third party and are not publicly available. Data is stored at
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22 Agency and The Danish Health Data Authority.
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17 perspectives on having a cancer diagnosis and other comorbid diseases: A
18 qualitative study. *Chronic Illn* 2018:1742395318815954.
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Figure legends

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29 **Figure 1.** Study population.

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31 **Figure 2.** All (45) combinations of multimorbidity (two diagnosis groups) and the association
32 to number of symptoms.
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34 **Figure 3.** All (45) combinations of multimorbidity (two diagnosis groups) and the association
35 to influence on daily activities.
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38 **Figure 4.** All (45) combinations of multimorbidity (two diagnosis groups) and the association
39 to concern about symptoms.
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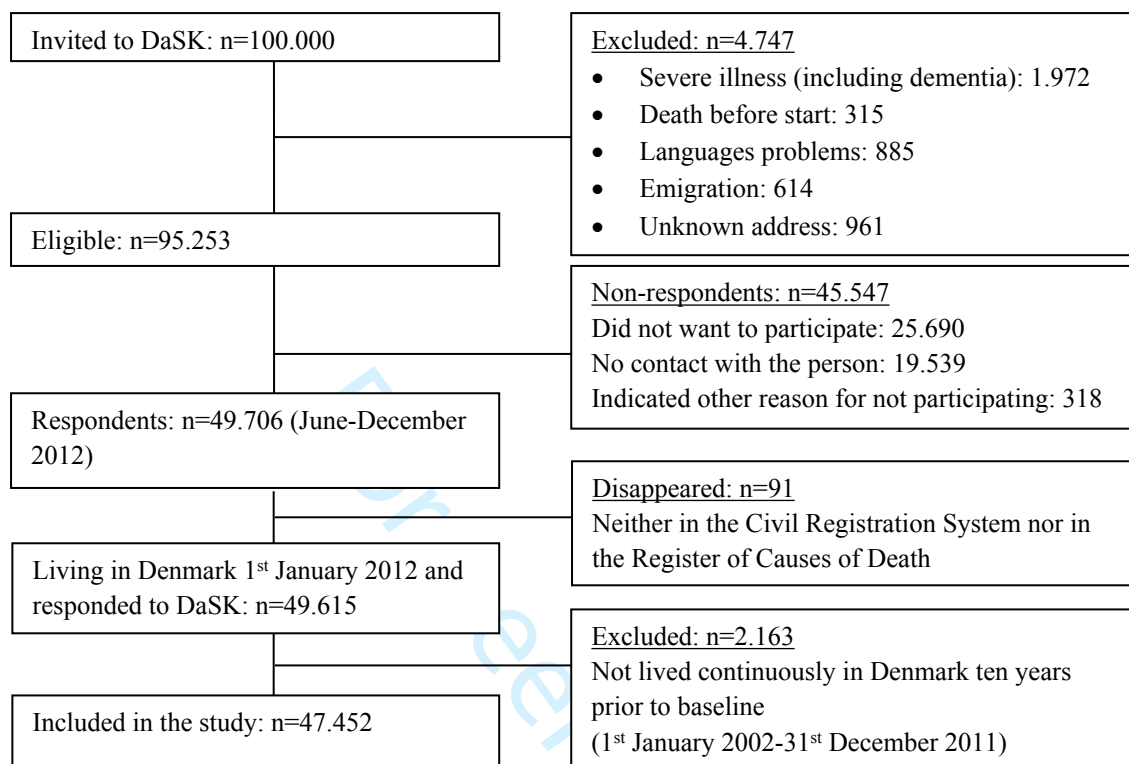


Figure 1. Study population.

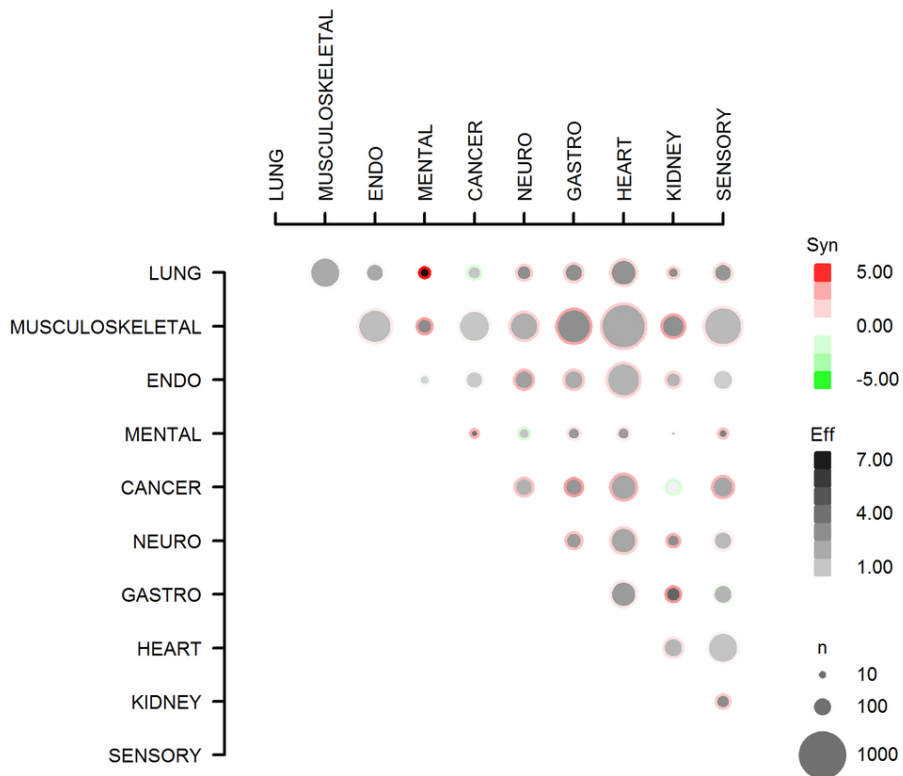


Figure 2. All (45) combinations of multimorbidity (two diagnosis groups) and the association to number of symptoms.

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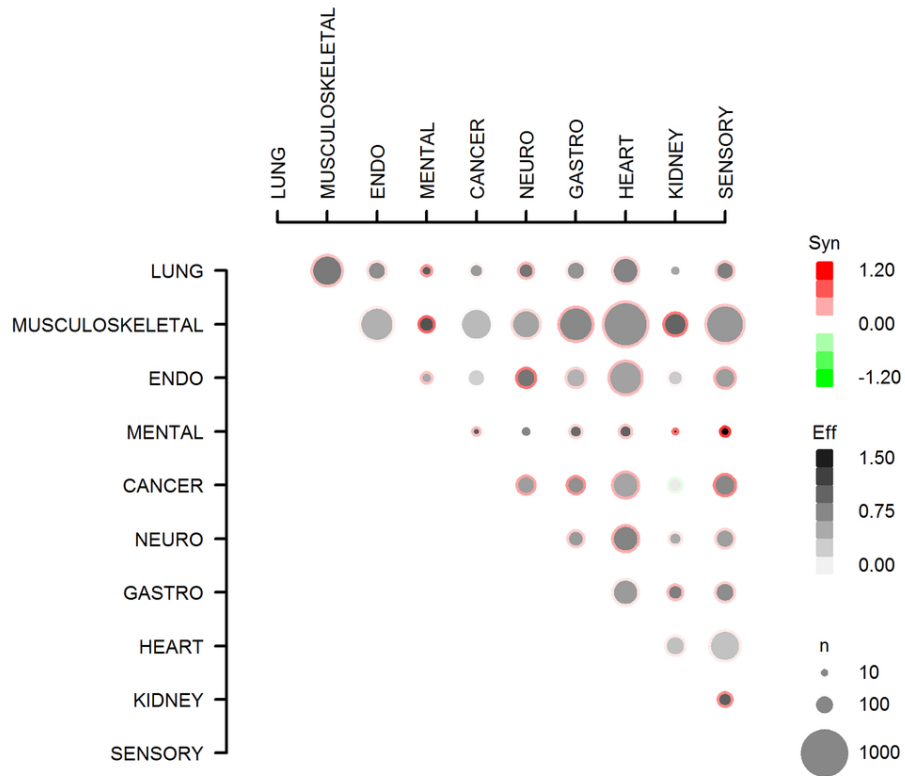


Figure 3. All (45) combinations of multimorbidity (two diagnosis groups) and the association to influence on daily activities.

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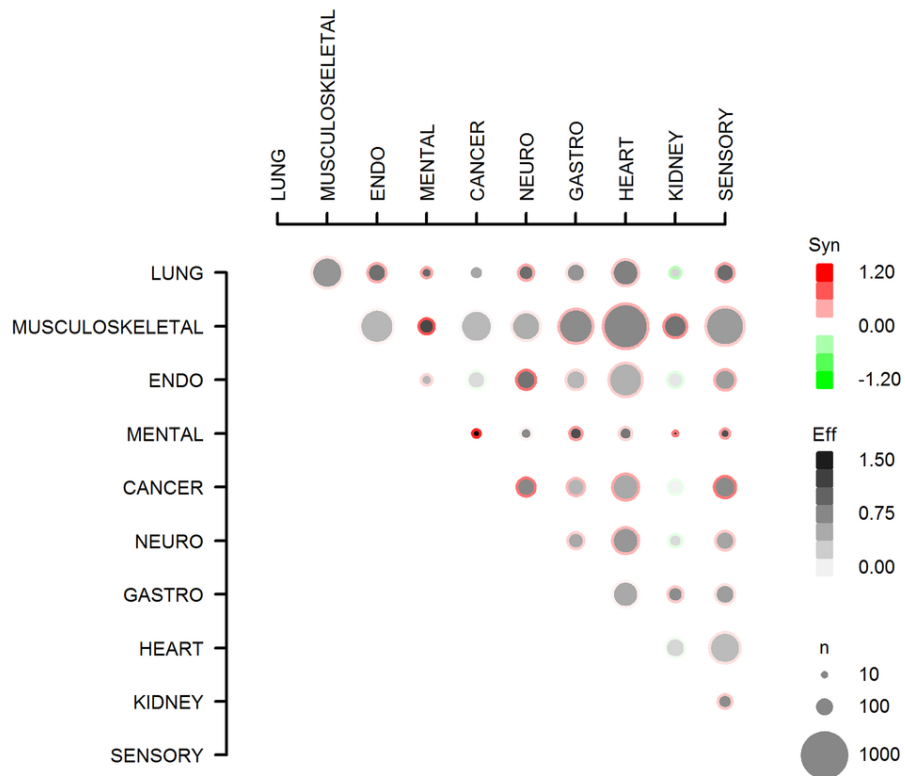


Figure 4. All (45) combinations of multimorbidity (two diagnosis groups) and the association to concern about symptoms.

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Supplementary File 1

Welcome to the Danish Symptom Cohort – a survey about health, symptoms and healthcare-seeking

The questionnaire was not available in hard copy, but for illustrative purposes it has been reproduced in this appendix.

In order to address sex specific items with minimal disturbance to respondents, the questionnaire was distributed in two different versions; one for males and another for females. In this appendix questions from both versions are included, and each of the sex specific questions is marked with explanatory captions in italic.

The web-based questionnaire contains several leaps based on answers provide by the respondents (marked with explanatory captions in italic).

We appreciate that you will take the time to complete the questionnaire.

The questionnaire is to be used for the identification of a number of bodily sensations, symptom experiences and discomfort. You may find that some of the questions are similar. It is important that you answer them all anyway. You can also answer the questions, even if you feel perfectly healthy. There is a commentary box at the end of the questionnaire, in which you can note any additional remarks.

Should you get disrupted while answering the questionnaire, you can always log on again. The system automatically saves your answers. Simply use your personal logon information again, and you can continue the survey.

When completing the questionnaire, it is also possible to return to previously answered questions.

If you have any questions or experience problems while filling in the questionnaire, please feel free to contact us by e-mail: dask@health.sdu.dk or by phone: 29 71 44 24 weekdays between the hours 10:00-15:00 and 19:00-21:00.

For further information about the survey, please visit our website www.sdu.dk/dask. Here you will also find answers to some frequently asked questions.

Completing the questionnaire will take approximately 20-30 min.

Participant acceptance:

I accept that my answers can be used for research, and I hereby give consent to obtain information from health records and medical records for research purposes. All my answers will be treated with the strictest confidence and used solely for research purposes. The responses will be used only in anonymous form. It is of course voluntary to participate, and I may at any time withdraw this consent.

The study was approved by the Danish Data Protection Agency, Science Ethics Committee and the Danish Health and Medicines Authority, and thus complies with current legal and ethical regulations.

I accept the above

We are interested to hear if you have experienced any bodily sensations, symptoms or discomfort within the last four weeks. Later you will be asked when you first experienced these, and how you reacted with regard to these experiences.

Have you within **the last 4 weeks** experienced any of these? (You may tick more than one box)

- Abdominal pain
- Nausea
- Repeated vomiting
- Blood in vomit
- Difficulty swallowing

- Abdominal bloating
- Increased waist circumference (trousers tighter than normal)
- Change in stool texture (i.e. having hard or lumpy stools, although you usually tend to have loose or watery stools or vice versa)
- Change in frequency of bowel movements (i.e. passing stools more or less frequently than usual)

- Rectal bleeding/Blood in stool
- Black shiny stools
- Frequent, loose or watery stools
- Hard and lumpy stools

- Tiredness
- Lack of energy
- Feeling unwell or sick
- Memory problems
- Concentration problems
- Weight loss of more than 2 kg without making an effort

- Coughing
- Coughing up blood
- Shortness of breath
- Hoarseness

- Dizziness
- Headache
- Back pain
- Swollen legs
- Loss of appetite
- Lump/swollen lymph node
- Fever

- That you need to urinate more often than usual
- That you have to get up to urinate at night
- Difficulty emptying the bladder completely when urinating

- Pain or burning sensation when urinating
- Urge to urinate so strong that you cannot make it to the toilet in time
- Involuntary urination (incontinence) during exertion, e.g. coughing, sneezing, lifting and exercise
- Involuntary urination (incontinence) without exertion and urge (leakage)
- Blood in urine

Only for women:

The next questions are about sexual relations. Some of the questions may seem private, but your response may contribute to a greater understanding of whether there is a correlation between sexual relations and symptoms or discomfort from the lower abdomen. If there are questions you do not wish to answer, simply tick the category "do not wish to answer."

Have you within the **last 4 weeks** experienced any of the following?

Pelvic pain

- Yes
- No
- I don't wish to answer

Vaginal bleeding after menopause (i.e. absence of menstrual periods for more than 12 months.)

- Not relevant, as I have not yet reached menopause
- Yes
- No
- I don't wish to answer

Vaginal bleeding during or after sexual intercourse

- Not relevant, as I am not sexually active
- Yes
- No
- I don't wish to answer

Pelvic pain during intercourse

- Not relevant, as I am not sexually active
- Yes
- No
- I don't wish to answer

The next question may seem private, but your response may contribute to a greater understanding of the prevalence of symptoms or discomfort in the population. If you do not wish to answer the question, simply tick the category "Do not wish to answer."

Only for men:

Have you within **the last 4 weeks** experienced any of the following?

- Erectile dysfunction
- Blood in the semen
- None of the above
- I don't wish to answer

Only for women, and only if stated that they had not yet reached the menopause:

Are you currently pregnant, or have you been pregnant within **the last 6 months**?

- Yes
- No
- I don't know/ I don't wish to answer

Only for women

How many sexual relationships have you had altogether from your sexual debut and until now?

- Have not yet had my sexual debut
- 1-5
- 6-10
- 11-15
- 16-20
- 21-25
- More than 26
- I don't wish to answer

How many sexual relationships have you had within the last year?

- 0
- 1-5
- 6-10
- 11-15
- 16-20
- 21-25
- More end 26
- I don't wish to answer

The following questions only appeared in relation to a positive expression of one or more experienced symptom(s) - by a leap structure in the electronic survey to the symptom experience

We will now ask you some elaborating questions, which deal with the sensations, symptoms or discomfort that you have just stated.

When did you experience these for the first time:

	Less than a month ago	1-3 months ago	3-6 months ago	More than 6 months ago
Abdominal pain Etc...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Within **the last 4 weeks**: To what extent did you experience that the following symptoms or discomfort interfered with your usual daily activities?

	Not at all	Slightly	Moderate	Quite a bit	Extremely
Abdominal Pain Etc...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Within the last 4 weeks: To what extent were you concerned about the following symptoms or discomfort?

	Not at all	Slightly	Moderate	Quite a bit	Extremely
Abdominal Pain Etc...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The following questions only appeared in relation to a positive expression of one or more experienced symptom(s) - by a leap structure in the electronic survey to the symptom experience

We will now ask you some questions concerning who you have talked to about the symptoms or discomfort you experienced **in the last 4 weeks**.

Have you contacted your general practitioner with any of the following symptoms or discomfort? (Through appointment, by telephone or by email)

- Yes
- No

The following questions only appeared in relation to a positive expression of one or more experienced symptom(s) - by a leap structure in the electronic survey to the symptom experience

You have been in contact with your general practitioner regarding the following symptoms and discomforts. We would now like to know, whether you had some of the following considerations, **before** contacting your general practitioner? (You may tick more than one box)

		Yes	No
	I would be too embarrassed	<input type="checkbox"/>	<input type="checkbox"/>
	I would be worried about wasting the doctor's time	<input type="checkbox"/>	<input type="checkbox"/>
Abdominal pain	I would be worried about what the doctor might find	<input type="checkbox"/>	<input type="checkbox"/>
Etc.	I would be too busy to make time to go to the doctor	<input type="checkbox"/>	<input type="checkbox"/>
	Other considerations [box for free text commentaries]		

The following questions only appeared in relation to a positive expression of one or more experienced symptom(s) - by a leap structure in the electronic survey to the symptom experience

You have **not** been in contact with your general practitioner regarding the following symptoms and discomforts. We would now like to know, whether you had some of the following considerations, regarding contact to your general practitioner? (You may tick more than one box)

		Yes	No
	I would be too embarrassed	<input type="checkbox"/>	<input type="checkbox"/>
	I would be worried about wasting the doctor's time	<input type="checkbox"/>	<input type="checkbox"/>
Abdominal pain	I would be worried about what the doctor might find	<input type="checkbox"/>	<input type="checkbox"/>
Etc.	I would be too busy to make time to go to the doctor	<input type="checkbox"/>	<input type="checkbox"/>
	Other considerations [box for free text commentaries]		

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6 Which of the following other health care professionals or therapists have you talked to/consulted
7 regarding the symptoms or discomforts listed below (through appointment, by telephone or by
8 email)? (you may tick more than one box)
9

- 10
11
12
13 Abdominal pain
14 Etc.
15
16
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18
19
- None
 - Another doctor (practicing specialist, out-of-hours physician or hospital physician)
 - Physiotherapist/chiropractor
 - Home help/district nurse
 - Pharmacy staff
 - Alternative therapist (e.g. homeopath, healer, reflexologist)
 - Other

20
21 Which of the following members of your family or social network have you talked to about the
22 symptoms or discomforts listed below? (you may tick more than one box)
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- 24
25
26 Abdominal pain
27 Etc.
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- None
 - Spouse/partner
 - Children
 - Parents
 - Colleague /classmate
 - Friend
 - Neighbour
 - Other

We will proceed to another category of questions regarding abdominal pain. Furthermore we ask questions regarding various factors that may have impact on abdominal pain and discomfort. Because we use several different questionnaires you might experience that some of the questions appear similar. There are however nuances in the items that are important for the survey.

In **the last 3 months**, how often did you have acid regurgitation or heartburn (a burning epigastric discomfort or burning pain in your chest)?

- Never
- Less than one day a month
- One day a month
- Two to three days a month
- One day a week
- More than one day a week
- Everyday

The next three questions are skipped if the answer is “never” in the above-mentioned questions.

When you experience acid regurgitation or heartburn (a burning epigastric discomfort or burning pain in your chest), how severe are your discomforts?

- Very mild
- Mild
- Moderately
- Severe
- Very severe

To what extent does your acid regurgitation or heartburn (a burning epigastric discomfort or burning pain in your chest) affect your sleep?

- My sleep is not affected
- My sleep is affected to some extent
- My sleep is affected to a great extent

To what extent does your acid regurgitation or heartburn (a burning epigastric discomfort or burning pain in your chest) affect your everyday activities?

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

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The following questions concern abdominal pain and bowel habits.

The next questions are related to the Rome 3 criteria for IBS: IF the symptoms are experienced less than two to three days a month, the rest of the questions for IBS are skipped

- In **the last 3 months**, how often did you have discomfort or pain anywhere in your abdomen?
- Never
 - Less than one day a month
 - One day a month
 - Two to three days a month
 - One day a week
 - More than one day a week
 - Every day

- For women:* Did this discomfort or pain occur only during your menstrual bleeding and not at other times?
- No
 - Yes
 - Does not apply because I have had the change in life (menopause) or I am a male

- Have you had this discomfort or pain **6 months or longer**?
- No
 - Yes

- How often did this discomfort or pain get better or stop after you had a bowel movement?
- Never or rarely
 - Sometimes
 - Often
 - Most of the time
 - Always

- When this discomfort or pain started, did you have more frequent bowel movements?
- Never or rarely
 - Sometimes
 - Often
 - Most of the time
 - Always

- When this discomfort or pain started, did you have less frequent bowel movements?
- Never or rarely
 - Sometimes
 - Often
 - Most of the time
 - Always

- When this discomfort or pain
- Never or rarely

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4 started, were your stools (bowel
5 movements) looser?

- Sometimes
- Often
- Most of the time
- Always

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11 When this discomfort or pain
12 started, how often did you have
13 harder stools?

- Never or rarely
- Sometimes
- Often
- Most of the time
- Always

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18 In the **last 3 months**, how often
19 did you have hard or lumpy stools?

- Never or rarely
- About 25% of the time
- About 50% of the time
- About 75% of the time
- Always, 100% of the time

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25 In the **last 3 months**, how often
26 did you have loose, mushy or
27 watery stools?

- Never or rarely
 - About 25% of the time
 - About 50% of the time
 - About 75% of the time
 - Always, 100% of the time
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The following questions concern feeling of fullness after meals and pain or burning sensation in the stomach.

