Multimorbidity Healthcare Expenditure in Belgium: A Four-Year Analysis (COMORB study)

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Research Article

Keywords: cost analysis, healthcare expenditure, multimorbidity, chronic diseases, noncommunicable diseases, disease interaction, integrated care, Belgium

Posted Date: November 29th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3548148/v1

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Version of Record: A version of this preprint was published at Health Research Policy and Systems on March 22nd, 2024. See the published version at https://doi.org/10.1186/s12961-024-01113-x.
Abstract

Background

The complex management of health needs in multimorbid patients, alongside limited cost data, presents challenges in developing cost-effective patient-care pathways. We estimated the costs of managing 171 dyads and 969 triads in Belgium, taking into account the influence of morbidity interactions on costs.

Methods

We followed a retrospective longitudinal study design, using the linked Belgian Health Interview Survey 2018 and the administrative claim database 2017–2020 hosted by the Intermutualistic Agency. We included people aged 15 and older, who had complete profiles (N = 9,753). Applying a system costing perspective, average annual direct cost per person per dyad/triad was presented in 2022 Euro and comprised mainly of direct medical costs. We developed mixed models to analyze the impact of single chronic conditions, dyads, and triads on healthcare costs, considering two/three-way interactions within dyads/triads, key cost determinants, and clustering at the household level.

Results

People with multimorbidity constituted nearly half of the study population and their total healthcare cost constituted around three-quarters of the healthcare cost of the study population. The most common dyad, Arthropathies + Dorsopathies, with 14% prevalence rate, accounted for 11% of the total national health expenditure. The most frequent triad, Arthropathies + Dorsopathies + Hypertension, with 5% prevalence rate, contributed 5%. The average annual direct costs per person for dyads and triads were €3,515 (95%CI:3,093 – 3,937) and €4,592 (95%CI:3,920-5,264), respectively. Dyads and triads associated with cancer, diabetes, chronic fatigue, and genitourinary problems incurred the highest costs. In most cases, the cost associated with multimorbidity was lower or not substantially different from the combined cost of the same conditions observed in separate patients.

Conclusion

Prevalent morbidity combinations, rather than high-cost ones, made a greater contribution to total national health expenditure. Our study contributes to the sparse evidence on this topic globally and in Europe, with the aim of improving cost-effective care for patients with diverse needs.

Background

A new challenge has arisen in global health. Traditionally, approaches to morbidity management have used classifications such as communicable/non-communicable and chronic/acute, we today face a more complex phenomenon as an increasing number of people across the globe live with multimorbidity(1). The management of health needs in these patients is creating challenges in the development of cost-effective patient-care pathways, posing heavy economic burdens on households, health systems, and societies(2).

Multimorbidity is often defined as the co-occurrence of two or more chronic conditions in the same person(3). Comparing multimorbidity rates between studies is challenging as there are significant differences in the populations and the methodological choices made. However, the standardized prevalence rate of multimorbidity has been shown to rise significantly for all sexes and age groups between 2000 and 2015 in Belgium(4). The increase in multimorbidity is frequently attributed to extended life expectancy and improvements in the management of chronic illnesses(5). In Belgium, however,
multimorbidity is rising fast among younger age groups. For those under 50 years of age, the standardized prevalence rate of multimorbidity doubled between 2000 and 2015(4).

While clinico-pathological research is ongoing, it is becoming more apparent how multimorbidity affects healthcare systems and societies as a whole(6, 7). The complexity of managing multiple conditions often requires a more intricate and coordinated approach from healthcare providers, increasing the demand for specialized and integrated care services(8). This, in turn, places strains on healthcare systems, potentially leading to resource allocation dilemmas and access disparities(9). The increased treatments, medications, and healthcare visits can result in escalated healthcare costs(10). Workforce productivity may decline, while caregiving demands intensify, impacting both the economy and social support networks(11).

Multimorbidity presents significant challenges for healthcare systems across the board, including high-income countries like Belgium, where a fragmented care system can exacerbate the issues of increased healthcare utilization and costs, as well as difficulties in coordinating and managing care(4, 12). Belgium's healthcare system allows patients and providers considerable freedom of choice, with fee-for-service payments as the primary mode of remuneration(13). Unlike gatekeeping systems, patients can consult any general practitioner or specialist(13). While acute care is commendable, there is room to bolster primary care and improve care coordination to address the increasing challenges posed by a rising number of individuals with chronic illnesses(13).

A recent systematic review on the costs of multimorbidity highlighted how research on this topic is limited in both scope and number(2). Previous studies have typically been limited to either 'cost-per-disease-count' or 'cost-per-additional-disease', and relying on data obtained from a single source. The research originated from a small pool of countries (predominantly the United States), with a striking lack of published studies on multimorbidity costs from Europe and low- and middle-income countries. Cost of multimorbidity studies focusing on specific morbidity combinations, are often limited to a single or a few combinations centered around an index disease of concern. Only a limited number of studies have taken a comprehensive approach, analyzing a broad array of morbidity combinations at the population level. These studies are from the United States, the United Kingdom, and New Zealand(14–16).

Further research is needed to understand the costs of specific combinations of chronic conditions, as a basis for identification and further exploring where and how costs can be averted/reduced while ensuring high-quality care. Dyads and triads—characterized by the co-existence of two or three conditions respectively—stand out as prominent subjects of multimorbidity research, due to their prevalence within multimorbidity populations, making them crucial targets for investigation. Concurrently, direct costs—which entail expenses tied to healthcare resources, interventions, or services—has garnered