The next questions are related to the Rome 3 criteria for functional dyspepsia

- In the **last 3 months**, how often did you feel uncomfortably full after a regular- sized meal?
- Never
 - Less than one day a month
 - One day a month
 - Two to three days a month
 - One day a week
 - More than one day a week
 - Every day

The next questions only appeared if symptoms are experienced for one day a week or more

- Have you had this uncomfortable fullness after meals **6 months or longer**?
- No
 - Yes

- In the **last 3 months**, how often were you unable to finish a regular size meal?
- Never
 - Less than one day a month
 - One day a month
 - Two to three days a month
 - One day a week
 - More than one day a week
 - Every day

- Have you had this inability to finish regular size meals **6 months or longer**?
- No
 - Yes

- In the **last 3 months**, how often did you have pain or burning in the middle of your abdomen, above your belly button but not in your chest?
- Never
 - Less than one day a month
 - One day a month
 - Two to three days a month
 - One day a week
 - More than one day a week
 - Every day

- Have you had this pain or burning **6 months or longer**?
- No
 - Yes

We now proceed to the next category of questions that concern symptoms or discomforts from many parts of the body and how this affects your everyday life.

Have you within **the last 4 weeks** experienced any of the following symptoms or discomforts? (You may tick more than one box)

- Palpitations/heart pounding?
- Precordial discomfort?
- Breathlessness without exertion?
- Hot or cold sweats?
- Dry mouth?
- None of the above

To what extent did you experience that the following symptoms or discomfort interfered with your usual daily activities?

- Not relevant, as I did not experience any of the above symptoms or discomforts
- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

Have you within the **last 4 weeks** experienced any of the following symptoms or discomforts? (You may tick more than one box)

- Pains in arms or legs?
- Muscular aches or pains?
- Pains in the joints?
- Feeling of paresis or localized weakness?
- Pain moving from one place to another?
- Unpleasant numbness or tingling sensations?
- None of the above

To what extent did you experience that the following symptoms or discomfort interfered with your usual daily activities?

- Not relevant, as I did not experience any of the above symptoms or discomforts
- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

The following questions concern trembling of the hands and trembling of other parts of the body. Your answers may contribute to a larger understanding of what part trembling plays for the quality of life and for health in general.

Do you have problems with your hands trembling when you have to drink a cup or a glass or pour it?

- Yes
- No

Do you often experience that your hands, arms or the voice tremble and quiver without you being able to control it?

- Yes
- No

Has a doctor diagnosed you with:

- Familial tremor or essential tremor
- Parkinson's disease
- None of the above

Does anyone in your family have or have had the same type of trembling as you?

- Yes
- No
- I don't know

How many of your relatives suffer from a similar trembling?

- None
- 1
- 2
- 3
- More than 3
- I don't know

Consumption of alcohol can alter certain types of trembling. When you drink alcohol, do you then experience that you trembling:

- Decreases
- Worsens
- Remains unchanged
- I don't know, because I don't drink alcohol

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5 How old were you when your trembling began?
6

7 _____ years
8

9 Within **the last week**: If you sit at the table, do you have problems with drinking liquid from a glass?
10

- 11 I haven't had problems drinking from the glass
12 I can drink from the glass with one hand, but if I must avoid spilling, there may not be much
13 liquid in the glass.
14 I cannot drink from the glass with only one hand, but must use both hands.
15 I cannot drink from the glass even if I use both hands, but must use a straw.
16
17

18 Has a doctor diagnosed one of the following causes for your trembling?
19

- 20 I have not been diagnosed
21 Stroke
22 Dystonia
23 Medication
24 Other
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We have now finished asking about specific symptoms and discomforts. The next questions are of a general nature and concern your own perception of your health, your lifestyle, your management of problems and your worry about disease.

In general, would you say your health is:

- Excellent
- Very good
- Good
- Fair
- Poor

Do you feel well enough to do what you feel like doing?

- Yes, mostly
- Yes, sometimes
- No, almost never
- I don't know

The following questions are about physical activity, smoking and alcohol habits.

How do you rate your physical fitness?

- Very good
- Good
- Fair
- Not so good
- Poor

Do you smoke?

- Yes, every day
- Yes, at least once a week
- Yes, less than once a week
- No, I have stopped
- No, I have never smoked

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5 How often do you drink anything containing alcohol?
6
7

- 8 Never
9 Once a month at the most
10 2-4 times a month
11 2-3 times a week
12 4 times a week or more
13

14
15 *The following questions only appeared in relation to a positive expression of smoking and/or*
16 *alcohol intake - by a leap structure in the electronic survey*
17

18 How many units do you drink per week on average? (One unit corresponds to a normal beer (33 cl),
19 a glass of wine (12 cl) or spirits (4 cl))
20

- 21 1-7 units/week
22 8-14 units/week
23 15-21 units/week
24 22-28 units/week
25 More than 29 units/week
26
27

28
29 For how many years have you smoked?
30

31 I have smoked for approximately
32

33 _____ years (State the number of years in whole numbers)
34
35

36
37 How much do/did you smoke on average a day?
38

39 On average I smoke approximately
40

41 _____ cigarettes (state the approximate number of cigarettes in whole numbers)
42

43 _____ cheroots (state the approximate number of cheroots in whole numbers)
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45 _____ cigars (state the approximate number of cigars in whole numbers)
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47 _____ pipes (state the approximate number of pipes in whole numbers)
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The following questions are about your height and weight.

How tall are you (without shoes)?

State your height in whole numbers measured in cm (e.g. 172)

_____cm

How much do you weigh (without clothes)?

State your weight in full kg (e.g. 67)

_____kg

The next questions are about your own concerns about your current health and whether other people have expressed concern about your current health.

To what extent are you **concerned** about your current health?

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

Has a doctor expressed concern about your current health?

- Yes
- No
- I don't know

Have people in your family or social network expressed concern about your current health?

- Yes
- No
- I don't know

The following questions are about your experiences with your own disease or in your social network.

Do you have any chronic disease, long-term effects after injuries, disability or other chronic disorder?

- Yes
- No
- I don't know

Have people in your immediate family (siblings, children, spouse, parents) had a serious illness?

- Yes
- No
- I don't know

Have people in your social network (friends, neighbours etc.) had a serious illness?

The following questions are about your contact with other people

How often are you in contact with friends, acquaintances or family that you do not live with? By contact is meant that you are together, talking with each other on the phone, writing to each other etc.

- Daily or almost daily
- 1-2 times a week
- 1 or more times a month
- Less than once a month
- Never
- I don't know

If you become ill and need help with practical things, can you count on help from others? (By others is meant people you do not live with)

- Yes, definitely
- Yes, maybe
- No

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4 Does it ever happen that you are alone, even if you want to be in the company of others?
5

- 6 Yes, often
7 Yes, once in a while
8 Yes, but rarely
9 No, never or almost never
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12 Do you have someone to talk to if you have problems or need support?
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- 14 Yes, often
15 Yes, mostly
16 Yes, sometimes
17 No, never or almost never
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The questions on this page deal with how you usually act in relation to problems and disease. For each item, place a tick in the box that best fits what you think about yourself just now. The questions are written in 'I' form, and you place your tick depending on how much you agree/disagree.

	Agree completely	Tend to agree	Yes and no	Tend to disagree	Disagree completely
I say so if I am angry or sad.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I like to talk with few chosen people when things get too much for me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I make an active effort to find a solution to my problems.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Physical exercise is important to me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I think something positive could come out of my complaints/problems.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I firmly believe that my problems will decrease (and my situation improves).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I try to forget my problems.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I put my problems behind me by concentrating on something else.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I bury myself in work to keep my problems at a distance.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I often find it difficult to do something new.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am well on the way towards feeling I have given up.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I withdraw from other people when things get difficult.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The last group of questions concern your attitude to risk and your satisfaction with your life in general

Imagine that you unexpectedly inherited DKK 10,000 (approximately USD 2,000) from a distant relative. Subsequently you have the possibility of participating in a lottery with an equal chance of doubling the money or losing the money. That means that there is a 50% chance of you winning DKK 20,000 and a 50% chance of losing the DKK 10,000.

What do you choose?

- I choose to participate in the lottery
- I choose not to participate in the lottery
- I don't know

How do you normally react in relation to health and disease. Please tick one box for each statements to show how much you agree/disagree.

	Completely agree	Tend to agree	Yes and no	Tend to disagree	Completely disagree
I focus a lot on having a healthy behaviour and prefer to avoid risks that can affect my health.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If I experience symptoms, I generally count on it passing.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I do not like to take chances regarding my health and prefer to see my GP once too often than once too little.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

In the following we will inform you how old people at your age on average can expect to become.
If you do not want the information, please tick the box.

How old are you?

____ Year

I don't want the information

Men, your age can expect to live, on average, until they are

____ Year

Women, your age can expect to live, on average, until they are

____ Year

Do you think that you will live longer or shorter than the average person?

- Longer than the average person
- Like the average person
- Shorter than the average person
- I don't know

On a scale from 0 till 10, where 0 means that you are very dissatisfied and 10 means that you are completely satisfied, how satisfied are you with your life in general.

Dissatisfied 0 1 2 3 4 5 6 7 8 9 10 Completely satisfied

Should you have any comments to the questionnaire, please feel free to list them here:

You have now finished the questionnaire.

Thank you very much for your reply.

If any of the questions have made you concerned about your health, we recommend that you contact
your general practitioner.

Press exit to close the window

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4 **Supplementary File 2**
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6 **List of the 36 symptoms from The Danish Symptom Cohort included in this study.**
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Symptoms	
Tiredness	Swollen legs
Night-time urination	Difficulty in emptying the bladder
Lack of energy	Frequent urination
Headache	Stress incontinence
Back pain	Shortness of breath
Abdominal bloating	Hoarseness
Memory problems	Urge incontinence
Abdominal pain	Loss of appetite
Coughing	Blood in stool/rectal bleeding
Concentration problems	Fever
Change in stool texture	Difficulty swallowing
Dizziness	Weight loss
Feeling unwell	Incontinence without stress/urge
Constipation	Pain/burning when urinating
Increase in waist circumference	Lump/swollen lymph node
Change in stool frequency	Black stool
Diarrhoea	Repeated vomiting
Nausea	Blood in urine

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Supplementary File 3

Symptom burden in multimorbidity. A Danish population study.

Definition of Multimorbidity

In this article multimorbidity was defined in to steps

- 1) Selection of diagnoses
- 2) Grouping of diagnoses according to different systems of the body

Selection of diagnoses

By this definition of multimorbidity we aim to have a simple and clinically relevant definition that at the same time is able to embrace complexity. Therefore, the definition is organized according to clinical picture rather than disease etiology. Diagnoses are considered on the basis of the following criteria:

- Diagnoses with high prevalence in the Danish population. (Risk factors are not included because of the low completeness of this information in the registers)
- Diagnoses relevant for general practice
- Diagnoses causing severe loss of function and/or loss of quality of life
- Diagnoses combined with reduced life expectancy
- Diagnoses resulting in a considerable treatment burden for the patient
- Chronic conditions (e.g. conditions that "require ongoing management over a period of years or decades"(1)).

Congenital diseases are not included.

Grouping of diagnoses according to different systems of the body

To have multimorbidity, a patient has to have a least one diagnosis from each of two different groups of diagnoses. E.g., if a patient has asthma and COPD this patient is categorized as lung sick instead of multimorbid. This choice rests on the assumption that it is more complex from an organizational and physiological point of view if the patient suffers from diagnoses from different bodily systems. Furthermore, concordant conditions (conditions with overlapping pathophysiology and management) are intended to be gathered in the same group (2). However, diabetes and cardiovascular diseases which could be expected to share both pathophysiology and risk factors are distributed over two different groups because they after all have different clinical manifestations and different treatments. The grouping of diagnoses and count of bodily system morbidity instead of single diagnoses may better relate to the way health care is organized as well as to the complexity and burden of morbidity (3).

See table A below for the selected diagnoses and bodily systems.

Background for redefining multimorbidity

In the literature the variation in how to define multimorbidity is large and the lack of consensus is evident (4-6). Most studies on multimorbidity include diagnoses based on the argument that the

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4 diagnoses are common (6). However, if only selecting diagnoses based on prevalence there would
5 be a risk of excluding many relevant conditions. In some studies authors selected a limited number
6 of diagnoses thoroughly (7), others included all chronic ICPC codes (8), or selected specific chronic
7 diagnoses from ICPC (9, 10). Others selected all existing ICD-10 codes without further explanation
8 (11) or let the diagnoses count for the chapter in the ICD-10 system they came from (12). Some
9 authors used indices, mainly developed for comorbidity, e.g. Charlson Comorbidity Index (CCI)
10 (13, 14) and Cumulative Illness Rating Scale (CIRS) (15-17).
11
12

13 We could have included all possible codes from the ICD-10 system. However, doing so would have
14 resulted in some rather small groups of multimorbidity combinations and diagnoses of less
15 importance in relation to prevalence and mortality. To use chapters from ICD-10 could be an
16 option, but some chapters are difficult to apply to the above stated selection criteria. Furthermore,
17 an already existing index could be used. However, CCI was primarily developed for studying one-
18 year mortality and we prefer a broader pallet of diagnoses than they suggest. On the other hand,
19 CIRS could be interesting because it takes severity in to account, nevertheless, this would require
20 access to medical records that were not available in the present register study.
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24 Tonelli et al. (18) suggested a panel of 30 conditions when doing research on multimorbidity and
25 their recommendation was based on 40 conditions included in a Scottish study (7). Of notice, most
26 diagnoses used in these two studies were also included in our study, with a few exceptions:
27 connective tissue disorders, chronic pain, hypertension, severe constipation, transient ischemic
28 attacks, diverticular disease of intestine, peripheral vascular disease, prostate disorders, chronic
29 sinusitis, learning disability, bronchiectasis and viral hepatitis. The reason for not including these
30 conditions is that some of them are acute rather than chronic, some of them are closely related to
31 other conditions covered by our diagnosis groups, and the validity of the coding in the national
32 registers is relatively low for some of the diagnoses mentioned above. In particular risk factors, like
33 hypertension, are underreported, leading to low completeness and a larger underestimation of these
34 conditions compared with others.
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37 By this definition complexity can be grasped, and prevalent diseases with significant impact on
38 patients' lives can be included, but without the need of including all possible ICD-10 codes.
39
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41 Registers

42
43 The data was extracted from the following registers:
44

- 45 The Danish National Patient Registry (NPR) (19)
 - 46 The Danish Psychiatric Central Research Register (PCRR) (20)
 - 47 The Danish Cancer Register (CR) (21)
- 48
49

50 The registers contain information solely from the Danish hospital sector. Since we are interested in
51 general medicine it would be optimal to use ICPC codes from primary care. However, there is no
52 access to ICPC codes and there exist no registers validated for research with primary care data in
53 Denmark yet.
54

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56 All codes are based on International Classification of Diseases, 10th edition (ICD-10) and the earlier
57 8th edition (ICD-8). ICD is a well-established coding system used in 117 countries and translated
58 into 40 languages. The coding system is based on the medical specialties and hence coded in 21
59
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chapters. The coding system is reliable because of the long history, the many editions with continuous improvements and the involvement of medical experts (22). ICD-10 was introduced in Denmark 1 January 1994 and the present study contains both ICD-8 and ICD-10 diagnoses. NPR contains information on all inpatient care contacts in secondary care since 1977 and from 1995 also outpatient and emergency care contacts. Psychiatric diagnoses were included in NPR from 1995 (19). ICD-8 and ICD-10 are not comparable in every detail, and this has required a pragmatic approach when selecting diagnoses. In certain cases, one cannot distinguish between acute and chronic diagnoses in ICD-8, which sometimes leads to inclusion of the corresponding broader ICD-10 diagnoses with less relevant subcategories.

The validity and completeness of the registers vary. NPR constantly control data received from hospitals for incorrect codes and inconsistencies between sex and diagnoses in order to increase validity and completeness. Validation studies have shown variation in positive predictive value (PPV) between specialties and PPV showed to be higher when including three-number digits in ICD compared to five-number digits (23). In our definition of multimorbidity the three digit level is used as the highest level. Moreover, by using groups of conditions the need of high validity of some of the variables is reduced, e.g. whether atrial fibrillation is correctly coded as fibrillation or incorrectly as atrial flutter is of minor importance, since both conditions are included in the same diagnosis group: heart disease.

In our study we included diagnoses from a window ten years back in time from year 2000. Due to this choice some prevalent cases will be mistaken for being incident. The change from ICD-8 to ICD-10 in 1994 will probably lead to a higher number of incident cases around that year (23). Since 1994 is placed in the middle of our collection period a larger number of truly prevalent cases will probably be collected before 1994 and a larger number of cases falsely considered being incident in the year after. However, we do not necessarily consider prevalent cases less important than incident. Changes in diagnostic criteria and methods over time may also have affected how to interpret incidence (19).

For CR the validity is secured through daily control routines and yearly publications where checks for internal consistency are performed. Furthermore, the register uses several sources e.g. pathology to check their own information leading to high completeness of the register (21).

Validation studies on certain diagnoses have turned out well for PCRR (24, 25), but a systematic validation of the whole register has never been performed. There exist no private hospitals in Denmark for treating psychiatric patients therefore PCRR has high completeness. It has to be kept in mind, however, that the relatively large number of people treated for psychiatric diagnoses in primary care and at private practicing psychiatrists is not included in the register (20).

Diagnoses and organ systems included in the multimorbidity definition

	ICD-10	ICD-8
Lung diagnoses (LUNG)		
COPD	J44	490
Chronic bronchitis	J41-J42	491
Emphysema	J43	492
Asthma	J45-J46	493

Musculoskeletal diagnoses (MUSCULOSKELETAL)		
Rheumatic diagnoses / arthritis	L40.5, M05-M07	696.09, 712, 715
Arthrosis	M15-M17	713.00-09
Back diagnoses	M45, M47, M50-M51, M53-M54	712.49, 725, 728
Osteoporosis	M80-M82	723.09
Endocrine diagnoses (ENDO)		
Hypothyroidisme	E03	244
Hyperthyroidisme	E05	242
Diabetes	E10-E14	249-250
Mental diagnoses (MENTAL)		
Inclusion of all patients registered with a psychiatric diagnose in Psychiatric Central Register (except for patients having only Y - or Z-diagnoses) (26) and the following dementia and alcohol-related diagnoses from DNPR:		
Dementia	G30, G31.8-9, F00, F01, F02.0, F02.3, F03	290, 293
Alcohol	F10.1-F10.9	291, 303
Cancer (CANCER)		
All diagnoses from CR except C44, non-melanoma skin cancer.		
Neurological diagnoses (NEURO)		
Apoplexia cerebri (stroke)	I60-I64, I69	430-431, 433-434, 436-437
Multiple sclerosis	G35	340
Epilepsy	G40	345
Migraine	G43	346
Parkinson disease	G20	342
Gastrointestinal diagnoses (GASTRO)		
Dyspepsia	K30	536.90-91
Mb. Crohn and colitis ulcerosa	K50-K51	563
Colon irritabile	K58	564.19
Chronic liver disease	K70-K76	571-573
Chronic pancreatitis	K86.0, K86.1	577.10, 577.11, 577.19
Cardiovascular diagnoses (HEART)		
Ischemic heart disease	I20-I25	410-413
Heart failure and arrhythmia	I44.1-7, I45.2-9, I47-I50	427.09, 427.19, 427.23-24, 427.90-97, 428
Heart valve diagnoses	I05-I08, I34-I37	394-396, 397.00, 397.01, 424.00-19, 424.90-92
Genitourinary diagnoses (KIDNEY)		

Chronic kidney disease	N03-N05, N11-N12, N18-N19, Z49, Z99.2	581, 582, 583, 590.09, 590.15, 792
Urinary incontinence	N39.3-4	786.29
Endometriosis	N80	625.30-39
Diagnoses in sensory organs (SENSORY)		
Glaucoma	H40	375
Blindness and low vision	H54.0-54.3, H54.7	379.09, 379.19
Loss of hearing	H90.0, H90.2, H90.3, H90.5, H90.6, H90.8, H91	388, 389.09, 389.99
Psoriasis	L40	696.10, 696.19

Table A. In order to have multimorbidity the patient needs at least one diagnosis from two different bodily systems; for instance COPD from LUNG and multiple sclerosis from NEURO.

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Supplementary File 4 Prevalence of symptoms for the ten diagnosis groups and for the group without diagnoses.

Symptom	Total		No diagnosis		LUNG		MUSKULO SKELETAL		ENDO		MENTAL		CANCER		NEURO		GASTRO		HEART		KIDNEY		SENSORY	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	47452	100.0	30225	63.7	1595	3.4	6957	14.7	2214	4.7	471	1.0	2457	5.2	1679	3.5	2202	4.6	3878	8.2	1067	2.3	2614	5.5
No symptom	4224	8.9	2990	9.9	72	4.5	475	6.8	136	6.1	27	5.7	195	7.9	93	5.5	104	4.7	281	7.2	68	6.4	209	8.0
Tiredness	23252	49.0	14598	48.3	914	57.3	3422	49.2	1211	54.7	271	57.5	1226	49.9	965	57.5	1294	58.8	1896	48.9	632	59.2	1155	44.2
Night-time urination	23122	48.7	13136	43.5	919	57.6	4126	59.3	1353	61.1	291	61.8	1408	57.3	991	59.0	1265	57.4	2520	65.0	588	55.1	1646	63.0
Lack of energy	17623	37.1	10962	36.3	744	46.6	2671	38.4	888	40.1	229	48.6	943	38.4	728	43.4	1013	46.0	1477	38.1	483	45.3	894	34.2
Headache	16969	35.8	11294	37.4	558	35.0	2316	33.3	667	30.1	149	31.6	736	30.0	651	38.8	942	42.8	986	25.4	447	41.9	624	23.9
Back pain	15200	32.0	8689	28.7	617	38.7	3256	46.8	791	35.7	189	40.1	758	30.9	575	34.2	949	43.1	1373	35.4	444	41.6	900	34.4
Abdominal bloating	13951	29.4	8886	29.4	540	33.9	2024	29.1	662	29.9	112	23.8	665	27.1	507	30.2	931	42.3	1022	26.4	385	36.1	626	23.9
Memory problems	9365	19.7	5254	17.4	440	27.6	1639	23.6	533	24.1	186	39.5	578	23.5	566	33.7	644	29.2	912	23.5	300	28.1	656	25.1
Abdominal pain	9189	19.4	5491	18.2	395	24.8	1487	21.4	455	20.6	107	22.7	500	20.4	382	22.8	825	37.5	724	18.7	292	27.4	453	17.3
Coughing	8396	17.7	5033	16.7	598	37.5	1341	19.3	442	20.0	145	30.8	422	17.2	343	20.4	478	21.7	757	19.5	233	21.8	471	18.0
Concentration problems	8154	17.2	4940	16.3	339	21.3	1263	18.2	417	18.8	165	35.0	455	18.5	454	27.0	563	25.6	636	16.4	245	23.0	412	15.8
Change in stool texture	8055	17.0	4900	16.2	341	21.4	1257	18.1	414	18.7	105	22.3	418	17.0	323	19.2	565	25.7	687	17.7	240	22.5	427	16.3
Dizziness	7476	15.8	4138	13.7	355	22.3	1313	18.9	476	21.5	116	24.6	426	17.3	459	27.3	521	23.7	877	22.6	242	22.7	560	21.4
Feeling unwell	6903	14.6	4240	14.0	333	20.9	1065	15.3	387	17.5	92	19.5	350	14.2	303	18.0	503	22.8	547	14.1	214	20.1	332	12.7
Constipation	6847	14.4	3891	12.9	277	17.4	1207	17.3	389	17.6	78	16.6	426	17.3	352	21.0	449	20.4	695	17.9	256	24.0	402	15.4
Increase in	6223	13.1	3774	12.5	279	17.5	985	14.2	295	13.3	70	14.9	308	12.5	238	14.2	428	19.4	514	13.3	212	19.9	320	12.2

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waist circumference																								
Change in stool frequency	6107	12.9	3634	12.0	262	16.4	999	14.4	345	15.6	74	15.7	349	14.2	247	14.7	444	20.2	542	14.0	189	17.7	357	13.7
Diarrhoea	6020	12.7	3700	12.2	276	17.3	925	13.3	316	14.3	77	16.3	320	13.0	225	13.4	502	22.8	464	12.0	171	16.0	260	9.9
Nausea	5884	12.4	3509	11.6	269	16.9	941	13.5	334	15.1	92	19.5	350	14.2	280	16.7	446	20.3	480	12.4	212	19.9	258	9.9
Swollen legs	5852	12.3	2634	8.7	369	23.1	1481	21.3	530	23.9	89	18.9	456	18.6	344	20.5	405	18.4	913	23.5	275	25.8	498	19.1
Difficulty in emptying the bladder	5542	11.7	2765	9.1	292	18.3	1146	16.5	358	16.2	102	21.7	361	14.7	347	20.7	408	18.5	751	19.4	216	20.2	505	19.3
Frequent urination	4972	10.5	2641	8.7	228	14.3	970	13.9	327	14.8	106	22.5	342	13.9	298	17.7	325	14.8	632	16.3	162	15.2	398	15.2
Stress incontinence	4639	9.8	2511	8.3	253	15.9	991	14.2	298	13.5	50	10.6	350	14.2	200	11.9	297	13.5	415	10.7	279	26.1	312	11.9
Shortness of breath	3782	8.0	1670	5.5	659	41.3	861	12.4	264	11.9	105	22.3	214	8.7	218	13.0	304	13.8	641	16.5	140	13.1	323	12.4
Hoarseness	3630	7.7	2000	6.6	291	18.2	630	9.1	231	10.4	59	12.5	220	9.0	196	11.7	236	10.7	417	10.8	124	11.6	264	10.1
Urge incontinence	2976	6.3	1296	4.3	162	10.2	766	11.0	234	10.6	61	13.0	227	9.2	219	13.0	216	9.8	454	11.7	193	18.1	331	12.7
Loss of appetite	2902	6.1	1609	5.3	182	11.4	513	7.4	190	8.6	95	20.2	201	8.2	192	11.4	247	11.2	288	7.4	92	8.6	174	6.7
Blood in stool/rectal bleeding	2141	4.5	1343	4.4	89	5.6	300	4.3	93	4.2	26	5.5	105	4.3	87	5.2	160	7.3	183	4.7	58	5.4	114	4.4
Fever	1805	3.8	1184	3.9	76	4.8	258	3.7	80	3.6	20	4.2	81	3.3	65	3.9	108	4.9	115	3.0	48	4.5	80	3.1
Difficulty swallowing	1665	3.5	843	2.8	111	7.0	321	4.6	122	5.5	36	7.6	117	4.8	123	7.3	156	7.1	207	5.3	66	6.2	124	4.7
Weight loss	1405	3.0	734	2.4	83	5.2	279	4.0	99	4.5	39	8.3	112	4.6	107	6.4	125	5.7	167	4.3	41	3.8	90	3.4
Incontinence without stress/urge	1136	2.4	441	1.5	74	4.6	293	4.2	92	4.2	37	7.9	111	4.5	88	5.2	110	5.0	165	4.3	137	12.8	141	5.4

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Pain/burning when urinating	971	2.0	483	1.6	48	3.0	211	3.0	71	3.2	10	2.1	83	3.4	55	3.3	86	3.9	118	3.0	54	5.1	76	2.9
Lump/swollen lymph node	753	1.6	456	1.5	35	2.2	117	1.7	39	1.8	12	2.5	63	2.6	26	1.5	47	2.1	58	1.5	29	2.7	30	1.1
Black stool	725	1.5	421	1.4	46	2.9	111	1.6	48	2.2	16	3.4	39	1.6	33	2.0	58	2.6	69	1.8	15	1.4	47	1.8
Repeated vomiting	586	1.2	316	1.0	34	2.1	115	1.7	46	2.1	27	5.7	41	1.7	34	2.0	54	2.5	53	1.4	29	2.7	32	1.2
Blood in urine	264	0.6	117	0.4	16	1.0	70	1.0	19	0.9	4	0.8	17	0.7	18	1.1	14	0.6	47	1.2	22	2.1	21	0.8
Coughing up blood	58	0.1	35	0.1	6	0.4	8	0.1	4	0.2	none	none	few		few		few		6	0.2	few	0	4	0.2
Blood in vomit	47	0.1	27	0.1	4	0.3	10	0.1	6	0.3	few		few		few		7	0.3	5	0.1	none	none	few	

LUNG = lung diagnoses, MUSCULOSKELETAL = musculoskeletal diagnoses, ENDO = endocrine diagnoses, MENTAL = mental diagnoses, CANCER = cancer diagnoses, NEURO = neurological diagnoses, GASTRO = gastrointestinal diagnoses, HEART = cardiovascular diagnoses, KIDNEY = genitourinary diagnoses, SENSORY = sensory organ diagnoses

Supplementary File 5 Descriptive overview of patient characteristics for the participants in The Danish Symptom Cohort at baseline for each diagnosis group.

Baseline characteristics*	Total	No diagnosis	LUNG	MUSCULO-SKELETAL	ENDO	MENTAL	CANCER	NEURO	GASTRO	HEART	KIDNEY	SENSORY
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total	47452 (100)	30225 (63.7)	1595 (3.4)	6957 (14.7)	2214 (4.7)	471 (1.0)	2457 (5.2)	1679 (3.5)	2202 (4.6)	3878 (8.2)	1067 (2.3)	2614 (5.5)
Sex												
Male	22278 (47.0)	14627 (48.4)	699 (43.8)	2759 (39.7)	969 (43.8)	299 (63.5)	882 (35.9)	787 (46.9)	922 (41.9)	2329 (60.1)	208 (19.5)	1427 (54.6)
Age												
20-39	11362 (23.9)	9266 (30.7)	234 (14.7)	607 (8.7)	220 (9.9)	35 (7.4)	366 (14.9)	244 (14.5)	373 (16.9)	135 (3.5)	144 (13.5)	113 (4.3)
40-64	25269 (53.3)	16493 (54.6)	747 (46.8)	3700 (53.2)	1148 (51.9)	277 (58.8)	1078 (43.9)	801 (47.7)	1193 (54.2)	1590 (41.0)	577 (54.1)	939 (35.9)
65-79	9602 (20.2)	4149 (13.7)	524 (32.9)	2287 (32.9)	734 (33.2)	129 (27.4)	871 (35.4)	523 (31.1)	564 (25.6)	1765 (45.5)	284 (26.6)	1194 (45.7)
80	1219 (2.6)	317 (1.0)	90 (5.6)	363 (5.2)	112 (5.1)	30 (6.4)	142 (5.8)	111 (6.6)	72 (3.3)	388 (10.0)	62 (5.8)	368 (14.1)
MM (≥2 diagnosis groups)												
Yes	5652 (11.9)		953 (59.7)	3127 (44.9)	1351 (61.0)	309 (65.6)	1183 (48.1)	997 (59.4)	1213 (55.1)	2332 (60.1)	613 (57.5)	1481 (56.7)
Highest education												
Primary school	9374 (19.8)	5153 (17.0)	431 (27.0)	1790 (25.7)	609 (27.5)	152 (32.3)	568 (23.1)	451 (26.9)	561 (25.5)	1067 (27.5)	280 (26.2)	682 (26.1)
Secondary school ¹	21635 (45.6)	14039 (46.4)	721 (45.2)	3095 (44.5)	1009 (45.6)	196 (41.6)	1046 (42.6)	738 (44.0)	1030 (46.8)	1670 (43.1)	440 (41.2)	1118 (42.8)
Higher educations ²	15869 (33.4)	10690 (35.4)	421 (26.4)	1989 (28.6)	565 (25.5)	110 (23.4)	815 (33.2)	465 (27.7)	591 (26.8)	1066 (27.5)	340 (31.9)	753 (28.8)
None registered	574 (1.2)	343 (1.1)	22 (1.4)	83 (1.2)	31 (1.4)	13 (2.8)	28 (1.1)	25 (1.5)	20 (0.9)	75 (1.9)	7 (0.7)	61 (2.3)
Income³												
0-179.999	11218 (23.6)	6637 (22.0)	536 (33.6)	1859 (26.7)	689 (31.1)	203 (43.1)	640 (26.0)	496 (29.5)	591 (26.8)	1187 (30.6)	273 (25.6)	796 (30.5)
180.000-239.999	12092 (25.5)	7450 (24.6)	441 (27.6)	1902 (27.3)	605 (27.3)	134 (28.5)	661 (26.9)	466 (27.8)	613 (27.8)	1044 (26.9)	308 (28.9)	734 (28.1)
240.000-309.999	12056 (25.4)	8004 (26.5)	317 (19.9)	1631 (23.4)	484 (21.9)	79 (16.8)	566 (23.0)	377 (22.5)	544 (24.7)	825 (21.3)	254 (23.8)	536 (20.5)
310.000+	12086 (25.5)	8134 (26.9)	301 (18.9)	1565 (22.5)	436 (19.7)	55 (11.7)	590 (24.0)	340 (20.3)	454 (20.6)	822 (21.2)	232 (21.7)	548 (21.0)
Working status												
Working	29205 (61.6)	21311 (70.5)	660 (41.4)	2924 (42.0)	892 (40.3)	133 (28.2)	1125 (45.8)	640 (38.1)	1097 (49.8)	1248 (32.2)	523 (49.0)	766 (29.3)
Out of workforce ⁴	6130 (12.9)	3766 (12.5)	274 (17.2)	1081 (15.5)	361 (16.3)	155 (32.9)	249 (10.1)	361 (21.5)	398 (18.1)	386 (10.0)	172 (16.1)	228 (8.7)
Pensioners	12117 (25.5)	5148 (17.0)	661 (41.4)	2952 (42.4)	961 (43.4)	183 (38.9)	1083 (44.1)	678 (40.4)	707 (32.1)	2244 (57.9)	372 (34.9)	1620 (62.0)

1													
2	Asset⁵												
3	<0	15695 (33.1)	10543 (34.9)	524 (32.9)	2017 (29.0)	717 (32.4)	196 (41.6)	695 (28.3)	516 (30.7)	771 (35.0)	960 (24.8)	357 (33.5)	511 (19.5)
4	0-399,999	15747 (33.2)	10131 (33.5)	550 (34.5)	2351 (33.8)	783 (35.4)	163 (34.6)	788 (32.1)	562 (33.5)	751 (34.1)	1210 (31.2)	391 (36.6)	838 (32.1)
5	400,000+	16010 (33.7)	9551 (31.6)	521 (32.7)	2589 (37.2)	714 (32.2)	112 (23.8)	974 (39.6)	601 (35.8)	680 (30.9)	1708 (44.0)	319 (29.9)	1265 (48.4)
6	Urbanisation degree⁶												
7	Rural	16621 (35.0)	10303 (34.1)	552 (34.6)	2581 (37.1)	803 (36.3)	157 (33.3)	863 (35.1)	605 (36.0)	879 (39.9)	1490 (38.4)	402 (37.7)	945 (36.2)
8	Small town	17346 (36.6)	10981 (36.3)	559 (35.0)	2548 (36.6)	763 (34.5)	148 (31.4)	940 (38.3)	596 (35.5)	804 (36.5)	1481 (38.2)	392 (36.7)	995 (38.1)
9	Capital city	13485 (28.4)	8941 (29.6)	484 (30.3)	1828 (26.3)	648 (29.3)	166 (35.2)	654 (26.6)	478 (28.5)	519 (23.6)	907 (23.4)	273 (25.6)	674 (25.8)
10	Cohabiting												
11	Yes	35614 (75.1)	22830 (75.5)	1098 (68.8)	5189 (74.6)	1601 (72.3)	239 (50.7)	1822 (74.2)	1194 (71.1)	1633 (74.2)	2899 (74.8)	791 (74.1)	1858 (71.1)
12	Smoking												
13	Yes, current	9860 (20.8)	6384 (21.1)	345 (21.6)	1390 (20.0)	470 (21.2)	223 (47.3)	480 (19.5)	362 (21.6)	463 (21.0)	663 (17.1)	206 (19.3)	442 (16.9)
14	Yes, former	15030 (31.7)	8493 (28.1)	656 (41.1)	2605 (37.4)	903 (40.8)	134 (28.5)	1026 (41.8)	595 (35.4)	789 (35.8)	1766 (45.5)	392 (36.7)	1102 (42.2)
15	Never	20754 (43.7)	14385 (47.6)	488 (30.6)	2641 (38.0)	734 (33.2)	76 (16.1)	821 (33.4)	617 (36.7)	842 (38.2)	1236 (31.9)	404 (37.9)	910 (34.8)
16	No answer	1808 (3.8)	963 (3.2)	106 (6.6)	321 (4.6)	107 (4.8)	38 (8.1)	130 (5.3)	105 (6.3)	108 (4.9)	213 (5.5)	65 (6.1)	160 (6.1)
17	Alcohol consumption⁷												
18	1-7 units/week	30261 (63.8)	19679 (65.1)	927 (58.1)	4326 (62.2)	1361 (61.5)	140 (29.7)	1538 (62.6)	1014 (60.4)	1396 (63.4)	2239 (57.7)	690 (64.7)	1515 (58.0)
19	8-21 units/week	10320 (21.8)	6696 (22.2)	309 (19.4)	1456 (20.9)	371 (16.8)	104 (22.1)	514 (20.9)	309 (18.4)	373 (16.9)	917 (23.6)	171 (16.0)	670 (25.6)
20	>21 units/week	1669 (3.5)	1058 (3.5)	60 (3.8)	218 (3.1)	66 (3.0)	61 (13.0)	82 (3.3)	48 (2.9)	66 (3.0)	175 (4.5)	15 (1.4)	107 (4.1)
21	Never	14515 (30.6)	1820 (6.0)	192 (12.0)	635 (9.1)	308 (13.9)	128 (27.2)	192 (7.8)	203 (12.1)	258 (11.7)	334 (8.6)	126 (11.8)	162 (6.2)
22	No answer	11623 (24.5)	972 (3.2)	107 (6.7)	322 (4.6)	108 (4.9)	38 (8.1)	131 (5.3)	105 (6.3)	109 (5.0)	213 (5.5)	65 (6.1)	160 (6.1)

*At baseline 1 January, 2012

¹ Secondary school: secondary school, high school and higher-level vocational studies.

² Higher educations: short and medium higher education or college diploma, university degree (bachelor or master), doctoral degree.

³ Income: divided in quartiles.

⁴ Out of workforce: unemployed, student, apprentice or intern, or incapacity benefits.

⁵ Asset: divided in tertiles.

⁶ Rural: at least 50 % of the population in the municipality lives in a thinly populated area. Small town: Intermediate density area. Less than 50 % of the population lives in a densely populated area and less than 50 % of the population lives in a thinly populated area. Capital: At least 50 % of the population lives in a densely populated area.

⁷ Moderate: 0-7 units/week women, 0-14 units/week men. High: >7units/week for women, >14units/week men. 1 unit=4 cl alcohol 40% or 1 glass of wine or 1 beer 33 cl 4.5%.

LUNG = lung diagnoses, MUSCULOSKELETAL = musculoskeletal diagnoses, ENDO = endocrine diagnoses, MENTAL = mental diagnoses, CANCER = cancer diagnoses, NEURO = neurological diagnoses, GASTRO = gastrointestinal diagnoses, HEART = cardiovascular diagnoses, KIDNEY = genitourinary diagnoses, SENSORY = sensory organ diagnoses

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	<p>(a) Indicate the study’s design with a commonly used term in the title or the abstract</p> <p>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</p>
		<p>1 (a) A combined population-based questionnaire- and registry study.</p> <p>(b) Design: A combined population-based questionnaire- and registry study. Participants: In 2012, 47,452 participants from the Danish Symptom Cohort answered a questionnaire on symptom presence, interference with usual daily activities and concern of symptoms. Setting: The Danish nationwide health registries were queried for these participants from 2002-2011 to see whether single diagnoses and multimorbidity occurred. Multimorbidity was defined as having diagnoses from at least two out of ten predefined groups of diagnoses. Multivariable models were used to estimate the association between symptom burden and diagnosis groups. Main outcome measure: Symptom burden. Results: Overall, 91.1% of the respondents reported one or more symptom(s) within the preceding four weeks, 36.3% of the study sample belonged to at least one diagnosis group and 11.9% had multimorbidity. Symptom burden was slightly higher for people with a diagnosis than for people not having the diagnosis in the registers. Mostly, symptom burden was increased for people with multimorbidity, and this increase was in excess of the sum of the increase attributable to the individual diagnosis groups. Conclusion: Patients with multimorbidity reported higher symptom burden than the sum of burden from two persons with the individual diagnoses, indicating symptom burden being supra-additive in multimorbidity.</p>
Introduction		
Background/rationale	2	<p>Explain the scientific background and rationale for the investigation being reported</p> <p>Please see page 4, the “<i>introduction</i>”.</p>
Objectives	3	<p>State specific objectives, including any prespecified hypotheses</p> <p>Stated on page 4.</p> <p>The aim of this study was to explore how symptom burden is affected when diagnosis groups appear in combination (multimorbidity) compared to when they appear separately. We hypothesized that symptom burden in multimorbidity is additive i.e. that symptom burden in patients having multimorbidity is equivalent to the sum of symptom burden reported from two persons belonging to the diagnosis groups individually.</p>
Methods		
Study design	4	<p>Present key elements of study design early in the paper</p> <p>4. Stated on page 4 in the article: “<i>Study design and population</i>” Participants were from the Danish Symptom Cohort (DaSK), a population-based study conducted in Denmark in June-December, 2012.</p>
Setting	5	<p>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</p> <p>Stated on page 4 in the section “<i>Study design and population</i>”</p>

1			“People invited for the study lived in Denmark 1 st January, 2012 (baseline). Of
2			100.000 persons randomly selected from the general Danish population aged 20 or
3			older, 95.253 persons were eligible and invited (Figure 1). Of these, 49.706 (52.2%)
4			answered the questionnaire (15). “
5			
6	Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of
7			participants. Describe methods of follow-up
8			
9			
10			(b) For matched studies, give matching criteria and number of exposed and unexposed
11			
12			(a) “People invited for the study lived in Denmark 1 st January, 2012 (baseline).
13			Of 100.000 persons randomly selected from the general Danish population
14			aged 20 or older, 95.253 persons were eligible and invited (Figure 1). Of
15			these, 49.706 (52.2%) answered the questionnaire (15). “
16			
17			(b) Not applicable.
18			
19	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect
20			modifiers. Give diagnostic criteria, if applicable
21			Please see page 4-6 and the sections “ <i>Symptoms and symptom burden</i> ” and
22			“ <i>Multimorbidity</i> ” and Supplementary File 5.
23			
24			
25	Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of
26			assessment (measurement). Describe comparability of assessment methods if there is
27			more than one group
28			Please see page 4-6 in the Methods section.
29			“All immigrated or live born individuals in Denmark receive a unique personal
30			identification number stored in the Danish Civil Registration System (CRS) (16). CRS
31			contains information on age, sex, vital status, etc., and CRS enables linking
32			information from different Danish registries. Information on diagnoses leading to
33			either inpatient or outpatient care was collected from the Danish National Patient
34			Register (NPR) (17), the Danish Cancer Registry (18), and the Danish Psychiatric
35			Central Research Register (PCRR) (19). Information on education (20), work status
36			(21), family income (22), assets (banks, stocks, bonds, and housing, within and
37			outside Denmark) (22), degree of urbanization and cohabitation status derived from
38			other nationwide registers stored in Statistics Denmark.”
39			
40			“Information on diagnoses is retrieved from the nationwide health registries in the ten
41			years period preceding baseline (1 st January, 2002-31 st December, 2011). Participants
42			are excluded if they have not been living continuously in Denmark during this 10-year
43			period”.
44			
45			Information on symptom burden is retrieved from the questionnaire.
46			
47	Bias	9	Describe any efforts to address potential sources of bias
48			Please see page 10 the section “ <i>Strengths and limitations</i> ”
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51	Study size	10	Explain how the study size was arrived at
52			Page 4: “Participants were from the Danish Symptom Cohort (DaSK), a population-
53			based study conducted in Denmark in June-December, 2012. People invited for the
54			study lived in Denmark 1 st January, 2012 (baseline). Of 100.000 persons randomly
55			selected from the general Danish population aged 20 or older, 95.253 persons were
56			eligible and invited (Figure 1). Of these, 49.706 (52.2%) answered the questionnaire
57			(15).”
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59	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,
60			describe which groupings were chosen and why

		Please see supplementary file 5 for baseline information. We had four quantitative variables: age, income, assets, and alcohol consumption. Income and assets were divided into quartiles. Age was divided into four groups, younger and older adults in the working age and younger and older among the retired adults. Alcohol was divided in moderate and high drinking for men and women.
Statistical methods	12	Please see page 6, the section “ <i>Statistical analysis</i> ” (a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses
Results		
Participants	13*	Please see the “ <i>Result</i> ” section (page 7) and Figure 1. (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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	Please see Supplementary file 5. (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount) Not done
Outcome data	15*	Report numbers of outcome events or summary measures over time Please see Table 1 and Supplementary file 4.
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 We adjusted for age, sex, socioeconomic status (highest completed education, income, assets, and work status), urbanization degree, cohabitation status, smoking and alcohol. They were included because we believe they can affect the relation between diagnoses and symptoms, as well as how symptoms are interpreted. Please see Supplementary File 5, Table 1, and Figure 2a-c. (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not done
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Please see page 6 “Statistical analyses”
Discussion Please see the discussion section, page 9-12.		
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if

1 applicable, for the original study on which the present article is based

2 Please see page 12.

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5 *Give information separately for exposed and unexposed groups.

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7 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
8 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
9 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
10 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
11 available at <http://www.strobe-statement.org>.
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Symptom burden in multimorbidity. A population-based combined questionnaire and registry study from Denmark

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6 **Symptom burden in multimorbidity. A population-based combined questionnaire and**
7 **registry study from Denmark**
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46 Tables: 2
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48 Figures: 4
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50 Words: 3340
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Abstract

Objective: Patients with multimorbidity may carry a large symptom burden. Symptoms are often what drive patients to seek healthcare, and they also assist doctors with diagnosis. We examined whether symptom burden is additive in people with multimorbidity compared to people with a single morbidity.

Design: Longitudinal cohort study drawing on questionnaire and Danish national registry data. Multimorbidity was defined as having diagnoses from at least two out of ten morbidity groups. Associations between morbidity groups and symptom burden were estimated with multivariable models.

Participants: In 2012, 47,452 participants from the Danish Symptom Cohort answered a questionnaire about symptoms (36 symptoms in total) including whether symptoms were affecting their daily activities (*impairment score*), and their worries about present symptoms (*worry score*) (the highest score among the 36 symptoms on a 0-4 scale).

Main outcome measure: The primary outcome was symptom burden.

Results: Participants without morbidity reported 4.77 symptoms (out of 36 possible). Participants with one, two, or three morbidities reported, respectively, (0.95 [CI 0.86-1.03]; 1.87 [1.73-2.01]; 2.89 [2.66-3.12]) more symptoms than patients without morbidity. Furthermore, they reported a higher impairment score, (0.36 [0.32-0.39]; 0.65 [0.60-0.70]; 1.06 [0.98-1.14]), and a higher worry score, (0.34 [0.31-0.37]; 0.62 [0.57-0.66]; 1.02 [0.94-1.10]) than participants without morbidity. In 45 possible combinations of multimorbidity (participants with two morbidities) interaction effects were additive in 37, 41 and 36 combinations, for number of symptoms, impairment score, and worry score, respectively.

Conclusion: Participants without morbidity reported a substantial number of symptoms. Having a single morbidity or multimorbidity resulted in approximately one extra symptom for each extra morbidity. In most combinations of multimorbidity symptom burden was additive.

Strengths and limitations of this study.

- This study combines high quality data from Danish national registries and questionnaire data from the background population.
- The questionnaire used in this study draws on a breadth of symptoms indicative of both serious and less harmful diseases.
- The selection of symptoms in the questionnaire is not exhaustive which may induce artificial differences between morbidities. Nevertheless, this does not bias synergy estimates.
- Multimorbidity is defined as having two or more morbidities. In this study, a morbidity is defined as having one or more chronic diagnoses from one of ten predefined morbidity groups: LUNG, MUSCULOSKELETAL, ENDOCRINE, MENTAL HEALTH, CANCER, NEUROLOGICAL, GASTROINTESTINAL, CARDIOVASCULAR, GENITOURINARY and SENSORY.

Introduction

Multimorbidity, most often defined as the co-occurrence of two or more chronic diseases,(1) affects mental health,(2) quality of life,(3) and survival,(4) and patients with multimorbidity often struggle to manage their symptoms.(5) Symptoms play a major part in how people self-rate their health.(6) Factors like disability, duration, and feelings of vulnerability are important drivers for how a sensation gradually turns into a symptom,(7) where interpretations of danger and intensity can be decisive in making a contact with healthcare.(8) Hence, the presence of symptoms is important for doctors to be able to formulate a diagnosis, and thereby symptoms become a pathway through which a person becomes a patient.(9) Symptoms, however, can be difficult to explain and doctors may focus solely on relieving them.(9, 10) Additionally, diagnoses are not always helpful in explaining symptom experiences,(11) and having one diagnosis increases the risk of being diagnosed with other diseases.(12) Patients with multimorbidity report a considerable symptom burden (5, 13) and more focus on symptom management in multimorbidity has been suggested.(14) Therefore, an understanding of the relationship between diagnoses and symptom burden is warranted, and especially an understanding of how symptom burden is experienced when diagnoses occur in multiples, ie multimorbidity. The aim of this study was to explore symptom burden in patients with one of ten morbidities compared with symptom burden in patients with multimorbidity. We hypothesised that symptom burden in multimorbidity was additive, ie that symptoms in patients with multimorbidity was equivalent to the sum of the symptoms attributable to the single morbidities.

Methods

Study design and population.

The study was a longitudinal cohort study. Participants were from the Danish Symptom Cohort, a population-based study conducted in Denmark in June-December, 2012. People invited to participate in the study were living in Denmark on 1st January, 2012 (baseline). Of 100,000 adults (≥ 20 years) randomly selected from the general Danish population, 95,253 were eligible and invited to participate (Figure 1). Of these, 49,706 (52.2%) completed the study questionnaire (Supplementary File 1).(15)

All Danish born and immigrant populations in Denmark have a unique personal identification number in the Danish Civil Registration System.(16) The register contains information about age, sex, vital status, etc, and enables information from different Danish registries to be

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3 linked. Information on diagnoses leading to either inpatient or outpatient care in the hospital
4 sector was collected from the Danish National Patient Register,(17) the Danish Cancer
5 Registry,(18) and the Danish Psychiatric Central Research Register.(19) Thus, only diagnoses
6 from secondary care were included in the study. Information on education,(20) work
7 status,(21) family income,(22) assets (banks, stocks, bonds, and housing),(22) degree of
8 urbanisation, and cohabitation status was obtained from the nationwide registries at baseline.
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15 *Symptom data*

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17 The Danish Symptom Cohort was established to investigate symptom experience in the
18 general population and healthcare-seeking in relation to general practice. According to the
19 random sample selected from the Danish population, the cohort included both healthy people
20 and people with diseases. Several articles have been published with data from the cohort.(23-
21 25) The focus of the present study was symptom burden in people with multimorbidity and
22 variables for the study was selected accordingly.(23) The median age of the participants in
23 the Danish Symptom Cohort was 52 years (IQR 40-64) and for non-participants it was 50
24 years (IQR 36-67). The respondents were reasonably representative of the study sample, but
25 non-responders were more often men, unmarried, with lower education, lower income level,
26 and with a generally looser attachment to the labour market.
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35 The survey consisted of a web-based questionnaire supported by a telephone interviewer if
36 warranted. The questionnaire was electronic and designed so that it was not possible to skip
37 items, and therefore there were no missing values for those who completed it. The process of
38 developing the questionnaire has been described by Rasmussen et al.(15) The questionnaire
39 had five domains: three about experience of symptoms and how participants acted upon them,
40 and two about factors related to symptom experience and healthcare-seeking behaviour
41 (Supplementary File 1). The questionnaire included 38 general symptoms, as well as two
42 specific symptoms for men and four for women (44 symptoms in total). The first sentence in
43 the questionnaire was: “We are interested to hear if you have experienced any bodily
44 sensations, symptoms, or discomfort within the last four weeks”. For the general symptoms
45 the following phrase was used: “Have you experienced any of these within the last 4 weeks?”
46 Respondents had the opportunity to tick more than one box in a list presenting the 38 general
47 symptoms (Supplementary File 1). Eight symptoms were excluded in the present analyses as
48 six of them were gender-specific (as mentioned above) and would have made comparisons
49 between men and women difficult, and the two symptoms “coughing up blood” and “blood in
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3 vomit” had low prevalence in the data. Therefore, we included 36 symptoms in the analyses
4 (Supplementary File 2).

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6 The questionnaire also included questions about how each symptom affected usual daily
7 activities (impairment score) and the participant’s concern about each symptom (worry
8 score): “Within the last 4 weeks, to what extent did you experience that the following
9 symptoms or discomfort interfered with your usual daily activities?”; and “Within the last 4
10 weeks, to what extent were you concerned about the following symptoms or discomfort?” For
11 each symptom, there were five response categories: “not at all”, “slightly”, “moderate”,
12 “quite a bit”, and “extremely”. The response categories were transformed in to a numeric
13 scale (0-4) where the experience rated 4 is worse than the experience rated 1.
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22 *Symptom burden*

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24 Three components defined symptom burden: 1) number of symptoms (*number score* 0-36);
25 how symptoms affect usual daily activities (*impairment score* 0-4 per symptom reported, and
26 concern about the symptoms (*worry score* 0-4 per symptom reported).
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30 For the impairment score and the worry score, we included the symptom with the highest
31 score in the analyses, eg if a patient scores 3 for tiredness, and scores 1 for dizziness their
32 overall score is 3. This is because we anticipated that the most burdensome symptoms affect
33 quality of life more heavily than a number of minor symptoms.(26)
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37 *Multimorbidity*

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39 Information on diagnoses was retrieved from the nationwide health registries in the 10-year
40 period preceding baseline (1st January, 2002-31st December, 2011). Participants were
41 excluded if they had not been living continuously in Denmark during this 10-year period.
42 Chronic disease diagnoses were grouped into ten domains: LUNG, MUSCULOSKELETAL,
43 ENDOCRINE, MENTAL HEALTH, CANCER, NEUROLOGICAL,
44 GASTROINTESTINAL, CARDIOVASCULAR, GENITOURINARY and SENSORY. In
45 each domain, relevant diagnoses from the International Classification of Diseases, 10th
46 edition (ICD-10) were included (Supplementary File 3). Morbidity is defined as having a
47 diagnosis from one domain and multimorbidity is defined as having a diagnosis from two or
48 more different domains.(27) This definition rests on the assumption that it is more complex
49 and realistic from a physiological and organisational point of view if the patient is living with
50 diagnoses from different domains of the body.(27) Often two chronic diagnoses refer to the
51 same disease entity, eg myocardial infarction and congestive heart failure. Therefore, our
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3 definition of multimorbidity relates more closely to how health care is organised and it grasps
4 some aspects of complexity to a greater extent than counting individual diagnoses
5 (Supplementary File 3). People who do not have any of the diagnoses included in the ten
6 domains were considered to have no morbidity.
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10 *Statistical analysis*

11 Symptom burden in people with a single morbidity and multimorbidity was explored using
12 multivariate analyses adjusted for age, sex, socioeconomic status (highest completed
13 education, income, assets, and work status), degree of urbanisation, cohabitation status,
14 smoking, and alcohol consumption. Excess symptom burden for people with multimorbidity
15 (combinations of two diagnosis domains) was assessed in multivariable linear regression
16 models. For each of the three measures of symptom burden (number of symptoms,
17 impairment score, and worry score) the $(10 \times 9) / 2 = 45$ regression coefficients pertaining to the
18 two-way interactions between diagnosis domains were retained from a multivariable linear
19 regression on all combinations of diagnosis domains, adjusted for the same covariates as
20 mentioned above. These coefficients were directly interpreted as the synergy effect, ie excess
21 symptom burden associated with having diagnoses from two diagnosis domains relative to
22 the sum of the symptom burden associated with having a diagnosis from the diagnosis
23 domains individually. Analyses were performed using SAS, version 9.4 (SAS Institute Inc.,
24 Cary, NC, USA).
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37 *Patient and public involvement*

38 No patients, nor any other members of the public, were involved in designing, conducting, or
39 reporting this study.
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43 *Ethical approval*

44 The Danish Symptom Cohort study was approved by the Ethics Committee and the National
45 Board of Health. Informed consent was obtained from all participants. The Danish Data
46 Protection Agency approved the Danish Symptom Cohort (journal number 2011-41-6651)
47 and approved linkage with other registers (journal number 2015-231-0149). For the present
48 analyses, the Danish Data Protection Agency, Statens Serum Institut and Statistics Denmark
49 approved the use of register data. Administrative register data were anonymised, and re-
50 approval from the Ethics Committee was not needed, nor did we need additional informed
51 consent from the participants.
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Results

The study sample consisted of 47,452 people ≥ 20 years old (Figure 1) out of which 17,227 (36.3%) had a single morbidity and 5,652 (11.9%) had multimorbidity (Table 1). Overall, 43,228 (91.1%) reported symptoms (Table 1 and Supplementary File 4), with 92.8% of people with a single morbidity or multimorbidity reporting at least one symptom, and 90.2% of people without morbidity reporting at least one symptom. On average, the participants experienced 4.8-7.4 symptoms depending on morbidities within the last four weeks (Supplementary Table A).

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Table 1. Baseline characteristics stratified for the various morbidity domains.

Baseline characteristics*	Total	No diagnosis	LUNG	MUSCULO SKELETAL	ENDO	MENTAL HEALTH	CANCER	NEURO	GASTRO	HEART	KIDNEY	SENSORY
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	47452 (100)	30225 (63.7)	1595 (3.4)	6957 (14.7)	2214 (4.7)	471 (1.0)	2457 (5.2)	1679 (3.5)	2202 (4.6)	3878 (8.2)	1067 (2.3)	2614 (5.5)
Sex												
Male	22278 (47.0)	14627 (48.4)	699 (43.8)	2759 (39.7)	969 (43.8)	299 (63.5)	882 (35.9)	787 (46.9)	922 (41.9)	2329 (60.1)	208 (19.5)	1427 (54.6)
Age												
20-39	11362 (23.9)	9266 (30.7)	234 (14.7)	607 (8.7)	220 (9.9)	35 (7.4)	366 (14.9)	244 (14.5)	373 (16.9)	135 (3.5)	144 (13.5)	113 (4.3)
40-64	25269 (53.3)	16493 (54.6)	747 (46.8)	3700 (53.2)	1148 (51.9)	277 (58.8)	1078 (43.9)	801 (47.7)	1193 (54.2)	1590 (41.0)	577 (54.1)	939 (35.9)
65-79	9602 (20.2)	4149 (13.7)	524 (32.9)	2287 (32.9)	734 (33.2)	129 (27.4)	871 (35.4)	523 (31.1)	564 (25.6)	1765 (45.5)	284 (26.6)	1194 (45.7)
>80	1219 (2.6)	317 (1.0)	90 (5.6)	363 (5.2)	112 (5.1)	30 (6.4)	142 (5.8)	111 (6.6)	72 (3.3)	388 (10.0)	62 (5.8)	368 (14.1)
MM (≥2 diagnosis groups)												
Yes	5652 (11.9)		953 (59.7)	3127 (44.9)	1351 (61.0)	309 (65.6)	1183 (48.1)	997 (59.4)	1213 (55.1)	2332 (60.1)	613 (57.5)	1481 (56.7)
Highest education												
Primary school	9374 (19.8)	5153 (17.0)	431 (27.0)	1790 (25.7)	609 (27.5)	152 (32.3)	568 (23.1)	451 (26.9)	561 (25.5)	1067 (27.5)	280 (26.2)	682 (26.1)
Secondary school ¹	21635 (45.6)	14039 (46.4)	721 (45.2)	3095 (44.5)	1009 (45.6)	196 (41.6)	1046 (42.6)	738 (44.0)	1030 (46.8)	1670 (43.1)	440 (41.2)	1118 (42.8)
Higher educations ²	15869 (33.4)	10690 (35.4)	421 (26.4)	1989 (28.6)	565 (25.5)	110 (23.4)	815 (33.2)	465 (27.7)	591 (26.8)	1066 (27.5)	340 (31.9)	753 (28.8)
None registered	574 (1.2)	343 (1.1)	22 (1.4)	83 (1.2)	31 (1.4)	13 (2.8)	28 (1.1)	25 (1.5)	20 (0.9)	75 (1.9)	7 (0.7)	61 (2.3)
Income³												
(low)	11218 (23.6)	6637 (22.0)	536 (33.6)	1859 (26.7)	689 (31.1)	203 (43.1)	640 (26.0)	496 (29.5)	591 (26.8)	1187 (30.6)	273 (25.6)	796 (30.5)
(middle)	12092 (25.5)	7450 (24.6)	441 (27.6)	1902 (27.3)	605 (27.3)	134 (28.5)	661 (26.9)	466 (27.8)	613 (27.8)	1044 (26.9)	308 (28.9)	734 (28.1)
(middle)	12056 (25.4)	8004 (26.5)	317 (19.9)	1631 (23.4)	484 (21.9)	79 (16.8)	566 (23.0)	377 (22.5)	544 (24.7)	825 (21.3)	254 (23.8)	536 (20.5)
(high)	12086 (25.5)	8134 (26.9)	301 (18.9)	1565 (22.5)	436 (19.7)	55 (11.7)	590 (24.0)	340 (20.3)	454 (20.6)	822 (21.2)	232 (21.7)	548 (21.0)
Working status												
Working	29205 (61.6)	21311 (70.5)	660 (41.4)	2924 (42.0)	892 (40.3)	133 (28.2)	1125 (45.8)	640 (38.1)	1097 (49.8)	1248 (32.2)	523 (49.0)	766 (29.3)
Out of workforce ⁴	6130 (12.9)	3766 (12.5)	274 (17.2)	1081 (15.5)	361 (16.3)	155 (32.9)	249 (10.1)	361 (21.5)	398 (18.1)	386 (10.0)	172 (16.1)	228 (8.7)
Pensioners	12117 (25.5)	5148 (17.0)	661 (41.4)	2952 (42.4)	961 (43.4)	183 (38.9)	1083 (44.1)	678 (40.4)	707 (32.1)	2244 (57.9)	372 (34.9)	1620 (62.0)
Asset⁵												
(no asset)	15695 (33.1)	10543 (34.9)	524 (32.9)	2017 (29.0)	717 (32.4)	196 (41.6)	695 (28.3)	516 (30.7)	771 (35.0)	960 (24.8)	357 (33.5)	511 (19.5)
(low asset)	15747 (33.2)	10131 (33.5)	550 (34.5)	2351 (33.8)	783 (35.4)	163 (34.6)	788 (32.1)	562 (33.5)	751 (34.1)	1210 (31.2)	391 (36.6)	838 (32.1)
(high asset)	16010 (33.7)	9551 (31.6)	521 (32.7)	2589 (37.2)	714 (32.2)	112 (23.8)	974 (39.6)	601 (35.8)	680 (30.9)	1708 (44.0)	319 (29.9)	1265 (48.4)
Urbanisation degree⁶												
Rural	16621 (35.0)	10303 (34.1)	552 (34.6)	2581 (37.1)	803 (36.3)	157 (33.3)	863 (35.1)	605 (36.0)	879 (39.9)	1490 (38.4)	402 (37.7)	945 (36.2)
Small town	17346 (36.6)	10981 (36.3)	559 (35.0)	2548 (36.6)	763 (34.5)	148 (31.4)	940 (38.3)	596 (35.5)	804 (36.5)	1481 (38.2)	392 (36.7)	995 (38.1)
Capital city	13485 (28.4)	8941 (29.6)	484 (30.3)	1828 (26.3)	648 (29.3)	166 (35.2)	654 (26.6)	478 (28.5)	519 (23.6)	907 (23.4)	273 (25.6)	674 (25.8)
Cohabiting												
Yes	35614 (75.1)	22830 (75.5)	1098 (68.8)	5189 (74.6)	1601 (72.3)	239 (50.7)	1822 (74.2)	1194 (71.1)	1633 (74.2)	2899 (74.8)	791 (74.1)	1858 (71.1)
Smoking												
Yes, current	9860 (20.8)	6384 (21.1)	345 (21.6)	1390 (20.0)	470 (21.2)	223 (47.3)	480 (19.5)	362 (21.6)	463 (21.0)	663 (17.1)	206 (19.3)	442 (16.9)
Yes, former	15030 (31.7)	8493 (28.1)	656 (41.1)	2605 (37.4)	903 (40.8)	134 (28.5)	1026 (41.8)	595 (35.4)	789 (35.8)	1766 (45.5)	392 (36.7)	1102 (42.2)

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3 Never	20754 (43.7)	14385 (47.6)	488 (30.6)	2641 (38.0)	734 (33.2)	76 (16.1)	821 (33.4)	617 (36.7)	842 (38.2)	1236 (31.9)	404 (37.9)	910 (34.8)
4 No answer	1808 (3.8)	963 (3.2)	106 (6.6)	321 (4.6)	107 (4.8)	38 (8.1)	130 (5.3)	105 (6.3)	108 (4.9)	213 (5.5)	65 (6.1)	160 (6.1)
5 Alcohol												
6 consumption⁷												
7 1-7 units/week	30261 (63.8)	19679 (65.1)	927 (58.1)	4326 (62.2)	1361 (61.5)	140 (29.7)	1538 (62.6)	1014 (60.4)	1396 (63.4)	2239 (57.7)	690 (64.7)	1515 (58.0)
8 8-21 units/week	10320 (21.8)	6696 (22.2)	309 (19.4)	1456 (20.9)	371 (16.8)	104 (22.1)	514 (20.9)	309 (18.4)	373 (16.9)	917 (23.6)	171 (16.0)	670 (25.6)
9 >21 units/week	1669 (3.5)	1058 (3.5)	60 (3.8)	218 (3.1)	66 (3.9)	61 (13.0)	82 (3.3)	48 (2.9)	66 (3.0)	175 (4.5)	15 (1.4)	107 (4.1)
10 Never	3381 (7.1)	1820 (6.0)	192 (12.0)	635 (9.1)	308 (13.9)	128 (27.2)	192 (7.8)	203 (12.1)	258 (11.7)	334 (8.6)	126 (11.8)	162 (6.2)
10 No answer	1821 (3.8)	972 (3.2)	107 (6.7)	322 (4.6)	108 (4.9)	38 (8.1)	131 (5.3)	105 (6.3)	109 (5.0)	213 (5.5)	65 (6.1)	160 (6.1)

*At baseline 1 January, 2012

¹ Secondary school: secondary school, high school and higher-level vocational studies.

² Higher educations: short and medium, higher education or college diploma, university degree (bachelor or master), doctoral degree.

³ Income: divided in quartiles.

⁴ Out of workforce: unemployed, student, apprentice or intern, or incapacity benefits.

⁵ Asset: divided in tertiles.

⁶ Rural: at least 50 % of the population in the municipality lives in a thinly populated area. Small town: Intermediate density area. Less than 50 % of the population lives in a densely populated area and less than 50 % of the population lives in a thinly populated area. Capital: At least 50 % of the population lives in a densely populated area.

⁷ Moderate: 0-7 units/week women, 0-14 units/week men. High: >7 units/week for women, >14 units/week men, 1 unit=4 cl alcohol 40% or 1 glass of wine or 1 beer 33 cl 4.5%.

LUNG = lung diagnoses. MUSCULOSKELETAL = musculoskeletal diagnoses. ENDO = endocrine diagnoses. MENTAL HEALTH= psychiatric diagnoses. CANCER = cancer diagnoses. NEURO = neurological diagnoses. GASTRO = gastrointestinal diagnoses. HEART = cardiovascular diagnoses. KIDNEY = genitourinary diagnoses. SENSORY = sensory organ diagnoses

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3 *Morbidity and symptom burden*
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5 Participants without morbidity reported 4.77 symptoms (SD 3.92) on average (Supplementary
6 Table A). The more morbidities a participant had, the more symptoms they reported. In
7 multivariable analysis adjusted for confounders, each extra morbidity was associated with
8 approximately one extra symptom (Table 2).
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Table 2. The increase in mean symptom burden with the number of morbidity domains.

	Number of morbidity domains (out of 10)							
	0 <i>(n=30225)</i>	1 <i>(n=11575)</i>	2 <i>(n=3963)</i>	3 <i>(n=1243)</i>	4 <i>(n=350)</i>	5 <i>(n=76)</i>	6 <i>(n=16)</i>	7 <i>(n=4)</i>
Number of symptoms								
Mean (SD)	4.77 (3.92)	5.50 (4.34)	6.29 (4.72)	7.32 (4.88)	8.16 (5.31)	9.64 (5.91)	11.44 (6.11)	7.50 (5.20)
Mean difference (95%CI) with 0 symptoms, adjusted analysis	(ref)	0.95 (0.86 ; 1.03)	1.87 (1.73 ; 2.01)	2.89 (2.66 ; 3.12)	3.70 (3.28 ; 4.12)	5.51 (4.61 ; 6.41)	6.61 (4.67 ; 8.54)	1.96 (-1.90 ; 5.81)
Interference with usual daily activities (impairment score)								
Mean (SD)	2.74 (1.46)	3.04 (1.48)	3.30 (1.47)	3.73 (1.33)	3.83 (1.32)	4.08 (1.14)	4.07 (1.33)	4.50 (0.58)
Mean difference (95%CI) with 0 symptoms, adjusted analysis	(ref)	0.36 (0.32 ; 0.39)	0.65 (0.60 ; 0.70)	1.06 (0.98 ; 1.14)	1.15 (1.00 ; 1.31)	1.47 (1.15 ; 1.80)	1.28 (0.57 ; 2.00)	1.50 (0.12 ; 2.89)
Concern about symptoms (worry score)								
Mean (SD)	2.16 (1.38)	2.49 (1.46)	2.77 (1.51)	3.20 (1.48)	3.27 (1.47)	3.67 (1.34)	3.80 (1.37)	3.75 (1.50)
Mean difference (95%CI) with 0 symptoms, adjusted analysis	(ref)	0.34 (0.31 ; 0.37)	0.62 (0.57 ; 0.66)	1.02 (0.94 ; 1.10)	1.07 (0.92 ; 1.22)	1.52 (1.20 ; 1.85)	1.50 (0.80 ; 2.21)	1.36 (0.00 ; 2.72)

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3 Participants without morbidity reported a mean impairment score of 2.74 (SD1.46). The more
4 morbidities a participant had, the higher their reported impairment score (Table 2). In
5 multivariable analysis adjusted for confounders, each extra morbidity was associated with an
6 approximately 0.35 higher impairment score (participants with one, two, or three morbidities)
7 than participants without morbidity. However, in participants with four or more morbidities
8 there was a levelling off in added impairment score with the number of morbidities (Table 2).
9 Participants without morbidity reported a worry score of 2.16 (SD 1.38). The more
10 morbidities, the higher the worry score participants reported (Table 2). In multivariable
11 analysis adjusted for confounders, each extra morbidity was associated with an approximately
12 0.34 higher worry score (participants with one, two, or three morbidities) than participants
13 without morbidity. In participants with four or more morbidities, however, there was a
14 levelling off in added worry score for each additional morbidity (Table 2).

25 *Multimorbidity and interaction effect of symptom burden*

26 Participants with multimorbidity (confined to participants with two morbidities) were
27 analysed for interaction effects regarding their number of symptoms, impairment score, and
28 worry score. We did this to estimate if the symptom burden was additive (equivalent to the
29 sum of two individual diagnoses), infra-additive (less than), or supra-additive (greater than)
30 in specific combinations of multimorbidity.

31 The number of symptoms reported by participants with specific combinations of
32 multimorbidity are outlined in Supplementary Tables A and B and depicted in Figure 2. In
33 multivariable analyses adjusted for confounders the number of symptoms reported by the
34 participants was additive in 37 out of 45 combinations of multimorbidity. The combinations
35 LUNG-MENTAL HEALTH, CANCER-HEART and CANCER-SENSORY were associated
36 with a supra-additive number of symptoms (Supplementary Table C). On the other hand, the
37 combinations LUNG-MUSCULOSKELETAL, ENDO-MENTAL HEALTH, NEURO-
38 MENTAL HEALTH, CANCER-KIDNEY and HEART-KIDNEY were associated with an
39 infra-additive number of reported symptoms (Supplementary Table C).

40 Impairment scores as reported by participants with multimorbidity are outlined in
41 Supplementary Tables D and E and depicted in Figure 3. In multivariable analyses adjusted
42 for confounders the impairment score was additive in 41 out of 45 combinations of two
43 morbidities. The combination CANCER-SENSORY was associated with a supra-additive
44 impairment score. The combinations LUNG-GASTRO, CANCER-KIDNEY and HEART-
45 KIDNEY were associated with an infra-additive impairment score.

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3 Worry scores as reported by participants with multimorbidity are outlined in Supplementary
4 Tables F and G and depicted in Figure 4. In multivariable analyses the worry score was
5 additive in 36 out of 45 combinations of two morbidities. The combinations CANCER-
6 MENTAL HEALTH, CANCER-NEURO and CANCER-SENSORY were associated with a
7 supra-additive worry score. The combinations LUNG-MUSCULOSKELETAL, LUNG-
8 KIDNEY, ENDO-KIDNEY, CANCER-KIDNEY, NEURO-KIDNEY and HEART-KIDNEY
9 were associated with an infra-additive impairment score.
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15 16 **Discussion**

17 *Main findings*

18 Participants without morbidity reported a number of symptom experiences (mean 4.8, median
19 4), and one extra symptom was added with each additional morbidity. Patients with a single
20 morbidity, therefore, reported 5.8 symptoms, patients with three morbidities reported 7.8
21 symptoms, and so forth. Thus, the number of symptoms was additive with one extra symptom
22 for each extra morbidity.
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28 The same pattern was seen for how the symptoms interfered with the participants' daily
29 activities and how much the participants were concerned about their symptoms. An
30 impairment score (2.7) and a worry score (2.2) were reported by participants with no
31 morbidity. Each morbidity added approximately 0.3 to the impairment and worry scores (up
32 to three morbidities). Hereafter the impairment and worry scores leveled off to a slow
33 increase with the number of morbidities (four, five, and six). Thus, the scores for how
34 symptoms interfered with the participants' daily activities and how much the participants
35 were concerned about their symptoms was relatively high in participants without morbidity,
36 and the increase in impairment and worry scores were additive for every extra morbidity up
37 to three. Hereafter, each morbidity (from four to seven morbidities) did not add much to the
38 impairment and worry scores.
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48 In regard to symptom burden among specific combinations of multimorbidity, most
49 combinations followed an additive pattern, i.e. the reported extra symptom burden in patients
50 with multimorbidity was equivalent to the sum of the symptom burdens attributable to the
51 individual morbidities. However, there were some exceptions to the overall additive pattern.
52 Most notably, the combination SENSORY-CANCER where the symptom burden was supra-
53 additive in all three components of symptom burden, and the combinations CANCER-
54 KIDNEY and HEART-KIDNEY where all three components of symptom burden were infra-
55 additive. Thus, SENSORY-CANCER seemed to be especially burdensome, whereas
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3 CANCER-KIDNEY and HEART-KIDNEY seemed to be less burdensome than other
4 combinations of multimorbidity.
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7 *Comparisons with existing literature*

9 In this study, many participants reported symptoms independent of morbidities. Since
10 symptoms are a main source of information when a doctor establishes a diagnosis (9, 10) and
11 symptoms are important mediators for healthcare-seeking behaviour (28) the high number of
12 symptoms independent of morbidity could seem unexpected. However, it is earlier shown
13 that only a limited part of experienced symptoms end up being presented to a doctor (23).
14 Furthermore, it highlights the fact that symptoms to some degree are prerequisites of human
15 condition (7) in contrast to diagnoses that are created by medicine.(10) However, symptoms
16 have been shown to be frequent in the population (28, 29) and, when interviewed, a large
17 number of people reported experiencing symptoms within a two week period.(30)
18 Furthermore, it is reasonable to believe that symptom burden affects self-rated health,(31, 32)
19 even though evidence suggests that it is not the symptom itself, but rather limitations on daily
20 activities, worry, and treatment burden related to the symptom that affect patients most.(33)
21 A person's self-rated health decreases with the number of chronic diseases they are living
22 with, and this is most pronounced in younger and previously healthy people,(34) which is in
23 line with our results.
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37 In this study, we found that the majority of multimorbidity combinations were additive and
38 even had a levelling off effect. This could indicate that the definition of multimorbidity we
39 used is clinically relevant, since the number of symptoms increases with the number of
40 morbidities. While prognosis in multimorbidity is worse than could be predicted by adding
41 the prognoses of individual diseases,(35) this is not the case for symptoms, according to the
42 present study. This finding may, however, be explained by the overlap of symptoms between
43 diagnoses. Another explanation could be that diagnoses are more likely to be made when
44 patients have many contacts with the healthcare system.(12) This could particularly add to the
45 amount of diagnoses made without symptoms. Furthermore, it is known that older people
46 seem to adapt to chronic conditions with a lower influence on their self-rated health as a
47 result.(35)
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57 This study shows that a mean of one new symptom is added for each morbidity, indicating
58 that the symptom burden of patients with multimorbidity may be substantial. This may help
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3 clinicians to understand why patients with multimorbidity struggle to recognise which
4 symptoms to focus on (36) and also help us understand why patients with multimorbidity are
5 sometimes overwhelmed by their symptom burden.(5, 13) With the number of morbidities
6 they have to live with, multimorbidity can quickly become a complex issue for patients,(37)
7 not only because of the burden of symptoms, but also because of the burden of treatment,(38)
8 the organisational challenges,(38) and the demands from everyday life.(33)
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15 In most combinations of multimorbidity, symptom burden was additive rather than supra-
16 additive. However, there were a few exceptions, eg the multimorbidity combination sensory-
17 cancer was supra-additive. Patients with multimorbidity combinations that included cancer
18 reported a supra-additive symptom burden, especially regarding their worry score. Cancer has
19 a certain status in the general population as something fatal and cancer alarm symptoms can
20 act as a mediator for making contact with a doctor.(31)
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26 Participants with multimorbidity that included a kidney morbidity most often reported an
27 infra-additive symptom burden, especially regarding their worry score. This could be
28 explained by the fact that a kidney diagnosis is more likely to come from a laboratory test and
29 general and often reported symptoms as e.g. tiredness. Furthermore, in the kidney domain of
30 our definition of multimorbidity, incontinence was an important and frequent diagnosis, but
31 not necessarily a worrying one.(39, 40)
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40 *Strengths and limitations*

41 The population-based cohort and high response rate are strengths of our study,(41) as well as
42 the questionnaire containing a breadth of symptoms indicative of both serious and less
43 harmful diseases, and the adjustments for several important factors. The relatively low
44 prevalence of multimorbidity in this study compared to other studies can be explained by the
45 definition based on ten groups of diagnoses from secondary care.(2, 42) The nationwide
46 registers have high validity and they require a referral to secondary care, thus ensuring that
47 the resulting diagnoses have a certain seriousness.(17, 18) In Denmark, primary care data on
48 diagnoses are not available. However, we believe our broader definition, in contrast to simple
49 disease counts (27, 43), better grasps the burden and complexity of multimorbidity.
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58 The selection of symptoms in the questionnaire is not exhaustive and are not selected in order
59 to represent the morbidity domains, however, they may show preference towards certain
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3 domains eg there are many urinary tract-related symptoms relative to only a few kidney
4 diagnoses. This may induce artificial differences between diagnoses groups. However, this
5 does not bias the synergy estimates. Furthermore, the presence of diagnoses from secondary
6 care contacts does not allow us to obtain adequate data on diagnosis duration which could be
7 of importance for symptom experience.(44) However, the time limit of four weeks in the
8 questionnaire was used to focus on relevant symptoms, while they can still be recalled.(15)
9 Finally, we cannot completely rule out that the multimorbidity combinations being supra- or
10 infra-additive may be a result of multiple testing.
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20 *Implications*

21 It is well known that patients with multimorbidity face challenges in relation to their
22 symptoms (5) and this study shows that symptom burden is, or rapidly becomes, substantial
23 for these patients. Little is known about optimal management of symptoms (14) which
24 underlines the need for increased attention to symptom burden among patients with
25 multimorbidity. Initiatives such as patient dairies, describing the quality of disease
26 management, paying attention to how patients explain their illness in order to understand
27 their stories and life themes,(45) and patient involvement in deciding the agenda and
28 achieving realistic goals, (33) are probably valuable for optimal management. In conclusion,
29 patients with multimorbidity add approximately one extra symptom for each additional
30 morbidity, and symptom burden in these patients is additive, ie equivalent to the sum of
31 symptoms attributable to the individual morbidity.
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55 contributed to the discussion. VS and DN performed the analyses, researched the data,
56 contributed to the discussion, and reviewed/edited the manuscript. RKR researched the data,
57 contributed to the discussion, and reviewed/edited the manuscript. ADG, DJ, SR made
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59
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3 important contributions to the discussion and content, and reviewed/edited the manuscript.
4 All authors approved the final version of the manuscript. TGW, VS, and DN have full access
5 to data and take full responsibility for the truthfulness in the data and in the data analyses.
6
7
8 TGW is the guarantor of this work.
9

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14
15

16
17 **Disclaimer** The study sponsors had no role in study design, data collection, and analysis or in
18 writing the manuscript.
19

20 21 22 **Competing interests**

23 None
24
25

26 27 28 **Patient consent for publication**

29 Not required
30
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32 33 **Data availability statement**

34 Data may be obtained from a third party and are not publicly available. Data is stored at
35 Statistics Denmark. To share data approvals are required from the Danish Data Protection
36 Agency and The Danish Health Data Authority.
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Figure legends

Figure 1. Study population.

Figure 2. All (45) combinations of multimorbidity (two diagnosis groups) and the association with number of symptoms. *Syn*=synergy, the excess number of symptoms for multimorbidity, compared to the sum of symptoms from two people having the two morbidity domains individually. *Eff*=effect, the number of symptoms for the multimorbidity combination. *N*=number, the number of people with the multimorbidity combination. Effects with a *p*-value <0.05 are marked with *.

Figure 3. All (45) combinations of multimorbidity (two diagnosis groups) and the association with influence on daily activities. *Syn*=synergy, the excess interference with usual daily activities score (from the symptom with the highest interference score, ranging 1-4 with 4 indicating the highest burden on usual daily activities) for multimorbidity, compared to the sum of the interference score from two people with the two morbidity domains individually. *Eff*=effect, the interference score for the multimorbidity combination. *N*=number, the number of people with the multimorbidity combination. Effects with a *p*-value <0.05 are marked with *.

Figure 4. All (45) combinations of multimorbidity (two diagnosis groups) and the association with concern about symptoms. *Syn*=synergy, the excess concern score (from the symptom with the highest concern score, ranging 1-4 with 4 indicating most concern) for multimorbidity, compared to the sum of the concern score from two people with the two morbidity domains individually. *Eff*=effect, the concern score for the multimorbidity combination. *N*=number, the number of people with the multimorbidity combination. Effects with a *p*-value <0.05 are marked with *.

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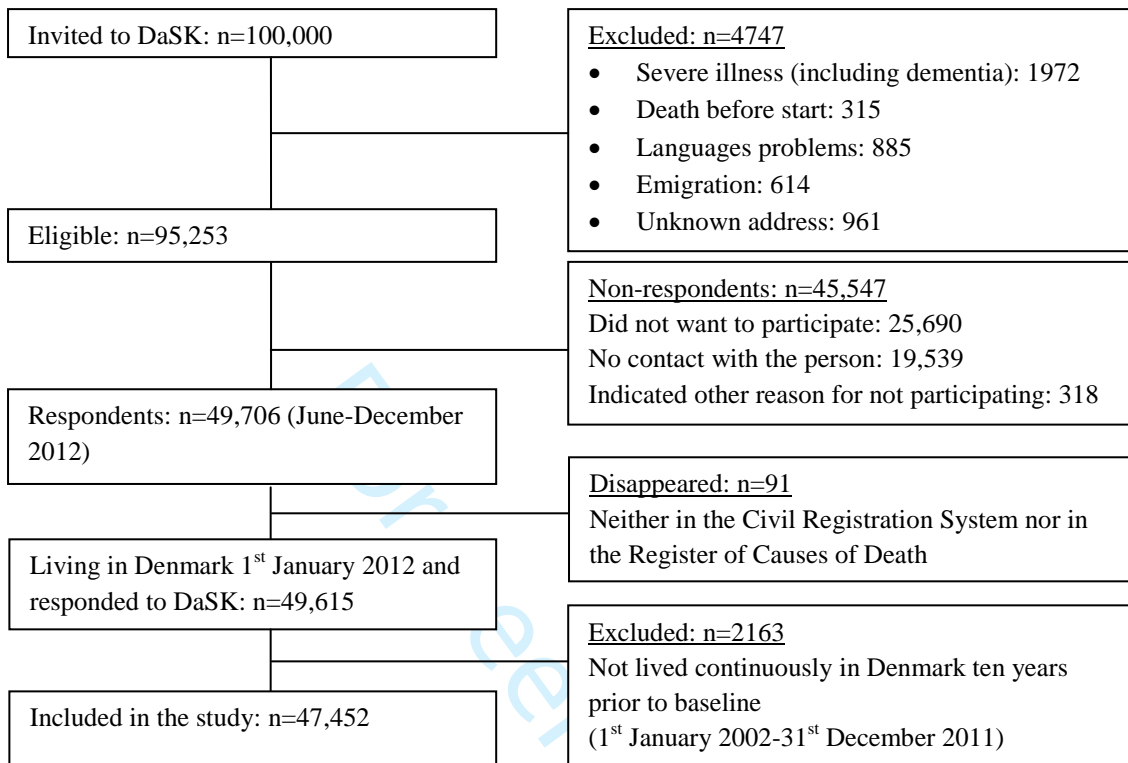
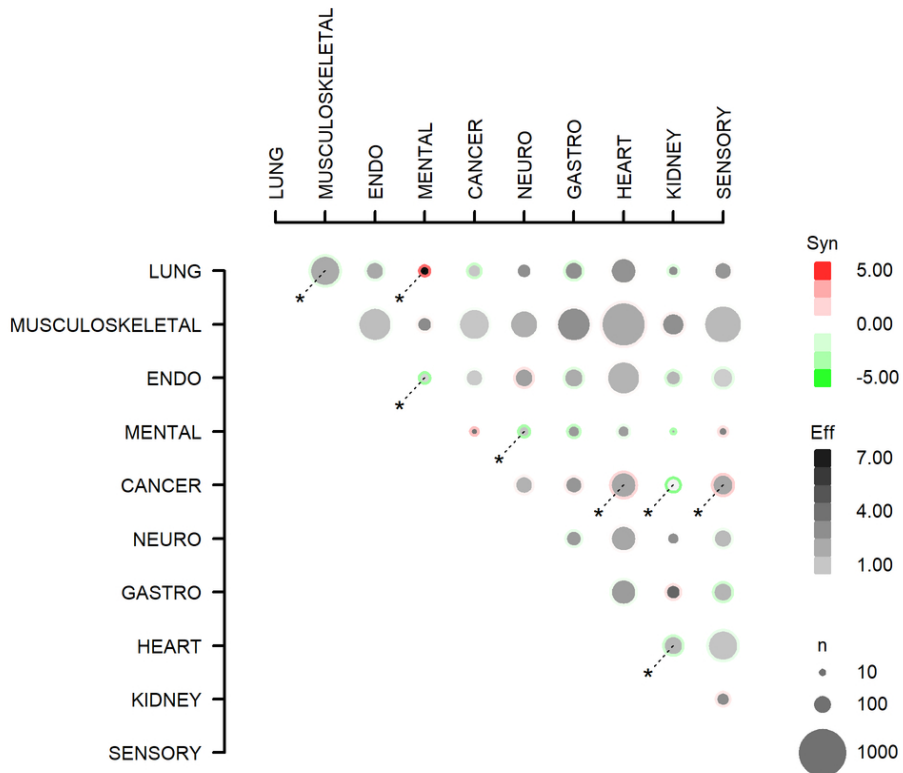
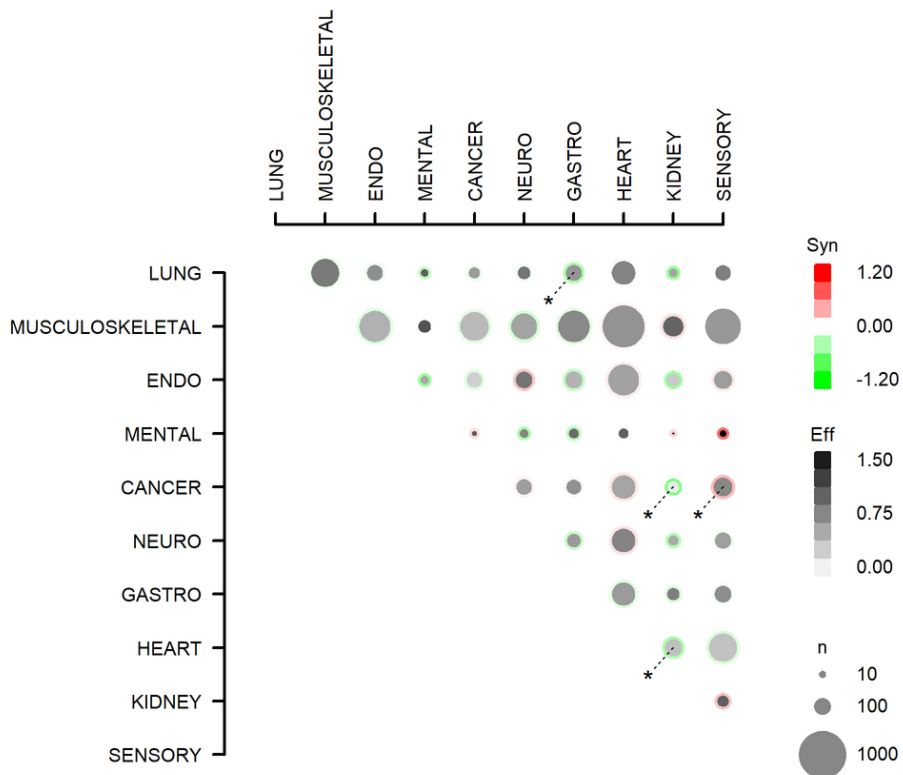


Figure 1. Danish symptom cohort study population.

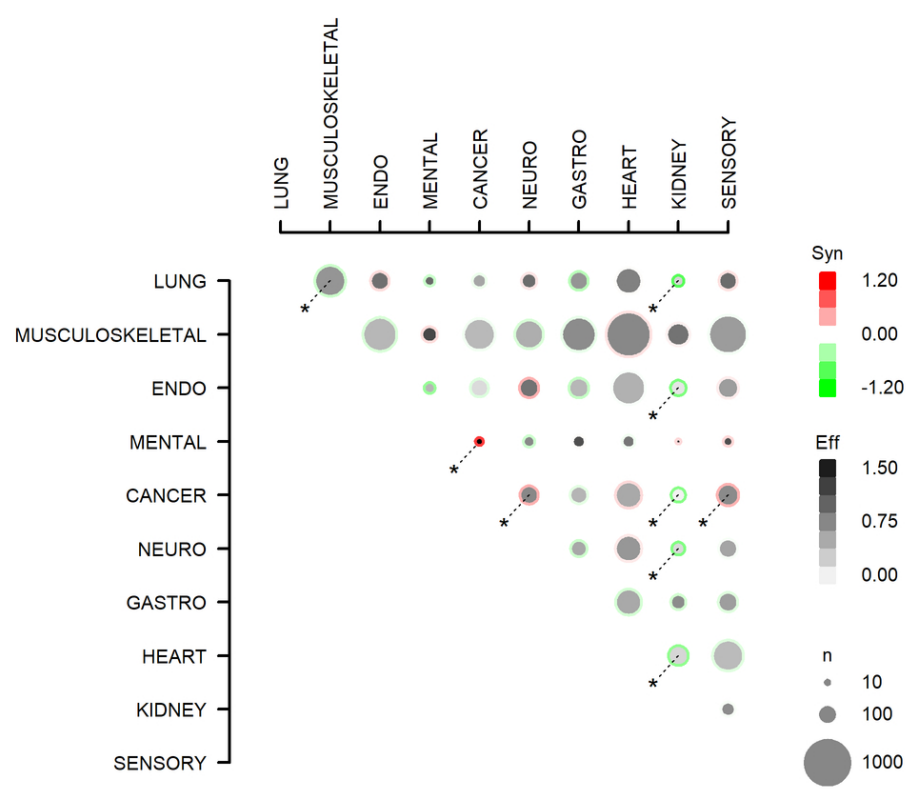
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Supplementary File 1

Welcome to the Danish Symptom Cohort – a survey about health, symptoms and healthcare-seeking

The questionnaire was not available in hard copy, but for illustrative purposes it has been reproduced in this appendix.

In order to address sex specific items with minimal disturbance to respondents, the questionnaire was distributed in two different versions; one for males and another for females. In this appendix questions from both versions are included, and each of the sex specific questions is marked with explanatory captions in italic.

The web-based questionnaire contains several leaps based on answers provide by the respondents (marked with explanatory captions in italic).

We appreciate that you will take the time to complete the questionnaire.

The questionnaire is to be used for the identification of a number of bodily sensations, symptom experiences and discomfort. You may find that some of the questions are similar. It is important that you answer them all anyway. You can also answer the questions, even if you feel perfectly healthy. There is a commentary box at the end of the questionnaire, in which you can note any additional remarks.

Should you get disrupted while answering the questionnaire, you can always log on again. The system automatically saves your answers. Simply use your personal logon information again, and you can continue the survey.

When completing the questionnaire, it is also possible to return to previously answered questions.

If you have any questions or experience problems while filling in the questionnaire, please feel free to contact us by e-mail: dask@health.sdu.dk or by phone: 29 71 44 24 weekdays between the hours 10:00-15:00 and 19:00-21:00.

For further information about the survey, please visit our website www.sdu.dk/dask. Here you will also find answers to some frequently asked questions.

Completing the questionnaire will take approximately 20-30 min.

Participant acceptance:

I accept that my answers can be used for research, and I hereby give consent to obtain information from health records and medical records for research purposes. All my answers will be treated with the strictest confidence and used solely for research purposes. The responses will be used only in anonymous form. It is of course voluntary to participate, and I may at any time withdraw this consent.

The study was approved by the Danish Data Protection Agency, Science Ethics Committee and the Danish Health and Medicines Authority, and thus complies with current legal and ethical regulations.

I accept the above

We are interested to hear if you have experienced any bodily sensations, symptoms or discomfort within the last four weeks. Later you will be asked when you first experienced these, and how you reacted with regard to these experiences.

Have you within **the last 4 weeks** experienced any of these? (You may tick more than one box)

- Abdominal pain
- Nausea
- Repeated vomiting
- Blood in vomit
- Difficulty swallowing

- Abdominal bloating
- Increased waist circumference (trousers tighter than normal)
- Change in stool texture (i.e. having hard or lumpy stools, although you usually tend to have loose or watery stools or vice versa)
- Change in frequency of bowel movements (i.e. passing stools more or less frequently than usual)

- Rectal bleeding/Blood in stool
- Black shiny stools
- Frequent, loose or watery stools
- Hard and lumpy stools

- Tiredness
- Lack of energy
- Feeling unwell or sick
- Memory problems
- Concentration problems
- Weight loss of more than 2 kg without making an effort

- Coughing
- Coughing up blood
- Shortness of breath
- Hoarseness

- Dizziness
- Headache
- Back pain
- Swollen legs
- Loss of appetite
- Lump/swollen lymph node
- Fever

- That you need to urinate more often than usual
- That you have to get up to urinate at night
- Difficulty emptying the bladder completely when urinating

- Pain or burning sensation when urinating
- Urge to urinate so strong that you cannot make it to the toilet in time
- Involuntary urination (incontinence) during exertion, e.g. coughing, sneezing, lifting and exercise
- Involuntary urination (incontinence) without exertion and urge (leakage)
- Blood in urine

Only for women:

The next questions are about sexual relations. Some of the questions may seem private, but your response may contribute to a greater understanding of whether there is a correlation between sexual relations and symptoms or discomfort from the lower abdomen. If there are questions you do not wish to answer, simply tick the category "do not wish to answer."

Have you within the **last 4 weeks** experienced any of the following?

Pelvic pain

- Yes
- No
- I don't wish to answer

Vaginal bleeding after menopause (i.e. absence of menstrual periods for more than 12 months.)

- Not relevant, as I have not yet reached menopause
- Yes
- No
- I don't wish to answer

Vaginal bleeding during or after sexual intercourse

- Not relevant, as I am not sexually active
- Yes
- No
- I don't wish to answer

Pelvic pain during intercourse

- Not relevant, as I am not sexually active
- Yes
- No
- I don't wish to answer

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The next question may seem private, but your response may contribute to a greater understanding of the prevalence of symptoms or discomfort in the population. If you do not wish to answer the question, simply tick the category "Do not wish to answer."

Only for men:

Have you within **the last 4 weeks** experienced any of the following?

- Erectile dysfunction
- Blood in the semen
- None of the above
- I don't wish to answer

Only for women, and only if stated that they had not yet reached the menopause:

Are you currently pregnant, or have you been pregnant within **the last 6 months**?

- Yes
- No
- I don't know/ I don't wish to answer

Only for women

How many sexual relationships have you had altogether from your sexual debut and until now?

- Have not yet had my sexual debut
- 1-5
- 6-10
- 11-15
- 16-20
- 21-25
- More than 26
- I don't wish to answer

How many sexual relationships have you had within the last year?

- 0
- 1-5
- 6-10
- 11-15
- 16-20
- 21-25
- More end 26
- I don't wish to answer

The following questions only appeared in relation to a positive expression of one or more experienced symptom(s) - by a leap structure in the electronic survey to the symptom experience

We will now ask you some elaborating questions, which deal with the sensations, symptoms or discomfort that you have just stated.

When did you experience these for the first time:

	Less than a month ago	1-3 months ago	3-6 months ago	More than 6 months ago
Abdominal pain Etc...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Within **the last 4 weeks**: To what extent did you experience that the following symptoms or discomfort interfered with your usual daily activities?

	Not at all	Slightly	Moderate	Quite a bit	Extremely
Abdominal Pain Etc...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Within the last 4 weeks: To what extent were you concerned about the following symptoms or discomfort?

	Not at all	Slightly	Moderate	Quite a bit	Extremely
Abdominal Pain Etc...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The following questions only appeared in relation to a positive expression of one or more experienced symptom(s) - by a leap structure in the electronic survey to the symptom experience

We will now ask you some questions concerning who you have talked to about the symptoms or discomfort you experienced **in the last 4 weeks**.

Have you contacted your general practitioner with any of the following symptoms or discomfort? (Through appointment, by telephone or by email)

- Yes
 No

The following questions only appeared in relation to a positive expression of one or more experienced symptom(s) - by a leap structure in the electronic survey to the symptom experience

You have been in contact with your general practitioner regarding the following symptoms and discomforts. We would now like to know, whether you had some of the following considerations, **before** contacting your general practitioner? (You may tick more than one box)

		Yes	No
Abdominal pain Etc.	I would be too embarrassed	<input type="checkbox"/>	<input type="checkbox"/>
	I would be worried about wasting the doctor's time	<input type="checkbox"/>	<input type="checkbox"/>
	I would be worried about what the doctor might find	<input type="checkbox"/>	<input type="checkbox"/>
	I would be too busy to make time to go to the doctor	<input type="checkbox"/>	<input type="checkbox"/>
	Other considerations [box for free text commentaries]		

The following questions only appeared in relation to a positive expression of one or more experienced symptom(s) - by a leap structure in the electronic survey to the symptom experience

You have **not** been in contact with your general practitioner regarding the following symptoms and discomforts. We would now like to know, whether you had some of the following considerations, regarding contact to your general practitioner? (You may tick more than one box)

		Yes	No
Abdominal pain Etc.	I would be too embarrassed	<input type="checkbox"/>	<input type="checkbox"/>
	I would be worried about wasting the doctor's time	<input type="checkbox"/>	<input type="checkbox"/>
	I would be worried about what the doctor might find	<input type="checkbox"/>	<input type="checkbox"/>
	I would be too busy to make time to go to the doctor	<input type="checkbox"/>	<input type="checkbox"/>
	Other considerations [box for free text commentaries]		

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6 Which of the following other health care professionals or therapists have you talked to/consulted
7 regarding the symptoms or discomforts listed below (through appointment, by telephone or by
8 email)? (you may tick more than one box)
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- 10
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12
13 Abdominal pain
14 Etc.
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- None
 - Another doctor (practicing specialist, out-of-hours physician or hospital physician)
 - Physiotherapist/chiropractor
 - Home help/district nurse
 - Pharmacy staff
 - Alternative therapist (e.g. homeopath, healer, reflexologist)
 - Other

20
21 Which of the following members of your family or social network have you talked to about the
22 symptoms or discomforts listed below? (you may tick more than one box)
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- 24
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26 Abdominal pain
27 Etc.
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- None
 - Spouse/partner
 - Children
 - Parents
 - Colleague /classmate
 - Friend
 - Neighbour
 - Other

We will proceed to another category of questions regarding abdominal pain. Furthermore we ask questions regarding various factors that may have impact on abdominal pain and discomfort. Because we use several different questionnaires you might experience that some of the questions appear similar. There are however nuances in the items that are important for the survey.

In **the last 3 months**, how often did you have acid regurgitation or heartburn (a burning epigastric discomfort or burning pain in your chest)?

- Never
- Less than one day a month
- One day a month
- Two to three days a month
- One day a week
- More than one day a week
- Everyday

The next three questions are skipped if the answer is "never" in the above-mentioned questions.

When you experience acid regurgitation or heartburn (a burning epigastric discomfort or burning pain in your chest), how severe are your discomforts?

- Very mild
- Mild
- Moderately
- Severe
- Very severe

To what extent does your acid regurgitation or heartburn (a burning epigastric discomfort or burning pain in your chest) affect your sleep?

- My sleep is not affected
- My sleep is affected to some extent
- My sleep is affected to a great extent

To what extent does your acid regurgitation or heartburn (a burning epigastric discomfort or burning pain in your chest) affect your everyday activities?

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

The following questions concern abdominal pain and bowel habits.

The next questions are related to the Rome 3 criteria for IBS: IF the symptoms are experienced less than two to three days a month, the rest of the questions for IBS are skipped

In the last 3 months, how often did you have discomfort or pain anywhere in your abdomen?

- Never
- Less than one day a month
- One day a month
- Two to three days a month
- One day a week
- More than one day a week
- Every day

For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?

- No
- Yes
- Does not apply because I have had the change in life (menopause) or I am a male

Have you had this discomfort or pain 6 months or longer?

- No
- Yes

How often did this discomfort or pain get better or stop after you had a bowel movement?

- Never or rarely
- Sometimes
- Often
- Most of the time
- Always

When this discomfort or pain started, did you have more frequent bowel movements?

- Never or rarely
- Sometimes
- Often
- Most of the time
- Always

When this discomfort or pain started, did you have less frequent bowel movements?

- Never or rarely
- Sometimes
- Often
- Most of the time
- Always

When this discomfort or pain

- Never or rarely

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started, were your stools (bowel movements) looser?

- Sometimes
- Often
- Most of the time
- Always

When this discomfort or pain started, how often did you have harder stools?

- Never or rarely
- Sometimes
- Often
- Most of the time
- Always

In the **last 3 months**, how often did you have hard or lumpy stools?

- Never or rarely
- About 25% of the time
- About 50% of the time
- About 75% of the time
- Always, 100% of the time

In the **last 3 months**, how often did you have loose, mushy or watery stools?

- Never or rarely
- About 25% of the time
- About 50% of the time
- About 75% of the time
- Always, 100% of the time

The following questions concern feeling of fullness after meals and pain or burning sensation in the stomach.

The next questions are related to the Rome 3 criteria for functional dyspepsia

- In the **last 3 months**, how often did you feel uncomfortably full after a regular- sized meal?
- Never
 - Less than one day a month
 - One day a month
 - Two to three days a month
 - One day a week
 - More than one day a week
 - Every day

The next questions only appeared if symptoms are experienced for one day a week or more

- Have you had this uncomfortable fullness after meals **6 months or longer**?
- No
 - Yes

- In the **last 3 months**, how often were you unable to finish a regular size meal?
- Never
 - Less than one day a month
 - One day a month
 - Two to three days a month
 - One day a week
 - More than one day a week
 - Every day

- Have you had this inability to finish regular size meals **6 months or longer**?
- No
 - Yes

- In the **last 3 months**, how often did you have pain or burning in the middle of your abdomen, above your belly button but not in your chest?
- Never
 - Less than one day a month
 - One day a month
 - Two to three days a month
 - One day a week
 - More than one day a week
 - Every day

- Have you had this pain or burning **6 months or longer**?
- No
 - Yes

We now proceed to the next category of questions that concern symptoms or discomforts from many parts of the body and how this affects your everyday life.

Have you within **the last 4 weeks** experienced any of the following symptoms or discomforts? (You may tick more than one box)

- Palpitations/heart pounding?
- Precordial discomfort?
- Breathlessness without exertion?
- Hot or cold sweats?
- Dry mouth?
- None of the above

To what extent did you experience that the following symptoms or discomfort interfered with your usual daily activities?

- Not relevant, as I did not experience any of the above symptoms or discomforts
- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

Have you within the **last 4 weeks** experienced any of the following symptoms or discomforts? (You may tick more than one box)

- Pains in arms or legs?
- Muscular aches or pains?
- Pains in the joints?
- Feeling of paresis or localized weakness?
- Pain moving from one place to another?
- Unpleasant numbness or tingling sensations?
- None of the above

To what extent did you experience that the following symptoms or discomfort interfered with your usual daily activities?

- Not relevant, as I did not experience any of the above symptoms or discomforts
- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

The following questions concern trembling of the hands and trembling of other parts of the body. Your answers may contribute to a larger understanding of what part trembling plays for the quality of life and for health in general.

Do you have problems with your hands trembling when you have to drink a cup or a glass or pour it?

- Yes
- No

Do you often experience that your hands, arms or the voice tremble and quiver without you being able to control it?

- Yes
- No

Has a doctor diagnosed you with:

- Familial tremor or essential tremor
- Parkinson's disease
- None of the above

Does anyone in your family have or have had the same type of trembling as you?

- Yes
- No
- I don't know

How many of your relatives suffer from a similar trembling?

- None
- 1
- 2
- 3
- More than 3
- I don't know

Consumption of alcohol can alter certain types of trembling. When you drink alcohol, do you then experience that you trembling:

- Decreases
- Worsens
- Remains unchanged
- I don't know, because I don't drink alcohol

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5 How old were you when your trembling began?
6
7 _____ years
8

9 Within **the last week**: If you sit at the table, do you have problems with drinking liquid from a glass?
10

- 11 I haven't had problems drinking from the glass
12 I can drink from the glass with one hand, but if I must avoid spilling, there may not be much
13 liquid in the glass.
14 I cannot drink from the glass with only one hand, but must use both hands.
15 I cannot drink from the glass even if I use both hands, but must use a straw.
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18 Has a doctor diagnosed one of the following causes for your trembling?
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- 20 I have not been diagnosed
21 Stroke
22 Dystonia
23 Medication
24 Other
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We have now finished asking about specific symptoms and discomforts. The next questions are of a general nature and concern your own perception of your health, your lifestyle, your management of problems and your worry about disease.

In general, would you say your health is:

- Excellent
- Very good
- Good
- Fair
- Poor

Do you feel well enough to do what you feel like doing?

- Yes, mostly
- Yes, sometimes
- No, almost never
- I don't know

The following questions are about physical activity, smoking and alcohol habits.

How do you rate your physical fitness?

- Very good
- Good
- Fair
- Not so good
- Poor

Do you smoke?

- Yes, every day
- Yes, at least once a week
- Yes, less than once a week
- No, I have stopped
- No, I have never smoked

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5 How often do you drink anything containing alcohol?
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- 8 Never
9 Once a month at the most
10 2-4 times a month
11 2-3 times a week
12 4 times a week or more
13

14
15 *The following questions only appeared in relation to a positive expression of smoking and/or*
16 *alcohol intake - by a leap structure in the electronic survey*
17

18 How many units do you drink per week on average? (One unit corresponds to a normal beer (33 cl),
19 a glass of wine (12 cl) or spirits (4 cl))
20

- 21 1-7 units/week
22 8-14 units/week
23 15-21 units/week
24 22-28 units/week
25 More than 29 units/week
26
27

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29 For how many years have you smoked?
30

31 I have smoked for approximately
32

33 _____ years (State the number of years in whole numbers)
34
35

36
37 How much do/did you smoke on average a day?
38

39 On average I smoke approximately
40

41 _____ cigarettes (state the approximate number of cigarettes in whole numbers)
42

43 _____ cheroots (state the approximate number of cheroots in whole numbers)
44

45 _____ cigars (state the approximate number of cigars in whole numbers)
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47 _____ pipes (state the approximate number of pipes in whole numbers)
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The following questions are about your height and weight.

How tall are you (without shoes)?

State your height in whole numbers measured in cm (e.g. 172)

_____cm

How much do you weigh (without clothes)?

State your weight in full kg (e.g. 67)

_____kg

The next questions are about your own concerns about your current health and whether other people have expressed concern about your current health.

To what extent are you **concerned** about your current health?

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

Has a doctor expressed concern about your current health?

- Yes
- No
- I don't know

Have people in your family or social network expressed concern about your current health?

- Yes
- No
- I don't know

The following questions are about your experiences with your own disease or in your social network.

Do you have any chronic disease, long-term effects after injuries, disability or other chronic disorder?

- Yes
- No
- I don't know

Have people in your immediate family (siblings, children, spouse, parents) had a serious illness?

- Yes
- No
- I don't know

Have people in your social network (friends, neighbours etc.) had a serious illness?

The following questions are about your contact with other people

How often are you in contact with friends, acquaintances or family that you do not live with? By contact is meant that you are together, talking with each other on the phone, writing to each other etc.

- Daily or almost daily
- 1-2 times a week
- 1 or more times a month
- Less than once a month
- Never
- I don't know

If you become ill and need help with practical things, can you count on help from others? (By others is meant people you do not live with)

- Yes, definitely
- Yes, maybe
- No

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4 Does it ever happen that you are alone, even if you want to be in the company of others?
5

- 6 Yes, often
7 Yes, once in a while
8 Yes, but rarely
9 No, never or almost never
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12 Do you have someone to talk to if you have problems or need support?
13

- 14 Yes, often
15 Yes, mostly
16 Yes, sometimes
17 No, never or almost never
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The questions on this page deal with how you usually act in relation to problems and disease. For each item, place a tick in the box that best fits what you think about yourself just now. The questions are written in 'I' form, and you place your tick depending on how much you agree/disagree.

	Agree completely	Tend to agree	Yes and no	Tend to disagree	Disagree completely
I say so if I am angry or sad.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I like to talk with few chosen people when things get too much for me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I make an active effort to find a solution to my problems.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Physical exercise is important to me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I think something positive could come out of my complaints/problems.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I firmly believe that my problems will decrease (and my situation improves).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I try to forget my problems.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I put my problems behind me by concentrating on something else.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I bury myself in work to keep my problems at a distance.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I often find it difficult to do something new.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am well on the way towards feeling I have given up.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I withdraw from other people when things get difficult.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The last group of questions concern your attitude to risk and your satisfaction with your life in general

Imagine that you unexpectedly inherited DKK 10,000 (approximately USD 2,000) from a distant relative. Subsequently you have the possibility of participating in a lottery with an equal chance of doubling the money or losing the money. That means that there is a 50% chance of you winning DKK 20,000 and a 50% chance of losing the DKK 10,000.

What do you choose?

- I choose to participate in the lottery
- I choose not to participate in the lottery
- I don't know

How do you normally react in relation to health and disease. Please tick one box for each statements to show how much you agree/disagree.

	Completely agree	Tend to agree	Yes and no	Tend to disagree	Completely disagree
I focus a lot on having a healthy behaviour and prefer to avoid risks that can affect my health.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If I experience symptoms, I generally count on it passing.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I do not like to take chances regarding my health and prefer to see my GP once too often than once too little.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

In the following we will inform you how old people at your age on average can expect to become. If you do not want the information, please tick the box.

How old are you?

____ Year

I don't want the information

Men, your age can expect to live, on average, until they are

____ Year

Women, your age can expect to live, on average, until they are

____ Year

Do you think that you will live longer or shorter than the average person?

- Longer than the average person
- Like the average person
- Shorter than the average person
- I don't know

On a scale from 0 till 10, where 0 means that you are very dissatisfied and 10 means that you are completely satisfied, how satisfied are you with your life in general.

Dissatisfied 0 1 2 3 4 5 6 7 8 9 10 Completely satisfied

Should you have any comments to the questionnaire, please feel free to list them here:

You have now finished the questionnaire.

Thank you very much for your reply.

If any of the questions have made you concerned about your health, we recommend that you contact your general practitioner.

Press exit to close the window

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4 **Supplementary File 2**

5
6 **List of the 36 symptoms from The Danish Symptom Cohort included in this study.**

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Symptoms	
Tiredness	Swollen legs
Night-time urination	Difficulty in emptying the bladder
Lack of energy	Frequent urination
Headache	Stress incontinence
Back pain	Shortness of breath
Abdominal bloating	Hoarseness
Memory problems	Urge incontinence
Abdominal pain	Loss of appetite
Coughing	Blood in stool/rectal bleeding
Concentration problems	Fever
Change in stool texture	Difficulty swallowing
Dizziness	Weight loss
Feeling unwell	Incontinence without stress/urge
Constipation	Pain/burning when urinating
Increase in waist circumference	Lump/swollen lymph node
Change in stool frequency	Black stool
Diarrhoea	Repeated vomiting
Nausea	Blood in urine

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Supplementary File 3

Symptom burden in multimorbidity. A Danish population study.

Definition of Multimorbidity

In this article multimorbidity was defined in to steps

- 1) Selection of diagnoses
- 2) Grouping of diagnoses according to different systems of the body

Selection of diagnoses

By this definition of multimorbidity we aim to have a simple and clinically relevant definition that at the same time is able to embrace complexity. Therefore, the definition is organized according to clinical picture rather than disease etiology. Diagnoses are considered on the basis of the following criteria:

- Diagnoses with high prevalence in the Danish population. (Risk factors are not included because of the low completeness of this information in the registers)
- Diagnoses relevant for general practice
- Diagnoses causing severe loss of function and/or loss of quality of life
- Diagnoses combined with reduced life expectancy
- Diagnoses resulting in a considerable treatment burden for the patient
- Chronic conditions (e.g. conditions that "require ongoing management over a period of years or decades"(1)).

Congenital diseases are not included.

Grouping of diagnoses according to different systems of the body

To have multimorbidity, a patient has to have a least one diagnosis from each of two different groups of diagnoses. E.g., if a patient has asthma and COPD this patient is categorized as lung sick instead of multimorbid. This choice rests on the assumption that it is more complex from an organizational and physiological point of view if the patient suffers from diagnoses from different bodily systems. Furthermore, concordant conditions (conditions with overlapping pathophysiology and management) are intended to be gathered in the same group (2). However, diabetes and cardiovascular diseases which could be expected to share both pathophysiology and risk factors are distributed over two different groups because they after all have different clinical manifestations and different treatments. The grouping of diagnoses and count of bodily system morbidity instead of single diagnoses may better relate to the way health care is organized as well as to the complexity and burden of morbidity (3).

See table A below for the selected diagnoses and bodily systems.

Background for redefining multimorbidity

In the literature the variation in how to define multimorbidity is large and the lack of consensus is evident (4-6). Most studies on multimorbidity include diagnoses based on the argument that the

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4 diagnoses are common (6). However, if only selecting diagnoses based on prevalence there would
5 be a risk of excluding many relevant conditions. In some studies authors selected a limited number
6 of diagnoses thoroughly (7), others included all chronic ICPC codes (8), or selected specific chronic
7 diagnoses from ICPC (9, 10). Others selected all existing ICD-10 codes without further explanation
8 (11) or let the diagnoses count for the chapter in the ICD-10 system they came from (12). Some
9 authors used indices, mainly developed for comorbidity, e.g. Charlson Comorbidity Index (CCI)
10 (13, 14) and Cumulative Illness Rating Scale (CIRS) (15-17).
11
12

13 We could have included all possible codes from the ICD-10 system. However, doing so would have
14 resulted in some rather small groups of multimorbidity combinations and diagnoses of less
15 importance in relation to prevalence and mortality. To use chapters from ICD-10 could be an
16 option, but some chapters are difficult to apply to the above stated selection criteria. Furthermore,
17 an already existing index could be used. However, CCI was primarily developed for studying one-
18 year mortality and we prefer a broader pallet of diagnoses than they suggest. On the other hand,
19 CIRS could be interesting because it takes severity in to account, nevertheless, this would require
20 access to medical records that were not available in the present register study.
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24 Tonelli et al. (18) suggested a panel of 30 conditions when doing research on multimorbidity and
25 their recommendation was based on 40 conditions included in a Scottish study (7). Of notice, most
26 diagnoses used in these two studies were also included in our study, with a few exceptions:
27 connective tissue disorders, chronic pain, hypertension, severe constipation, transient ischemic
28 attacks, diverticular disease of intestine, peripheral vascular disease, prostate disorders, chronic
29 sinusitis, learning disability, bronchiectasis and viral hepatitis. The reason for not including these
30 conditions is that some of them are acute rather than chronic, some of them are closely related to
31 other conditions covered by our diagnosis groups, and the validity of the coding in the national
32 registers is relatively low for some of the diagnoses mentioned above. In particular risk factors, like
33 hypertension, are underreported, leading to low completeness and a larger underestimation of these
34 conditions compared with others.
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37 By this definition complexity can be grasped, and prevalent diseases with significant impact on
38 patients' lives can be included, but without the need of including all possible ICD-10 codes.
39
40

41 Registers

42
43 The data was extracted from the following registers:
44

45 The Danish National Patient Registry (NPR) (19)

46 The Danish Psychiatric Central Research Register (PCRR) (20)

47 The Danish Cancer Register (CR) (21)
48
49

50 The registers contain information solely from the Danish hospital sector. Since we are interested in
51 general medicine it would be optimal to use ICPC codes from primary care. However, there is no
52 access to ICPC codes and there exist no registers validated for research with primary care data in
53 Denmark yet.
54
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56 All codes are based on International Classification of Diseases, 10th edition (ICD-10) and the earlier
57 8th edition (ICD-8). ICD is a well-established coding system used in 117 countries and translated
58 into 40 languages. The coding system is based on the medical specialties and hence coded in 21
59
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chapters. The coding system is reliable because of the long history, the many editions with continuous improvements and the involvement of medical experts (22). ICD-10 was introduced in Denmark 1 January 1994 and the present study contains both ICD-8 and ICD-10 diagnoses. NPR contains information on all inpatient care contacts in secondary care since 1977 and from 1995 also outpatient and emergency care contacts. Psychiatric diagnoses were included in NPR from 1995 (19). ICD-8 and ICD-10 are not comparable in every detail, and this has required a pragmatic approach when selecting diagnoses. In certain cases, one cannot distinguish between acute and chronic diagnoses in ICD-8, which sometimes leads to inclusion of the corresponding broader ICD-10 diagnoses with less relevant subcategories.

The validity and completeness of the registers vary. NPR constantly control data received from hospitals for incorrect codes and inconsistencies between sex and diagnoses in order to increase validity and completeness. Validation studies have shown variation in positive predictive value (PPV) between specialties and PPV showed to be higher when including three-number digits in ICD compared to five-number digits (23). In our definition of multimorbidity the three digit level is used as the highest level. Moreover, by using groups of conditions the need of high validity of some of the variables is reduced, e.g. whether atrial fibrillation is correctly coded as fibrillation or incorrectly as atrial flutter is of minor importance, since both conditions are included in the same diagnosis group: heart disease.

In our study we included diagnoses from a window ten years back in time from year 2000. Due to this choice some prevalent cases will be mistaken for being incident. The change from ICD-8 to ICD-10 in 1994 will probably lead to a higher number of incident cases around that year (23). Since 1994 is placed in the middle of our collection period a larger number of truly prevalent cases will probably be collected before 1994 and a larger number of cases falsely considered being incident in the year after. However, we do not necessarily consider prevalent cases less important than incident. Changes in diagnostic criteria and methods over time may also have affected how to interpret incidence (19).

For CR the validity is secured through daily control routines and yearly publications where checks for internal consistency are performed. Furthermore, the register uses several sources e.g. pathology to check their own information leading to high completeness of the register (21).

Validation studies on certain diagnoses have turned out well for PCRR (24, 25), but a systematic validation of the whole register has never been performed. There exist no private hospitals in Denmark for treating psychiatric patients therefore PCRR has high completeness. It has to be kept in mind, however, that the relatively large number of people treated for psychiatric diagnoses in primary care and at private practicing psychiatrists is not included in the register (20).

Diagnoses and organ systems included in the multimorbidity definition

	ICD-10	ICD-8
Lung diagnoses (LUNG)		
COPD	J44	490
Chronic bronchitis	J41-J42	491
Emphysema	J43	492
Asthma	J45-J46	493
Musculoskeletal diagnoses (MUSCULOSKELETAL)		

Rheumatic diagnoses / arthritis	L40.5, M05-M07	696.09, 712, 715
Arthrosis	M15-M17	713.00-09
Back diagnoses	M45, M47, M50-M51, M53-M54	712.49, 725, 728
Osteoporosis	M80-M82	723.09
Endocrine diagnoses (ENDO)		
Hypothyroidisme	E03	244
Hyperthyroidisme	E05	242
Diabetes	E10-E14	249-250
Mental health diagnoses (MENTAL HEALTH)		
Inclusion of all patients registered with a psychiatric diagnose in Psychiatric Central Register (except for patients having only Y - or Z-diagnoses) (26) and the following dementia and alcohol-related diagnoses from DNPR:		
Dementia	G30, G31.8-9, F00, F01, F02.0, F02.3, F03	290, 293
Alcohol	F10.1-F10.9	291, 303
Cancer (CANCER)		
All diagnoses from CR except C44, non-melanoma skin cancer.		
Neurological diagnoses (NEURO)		
Apoplexia cerebri (stroke)	I60-I64, I69	430-431, 433-434, 436-437
Multiple sclerosis	G35	340
Epilepsy	G40	345
Migraine	G43	346
Parkinson disease	G20	342
Gastrointestinal diagnoses (GASTRO)		
Dyspepsia	K30	536.90-91
Mb. Crohn and colitis ulcerosa	K50-K51	563
Colon irritabile	K58	564.19
Chronic liver disease	K70-K76	571-573
Chronic pancreatitis	K86.0, K86.1	577.10,577.11,577.19
Cardiovascular diagnoses (HEART)		
Ischemic heart disease	I20-I25	410-413
Heart failure and arrhythmia	I44.1-7, I45.2-9, I47-I50	427.09, 427.19, 427.23-24, 427.90-97, 428
Heart valve diagnoses	I05-I08, I34-I37	394-396, 397.00, 397.01, 424.00-19, 424.90-92
Genitourinary diagnoses (KIDNEY)		
Chronic kidney disease	N03-N05, N11-N12, N18-N19, Z49, Z99.2	581, 582, 583, 590.09, 590.15, 792
Urinary incontinence	N39.3-4	786.29
Endometriosis	N80	625.30-39

Diagnoses in sensory organs (SENSORY)		
Glaucoma	H40	375
Blindness and low vision	H54.0-54.3, H54.7	379.09, 379.19
Loss of hearing	H90.0, H90.2, H90.3, H90.5, H90.6, H90.8, H91	388, 389.09, 389.99
Psoriasis	L40	696.10, 696.19

Table A. In order to have multimorbidity the patient needs at least one diagnosis from two different bodily systems; for instance COPD from LUNG and multiple sclerosis from NEURO.

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Supplementary File 4 Prevalence of symptoms for the ten morbidity domains and for the group without diagnoses.

Symptom	Total		No diagnosis		LUNG		MUSKULO SKELETAL		ENDO		MENTAL HEALTH		CANCER		NEURO		GASTRO		HEART		KIDNEY		SENSORY	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	47452	100.0	30225	63.7	1595	3.4	6957	14.7	2214	4.7	471	1.0	2457	5.2	1679	3.5	2202	4.6	3878	8.2	1067	2.3	2614	5.5
No symptom	4224	8.9	2990	9.9	72	4.5	475	6.8	136	6.1	27	5.7	195	7.9	93	5.5	104	4.7	281	7.2	68	6.4	209	8.0
Tiredness	23252	49.0	14598	48.3	914	57.3	3422	49.2	1211	54.7	271	57.5	1226	49.9	965	57.5	1294	58.8	1896	48.9	632	59.2	1155	44.2
Night-time urination	23122	48.7	13136	43.5	919	57.6	4126	59.3	1353	61.1	291	61.8	1408	57.3	991	59.0	1265	57.4	2520	65.0	588	55.1	1646	63.0
Lack of energy	17623	37.1	10962	36.3	744	46.6	2671	38.4	888	40.1	229	48.6	943	38.4	728	43.4	1013	46.0	1477	38.1	483	45.3	894	34.2
Headache	16969	35.8	11294	37.4	558	35.0	2316	33.3	667	30.1	149	31.6	736	30.0	651	38.8	942	42.8	986	25.4	447	41.9	624	23.9
Back pain	15200	32.0	8689	28.7	617	38.7	3256	46.8	791	35.7	189	40.1	758	30.9	575	34.2	949	43.1	1373	35.4	444	41.6	900	34.4
Abdominal bloating	13951	29.4	8886	29.4	540	33.9	2024	29.1	662	29.9	112	23.8	665	27.1	507	30.2	931	42.3	1022	26.4	385	36.1	626	23.9
Memory problems	9365	19.7	5254	17.4	440	27.6	1639	23.6	533	24.1	186	39.5	578	23.5	566	33.7	644	29.2	912	23.5	300	28.1	656	25.1
Abdominal pain	9189	19.4	5491	18.2	395	24.8	1487	21.4	455	20.6	107	22.7	500	20.4	382	22.8	825	37.5	724	18.7	292	27.4	453	17.3
Coughing	8396	17.7	5033	16.7	598	37.5	1341	19.3	442	20.0	145	30.8	422	17.2	343	20.4	478	21.7	757	19.5	233	21.8	471	18.0
Concentration problems	8154	17.2	4940	16.3	339	21.3	1263	18.2	417	18.8	165	35.0	455	18.5	454	27.0	563	25.6	636	16.4	245	23.0	412	15.8
Change in stool texture	8055	17.0	4900	16.2	341	21.4	1257	18.1	414	18.7	105	22.3	418	17.0	323	19.2	565	25.7	687	17.7	240	22.5	427	16.3
Dizziness	7476	15.8	4138	13.7	355	22.3	1313	18.9	476	21.5	116	24.6	426	17.3	459	27.3	521	23.7	877	22.6	242	22.7	560	21.4
Feeling unwell	6903	14.6	4240	14.0	333	20.9	1065	15.3	387	17.5	92	19.5	350	14.2	303	18.0	503	22.8	547	14.1	214	20.1	332	12.7
Constipation	6847	14.4	3891	12.9	277	17.4	1207	17.3	389	17.6	78	16.6	426	17.3	352	21.0	449	20.4	695	17.9	256	24.0	402	15.4

1																									
2	Increase in waist circumference	6223	13.1	3774	12.5	279	17.5	985	14.2	295	13.3	70	14.9	308	12.5	238	14.2	428	19.4	514	13.3	212	19.9	320	12.2
3																									
4	Change in stool frequency	6107	12.9	3634	12.0	262	16.4	999	14.4	345	15.6	74	15.7	349	14.2	247	14.7	444	20.2	542	14.0	189	17.7	357	13.7
5																									
6	Diarrhoea	6020	12.7	3700	12.2	276	17.3	925	13.3	316	14.3	77	16.3	320	13.0	225	13.4	502	22.8	464	12.0	171	16.0	260	9.9
7																									
8	Nausea	5884	12.4	3509	11.6	269	16.9	941	13.5	334	15.1	92	19.5	350	14.2	280	16.7	446	20.3	480	12.4	212	19.9	258	9.9
9																									
10	Swollen legs	5852	12.3	2634	8.7	369	23.1	1481	21.3	530	23.9	89	18.9	456	18.6	344	20.5	405	18.4	913	23.5	275	25.8	498	19.1
11																									
12	Difficulty in emptying the bladder	5542	11.7	2765	9.1	292	18.3	1146	16.5	358	16.2	102	21.7	361	14.7	347	20.7	408	18.5	751	19.4	216	20.2	505	19.3
13																									
14	Frequent urination	4972	10.5	2641	8.7	228	14.3	970	13.9	327	14.8	106	22.5	342	13.9	298	17.7	325	14.8	632	16.3	162	15.2	398	15.2
15																									
16	Stress incontinence	4639	9.8	2511	8.3	253	15.9	991	14.2	298	13.5	50	10.6	350	14.2	200	11.9	297	13.5	415	10.7	279	26.1	312	11.9
17																									
18	Shortness of breath	3782	8.0	1670	5.5	659	41.3	861	12.4	264	11.9	105	22.3	214	8.7	218	13.0	304	13.8	641	16.5	140	13.1	323	12.4
19																									
20	Hoarseness	3630	7.7	2000	6.6	291	18.2	630	9.1	231	10.4	59	12.5	220	9.0	196	11.7	236	10.7	417	10.8	124	11.6	264	10.1
21																									
22	Urge incontinence	2976	6.3	1296	4.3	162	10.2	766	11.0	234	10.6	61	13.0	227	9.2	219	13.0	216	9.8	454	11.7	193	18.1	331	12.7
23																									
24	Loss of appetite	2902	6.1	1609	5.3	182	11.4	513	7.4	190	8.6	95	20.2	201	8.2	192	11.4	247	11.2	288	7.4	92	8.6	174	6.7
25																									
26	Blood in stool/rectal bleeding	2141	4.5	1343	4.4	89	5.6	300	4.3	93	4.2	26	5.5	105	4.3	87	5.2	160	7.3	183	4.7	58	5.4	114	4.4
27																									
28	Fever	1805	3.8	1184	3.9	76	4.8	258	3.7	80	3.6	20	4.2	81	3.3	65	3.9	108	4.9	115	3.0	48	4.5	80	3.1
29																									
30	Difficulty swallowing	1665	3.5	843	2.8	111	7.0	321	4.6	122	5.5	36	7.6	117	4.8	123	7.3	156	7.1	207	5.3	66	6.2	124	4.7
31																									
32	Weight loss	1405	3.0	734	2.4	83	5.2	279	4.0	99	4.5	39	8.3	112	4.6	107	6.4	125	5.7	167	4.3	41	3.8	90	3.4
33																									
34	Incontinence without	1136	2.4	441	1.5	74	4.6	293	4.2	92	4.2	37	7.9	111	4.5	88	5.2	110	5.0	165	4.3	137	12.8	141	5.4
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stress/urge																									
Pain/burning when urinating	971	2.0	483	1.6	48	3.0	211	3.0	71	3.2	10	2.1	83	3.4	55	3.3	86	3.9	118	3.0	54	5.1	76	2.9	
Lump/swollen lymph node	753	1.6	456	1.5	35	2.2	117	1.7	39	1.8	12	2.5	63	2.6	26	1.5	47	2.1	58	1.5	29	2.7	30	1.1	
Black stool	725	1.5	421	1.4	46	2.9	111	1.6	48	2.2	16	3.4	39	1.6	33	2.0	58	2.6	69	1.8	15	1.4	47	1.8	
Repeated vomiting	586	1.2	316	1.0	34	2.1	115	1.7	46	2.1	27	5.7	41	1.7	34	2.0	54	2.5	53	1.4	29	2.7	32	1.2	
Blood in urine	264	0.6	117	0.4	16	1.0	70	1.0	19	0.9	4	0.8	17	0.7	18	1.1	14	0.6	47	1.2	22	2.1	21	0.8	
Coughing up blood	58	0.1	35	0.1	6	0.4	8	0.1	4	0.2	none	none	few		few		few		6	0.2	few	0	4	0.2	
Blood in vomit	47	0.1	27	0.1	4	0.3	10	0.1	6	0.3	few		few		few		7	0.3	5	0.1	none	none	few		

LUNG = lung diagnoses, MUSCULOSKELETAL = musculoskeletal diagnoses, ENDO = endocrine diagnoses, MENTAL HEALTH = mental health diagnoses, CANCER = cancer diagnoses, NEURO = neurological diagnoses, GASTRO = gastrointestinal diagnoses, HEART = cardiovascular diagnoses, KIDNEY = genitourinary diagnoses, SENSORY = sensory organ diagnoses

Supplementary Table A. Mean number of symptoms for each morbidity domain with number of symptoms, interference with usual daily activities and concern of the symptoms.

	Number of symptoms (mean number)	Interference with usual daily activities (mean impairment score) ^α	Concern about symptoms (mean worry score) [×]
LUNG	7.3	2.6	2.0
MUSCULOSKELETAL	6.0	2.3	1.7
ENDO	6.1	2.3	1.7
MENTAL HEALTH	7.4	2.8	2.2
CANCER	5.6	2.1	1.5
NEURO	6.8	2.4	1.8
GASTRO	7.4	2.5	1.9
HEART	5.9	2.2	1.7
KIDNEY	7.3	2.5	1.9
SENSORY	5.5	2.1	1.3
No diagnosis	4.8	1.7	1.2
Total	5.2	1.9	1.3

LUNG = lung diagnoses. MUSCULOSKELETAL = musculoskeletal diagnoses. ENDO = endocrine diagnoses. MENTAL HEALTH = psychiatric diagnoses. CANCER = cancer diagnoses. NEURO = neurological diagnoses. GASTRO = gastrointestinal diagnoses. HEART = cardiovascular diagnoses. KIDNEY = genitourinary diagnoses. SENSORY = sensory organ diagnoses.

^α Mean activity score. Derived from the question: ‘within the last 4 weeks: to what extent did you experience that the following symptoms or discomfort interfered your usual daily activities?’ with the following response categories: not at all, slightly, moderate, quite a bit, extremely. The response categories were transformed in to a numeric 4 digit scale where e.g. 4 is worse than 2.

[×] Mean worry score. Derived from the question: ‘within the last 4 weeks: to what extent were you concerned about the following symptoms or discomfort?’ with the following response categories: not at all, slightly, moderate, quite a bit, extremely. The response categories were transformed in to a numeric 4 digit scale where e.g. 4 is worse than 2.

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Supplementary Table B. Mean difference in number of symptoms (with 95%CI) for the respondents having the indicated combination of morbidity domains relative to the respondent having no morbidity.

	LUNG	MUSCULO SKELETAL	ENDO	MENTAL HEALTH	CANCER	NEURO	GASTRO	HEART	KIDNEY	SENSORY
LUNG	1.88 (1.57 ; 2.18)	2.00 (1.43 ; 2.57)	2.03 (0.69 ; 3.37)	7.42 (4.99 ; 9.85)	1.00 (-0.45 ; 2.45)	2.94 (1.34 ; 4.54)	2.94 (1.89 ; 3.98)	2.82 (2.03 ; 3.61)	2.97 (0.91 ; 5.02)	2.70 (1.49 ; 3.92)
MUSCULO SKELETAL		0.81 (0.67 ; 0.94)	1.29 (0.76 ; 1.81)	3.05 (1.64 ; 4.45)	1.01 (0.52 ; 1.5)	1.84 (1.22 ; 2.45)	2.94 (2.47 ; 3.41)	2.00 (1.63 ; 2.38)	2.93 (2.16 ; 3.70)	1.44 (1.03 ; 1.84)
ENDO			0.65 (0.38 ; 0.91)	0.46 (-1.46 ; 2.38)	0.86 (-0.13 ; 1.84)	2.36 (1.21 ; 3.51)	1.92 (0.90 ; 2.93)	1.63 (1.10 ; 2.17)	1.58 (0.20 ; 2.96)	0.77 (-0.22 ; 1.76)
MENTAL HEALTH				2.02 (1.41 ; 2.63)	3.90 (1.47 ; 6.33)	1.08 (-0.73 ; 2.89)	2.58 (1.15 ; 4.01)	2.46 (0.78 ; 4.14)	1.89 (-2.54 ; 6.33)	3.42 (0.29 ; 6.56)
CANCER					0.36 (0.14 ; 0.59)	1.70 (0.79 ; 2.62)	2.70 (1.68 ; 3.71)	2.15 (1.50 ; 2.8)	-0.59 (-1.94 ; 0.77)	2.15 (1.33 ; 2.97)
NEURO						1.08 (0.78 ; 1.38)	2.55 (1.28 ; 3.81)	2.12 (1.37 ; 2.86)	2.95 (1.41 ; 4.48)	1.44 (0.36 ; 2.52)
GASTRO							1.96 (1.71 ; 2.21)	2.50 (1.76 ; 3.23)	4.44 (3.19 ; 5.68)	1.60 (0.48 ; 2.72)
HEART								0.89 (0.68 ; 1.09)	1.57 (0.60 ; 2.53)	1.07 (0.49 ; 1.65)
KIDNEY									1.83 (1.47 ; 2.19)	3.05 (1.44 ; 4.65)
SENSORY										0.71 (0.47 ; 0.94)

Supplementary Table C. Excess mean number of symptoms (with 95%CI) for the respondents having the indicated combination of morbidity domains relative to the added mean number of symptoms from two respondents having each morbidity of the combination separately.

	LUNG	MUSCULO SKELETAL	ENDO	MENTAL HEALTH	CANCER	NEURO	GASTRO	HEART	KIDNEY	SENSORY
LUNG		-0.68 (-1.35 ; -0.02)	-0.50 (-1.89 ; 0.9)	3.52 (1.00 ; 6.05)	-1.24 (-2.74 ; 0.26)	-0.02 (-1.67 ; 1.64)	-0.90 (-2.02 ; 0.22)	0.06 (-0.81 ; 0.93)	-0.74 (-2.85 ; 1.37)	0.12 (-1.16 ; 1.40)
MUSCULO SKELETAL			-0.17 (-0.77 ; 0.43)	0.22 (-1.32 ; 1.75)	-0.16 (-0.71 ; 0.39)	-0.05 (-0.75 ; 0.64)	0.17 (-0.38 ; 0.72)	0.31 (-0.14 ; 0.76)	0.29 (-0.57 ; 1.15)	-0.08 (-0.56 ; 0.41)
ENDO				-2.21 (-4.24 ; -0.18)	-0.16 (-1.20 ; 0.89)	0.63 (-0.58 ; 1.85)	-0.69 (-1.77 ; 0.39)	0.10 (-0.53 ; 0.73)	-0.90 (-2.35 ; 0.56)	-0.59 (-1.63 ; 0.46)
MENTAL HEALTH					1.51 (-1.00 ; 4.03)	-2.02 (-3.96 ; -0.09)	-1.40 (-2.97 ; 0.17)	-0.45 (-2.24 ; 1.35)	-1.96 (-6.45 ; 2.53)	0.69 (-2.51 ; 3.90)
CANCER						0.26 (-0.73 ; 1.24)	0.37 (-0.70 ; 1.44)	0.90 (0.18 ; 1.62)	-2.78 (-4.20 ; -1.36)	1.08 (0.19 ; 1.96)
NEURO							-0.50 (-1.82 ; 0.83)	0.15 (-0.68 ; 0.98)	0.03 (-1.57 ; 1.64)	-0.35 (-1.49 ; 0.79)
GASTRO								-0.35 (-1.15 ; 0.46)	0.65 (-0.68 ; 1.97)	-1.07 (-2.24 ; 0.10)
HEART									-1.15 (-2.20 ; -0.10)	-0.52 (-1.18 ; 0.13)
KIDNEY										0.51 (-1.15 ; 2.17)
SENSORY										

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Supplementary Table D. Mean difference in impairment score (with 95% CI) for the respondents having the indicated combination of morbidity domains relative to the respondent having no morbidity.

	LUNG	MUSCULO SKELETAL	ENDO	MENTAL HEALTH	CANCER	NEURO	GASTRO	HEART	KIDNEY	SENSORY
LUNG	0.54 (0.44 ; 0.64)	0.84 (0.66 ; 1.03)	0.70 (0.27 ; 1.13)	1.02 (0.24 ; 1.81)	0.61 (0.13 ; 1.08)	0.87 (0.36 ; 1.39)	0.65 (0.32 ; 0.99)	0.77 (0.51 ; 1.02)	0.54 (-0.13 ; 1.20)	0.80 (0.40 ; 1.21)
MUSCULO SKELETAL		0.37 (0.32 ; 0.41)	0.45 (0.28 ; 0.62)	1.11 (0.66 ; 1.56)	0.39 (0.23 ; 0.55)	0.54 (0.34 ; 0.74)	0.73 (0.58 ; 0.89)	0.66 (0.54 ; 0.78)	0.99 (0.74 ; 1.24)	0.63 (0.50 ; 0.76)
ENDO			0.23 (0.14 ; 0.32)	0.51 (-0.13 ; 1.15)	0.24 (-0.08 ; 0.55)	0.88 (0.51 ; 1.25)	0.44 (0.11 ; 0.77)	0.56 (0.39 ; 0.73)	0.27 (-0.18 ; 0.71)	0.59 (0.27 ; 0.91)
MENTAL HEALTH				0.75 (0.56 ; 0.95)	1.07 (0.28 ; 1.85)	0.75 (0.15 ; 1.35)	0.94 (0.48 ; 1.40)	1.01 (0.47 ; 1.55)	1.43 (0.00 ; 2.86)	1.69 (0.59 ; 2.80)
CANCER					0.15 (0.08 ; 0.23)	0.58 (0.29 ; 0.88)	0.68 (0.35 ; 1.01)	0.53 (0.32 ; 0.74)	0.04 (-0.40 ; 0.48)	0.74 (0.47 ; 1.01)
NEURO						0.38 (0.28 ; 0.48)	0.61 (0.20 ; 1.02)	0.77 (0.53 ; 1.01)	0.50 (-0.01 ; 1.02)	0.58 (0.23 ; 0.93)
GASTRO							0.49 (0.41 ; 0.57)	0.60 (0.36 ; 0.84)	0.80 (0.40 ; 1.21)	0.70 (0.33 ; 1.06)
HEART								0.25 (0.19 ; 0.32)	0.34 (0.03 ; 0.66)	0.33 (0.14 ; 0.52)
KIDNEY									0.49 (0.37 ; 0.61)	1.03 (0.50 ; 1.56)
SENSORY										0.26 (0.19 ; 0.34)
									0 (0 ; 0)	

Supplementary Table E. Excess mean impairment score (with 95%CI) for the respondents having the indicated combination of morbidity domains relative to the added mean impairment score from two respondents having each morbidity of the combination separately.

	LUNG	MUSCULO SKELETAL	ENDO	MENTAL HEALTH	CANCER	NEURO	GASTRO	HEART	KIDNEY	SENSORY
LUNG		-0.07 (-0.28 ; 0.15)	-0.07 (-0.53 ; 0.38)	-0.28 (-1.09 ; 0.54)	-0.09 (-0.58 ; 0.40)	-0.05 (-0.59 ; 0.48)	-0.38 (-0.74 ; -0.02)	-0.03 (-0.31 ; 0.25)	-0.49 (-1.18 ; 0.19)	0.00 (-0.43 ; 0.43)
MUSCULO SKELETAL			-0.14 (-0.34 ; 0.05)	-0.01 (-0.50 ; 0.49)	-0.13 (-0.31 ; 0.05)	-0.20 (-0.43 ; 0.02)	-0.12 (-0.30 ; 0.06)	0.04 (-0.10 ; 0.19)	0.14 (-0.14 ; 0.42)	0.00 (-0.16 ; 0.16)
ENDO				-0.47 (-1.14 ; 0.21)	-0.15 (-0.49 ; 0.19)	0.27 (-0.12 ; 0.66)	-0.28 (-0.63 ; 0.07)	0.08 (-0.13 ; 0.28)	-0.45 (-0.92 ; 0.02)	0.10 (-0.24 ; 0.44)
MENTAL HEALTH					0.16 (-0.65 ; 0.97)	-0.38 (-1.02 ; 0.26)	-0.30 (-0.81 ; 0.21)	0.01 (-0.57 ; 0.59)	0.19 (-1.26 ; 1.64)	0.68 (-0.45 ; 1.81)
CANCER						0.05 (-0.27 ; 0.37)	0.03 (-0.31 ; 0.38)	0.13 (-0.10 ; 0.36)	-0.60 (-1.06 ; -0.14)	0.32 (0.04 ; 0.61)
NEURO							-0.26 (-0.68 ; 0.17)	0.14 (-0.13 ; 0.41)	-0.36 (-0.90 ; 0.18)	-0.06 (-0.43 ; 0.31)
GASTRO								-0.14 (-0.40 ; 0.12)	-0.18 (-0.60 ; 0.25)	-0.05 (-0.44 ; 0.33)
HEART									-0.40 (-0.74 ; -0.05)	-0.18 (-0.39 ; 0.03)
KIDNEY										0.28 (-0.27 ; 0.83)
SENSORY										

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Supplementary Table F. Mean difference in worry score (with 95%CI) for the respondents having the indicated combination of morbidity domains relative to the respondent having no morbidity.

	LUNG	MUSCULO SKELETAL	ENDO	MENTAL HEALTH	CANCER	NEURO	GASTRO	HEART	KIDNEY	SENSORY
LUNG	0.52 (0.42 ; 0.62)	0.65 (0.46 ; 0.83)	0.91 (0.47 ; 1.34)	0.95 (0.16 ; 1.74)	0.53 (0.05 ; 1.01)	0.93 (0.41 ; 1.45)	0.65 (0.31 ; 0.99)	0.79 (0.53 ; 1.04)	0.19 (-0.47 ; 0.86)	0.94 (0.52 ; 1.36)
MUSCULO SKELETAL		0.36 (0.32 ; 0.4)	0.41 (0.24 ; 0.58)	1.19 (0.73 ; 1.64)	0.40 (0.24 ; 0.56)	0.47 (0.27 ; 0.67)	0.71 (0.56 ; 0.87)	0.74 (0.62 ; 0.87)	0.89 (0.64 ; 1.14)	0.60 (0.47 ; 0.73)
ENDO			0.22 (0.14 ; 0.31)	0.41 (-0.23 ; 1.06)	0.15 (-0.17 ; 0.47)	0.89 (0.52 ; 1.26)	0.41 (0.07 ; 0.75)	0.45 (0.28 ; 0.63)	0.08 (-0.37 ; 0.53)	0.59 (0.27 ; 0.91)
MENTAL HEALTH				0.67 (0.47 ; 0.87)	1.68 (0.90 ; 2.47)	0.73 (0.12 ; 1.33)	1.14 (0.68 ; 1.60)	0.86 (0.32 ; 1.41)	1.31 (-0.13 ; 2.75)	1.13 (0.02 ; 2.25)
CANCER					0.08 (0.01 ; 0.16)	0.74 (0.44 ; 1.04)	0.42 (0.09 ; 0.75)	0.50 (0.29 ; 0.72)	-0.02 (-0.46 ; 0.42)	0.72 (0.45 ; 0.99)
NEURO						0.29 (0.19 ; 0.39)	0.51 (0.10 ; 0.92)	0.64 (0.39 ; 0.88)	0.16 (-0.37 ; 0.69)	0.54 (0.19 ; 0.89)
GASTRO							0.46 (0.37 ; 0.54)	0.51 (0.26 ; 0.75)	0.71 (0.30 ; 1.12)	0.59 (0.22 ; 0.96)
HEART								0.25 (0.18 ; 0.31)	0.19 (-0.13 ; 0.51)	0.38 (0.19 ; 0.57)
KIDNEY									0.46 (0.34 ; 0.58)	0.71 (0.17 ; 1.24)
SENSORY										0.28 (0.20 ; 0.36)

Supplementary Table G. Excess mean worry score (with 95% CI) for the respondents having the indicated combination of morbidity domains relative to the added mean worry score from two respondents having each morbidity of the combination separately.

	LUNG	MUSCULO SKELETAL	ENDO	MENTAL HEALTH	CANCER	NEURO	GASTRO	HEART	KIDNEY	SENSORY
LUNG		-0.24 (-0.46 ; -0.02)	0.16 (-0.30 ; 0.61)	-0.24 (-1.06 ; 0.58)	-0.08 (-0.58 ; 0.42)	0.12 (-0.42 ; 0.65)	-0.33 (-0.69 ; 0.03)	0.02 (-0.27 ; 0.30)	-0.79 (-1.48 ; -0.11)	0.13 (-0.30 ; 0.57)
MUSCULO SKELETAL			-0.18 (-0.38 ; 0.02)	0.16 (-0.34 ; 0.66)	-0.05 (-0.23 ; 0.13)	-0.18 (-0.41 ; 0.05)	-0.11 (-0.29 ; 0.07)	0.13 (-0.01 ; 0.28)	0.06 (-0.22 ; 0.34)	-0.04 (-0.20 ; 0.12)
ENDO				-0.48 (-1.16 ; 0.20)	-0.16 (-0.50 ; 0.18)	0.37 (-0.02 ; 0.77)	-0.27 (-0.63 ; 0.09)	-0.02 (-0.23 ; 0.19)	-0.61 (-1.08 ; -0.14)	0.09 (-0.25 ; 0.43)
MENTAL HEALTH					0.93 (0.11 ; 1.75)	-0.23 (-0.87 ; 0.42)	0.02 (-0.50 ; 0.53)	-0.06 (-0.64 ; 0.53)	0.18 (-1.28 ; 1.64)	0.18 (-0.95 ; 1.32)
CANCER						0.37 (0.04 ; 0.69)	-0.12 (-0.47 ; 0.23)	0.17 (-0.06 ; 0.41)	-0.57 (-1.03 ; -0.10)	0.35 (0.06 ; 0.64)
NEURO							-0.23 (-0.66 ; 0.20)	0.10 (-0.17 ; 0.37)	-0.59 (-1.15 ; -0.04)	-0.03 (-0.41 ; 0.34)
GASTRO								-0.20 (-0.46 ; 0.07)	-0.21 (-0.64 ; 0.22)	-0.15 (-0.53 ; 0.24)
HEART									-0.52 (-0.87 ; -0.17)	-0.15 (-0.36 ; 0.07)
KIDNEY										-0.04 (-0.59 ; 0.51)
SENSORY										

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	<p>(a) Indicate the study's design with a commonly used term in the title or the abstract</p> <p>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</p> <p>(a) <i>Symptom burden in multimorbidity. A population-based combined questionnaire and registry study from Denmark</i></p> <p>(b) <i>Please see page 2.</i></p>
Background/rationale	2	<p>Explain the scientific background and rationale for the investigation being reported</p> <p><i>Please see page 4, the "Introduction".</i></p>
Objectives	3	<p>State specific objectives, including any prespecified hypotheses</p> <p><i>Please see page 4.</i></p> <p><i>The aim of this study was to explore symptom burden in patients with one of ten morbidities compared with symptom burden in patients with multimorbidity. We hypothesised that symptom burden in multimorbidity was additive, ie that symptoms in patients with multimorbidity was equivalent to the sum of the symptoms attributable to the single morbidities.</i></p>
Methods		
Study design	4	<p>Present key elements of study design early in the paper</p> <p><i>Stated on page 4:</i> <i>"Study design and population"</i> <i>The study was a longitudinal cohort study. Participants were from the Danish Symptom Cohort, a population-based study conducted in Denmark in June-December, 2012.</i></p>
Setting	5	<p>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</p> <p><i>Stated on page 4 in the section "Study design and population"</i> <i>People invited to participate in the study were living in Denmark on 1st January, 2012 (baseline). Of 100,000 adults (≥20 years) randomly selected from the general Danish population, 95,253 were eligible and invited to participate (Figure 1). Of these, 49,706 (52.2%) completed the study questionnaire (Supplementary File 1).(15)</i></p> <p><i>Furthermore, stated on page 6 in the section "Multimorbidity"</i> <i>"Information on diagnoses was retrieved from the nationwide health registries in the 10-year period preceding baseline (1st January, 2002-31st December, 2011). Participants were excluded if they had not been living continuously in Denmark during this 10-year period. Chronic disease diagnoses were grouped into ten domains: LUNG, MUSCULOSKELETAL, ENDOCRINE, MENTAL HEALTH, CANCER, NEUROLOGICAL, GASTROINTESTINAL, CARDIOVASCULAR, GENITOURINARY and SENSORY. In each domain, relevant diagnoses from the International Classification of Diseases, 10th edition (ICD-10) were included (Supplementary File 3)."</i></p>
Participants	6	<p>(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p>

(b) For matched studies, give matching criteria and number of exposed and unexposed

(a) Stated on page 4 and 5 in the section “Study design and population”

(b) Not applicable.

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
		<i>Please see page 5-6 and the sections “Symptom data” and “Symptom burden” and “Multimorbidity” and Table 1.</i>
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
		<i>Please see page 4-6 in the Methods section.</i>
		<i>“All Danish born and immigrant populations in Denmark have a unique personal identification number in the Danish Civil Registration System.(16) The register contains information about age, sex, vital status, etc, and enables information from different Danish registries to be linked. Information on diagnoses leading to either inpatient or outpatient care in the hospital sector was collected from the Danish National Patient Register,(17) the Danish Cancer Registry,(18) and the Danish Psychiatric Central Research Register.(19) Thus, only diagnoses from secondary care were included in the study. Information on education,(20) work status,(21) family income,(22) assets (banks, stocks, bonds, and housing),(22) degree of urbanisation, and cohabitation status was obtained from the nationwide registries at baseline.”</i>
		<i>“Information on diagnoses was retrieved from the nationwide health registries in the 10-year period preceding baseline (1st January, 2002-31st December, 2011). Participants were excluded if they had not been living continuously in Denmark during this 10-year period.”</i>
		<i>Information on symptom burden is retrieved from the questionnaire.</i>
Bias	9	Describe any efforts to address potential sources of bias
		<i>Please see page 4-6 in the “Methods” section and page 16 the section “Strengths and limitations”</i>
Study size	10	Explain how the study size was arrived at
		<i>Please see page 4.</i>
		<i>“People invited to participate in the study were living in Denmark on 1st January, 2012 (baseline). Of 100,000 adults (≥20 years) randomly selected from the general Danish population, 95,253 were eligible and invited to participate (Figure 1). Of these, 49,706 (52.2%) completed the study questionnaire (Supplementary File 1).(15)”</i>
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
		<i>Please see Table 1 for baseline information.</i>
		<i>We had four quantitative variables: age, income, assets, and alcohol consumption. Income and assets were divided into quartiles.</i>
		<i>Age was divided into four groups, younger and older adults in the working age and younger and older among the retired adults.</i>
		<i>Alcohol was divided in moderate and high drinking for men and women.</i>

1	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
2			(b) Describe any methods used to examine subgroups and interactions
3			(c) Explain how missing data were addressed
4			(d) If applicable, explain how loss to follow-up was addressed
5			(e) Describe any sensitivity analyses
6			
7			
8			<i>Please see page 7, the section “Statistical analysis”</i>
9			<i>Please also see page 5 the section “Symptom data”</i>
10			
11			
12			
13	Results		
14	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
15			(b) Give reasons for non-participation at each stage
16			(c) Consider use of a flow diagram
17			
18			<i>Please see the “Result” section (page 8) and Figure 1.</i>
19			
20			
21			
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23			
24			
25	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
26			(b) Indicate number of participants with missing data for each variable of interest
27			(c) Summarise follow-up time (eg, average and total amount)
28			
29			
30			
31			<i>(a) Please see Table 1.</i>
32			<i>(b) See the section “Symptom data” page 5.</i>
33			<i>(c) Not done</i>
34			
35			
36			
37	Outcome data	15*	Report numbers of outcome events or summary measures over time
38			<i>Please see Table 2, Supplementary file 4 and Supplementary Table A.</i>
39			
40			
41	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
42			
43			
44			
45			<i>We adjusted for age, sex, socioeconomic status (highest completed education, income, assets, and work status), urbanization degree, cohabitation status, smoking and alcohol. They were included because we believe they can affect the relation between diagnoses and symptoms, as well as how symptoms are interpreted.</i>
46			<i>Please see Table 1, Figure 2, 3 and 4, and Supplementary Tables A-G.</i>
47			
48			(b) Report category boundaries when continuous variables were categorized
49			
50			
51			<i>(b) Please see Table 1</i>
52			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
53			
54			<i>(c) Not done</i>
55			
56	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
57			<i>Please see page 7 “Statistical analyses”</i>
58			
59			
60			

Discussion <i>Please see the discussion section, page 14-17.</i>		
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
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 <i>Please see page 18.</i>

*Give information separately for exposed and unexposed groups.

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 <http://www.strobe-statement.org>.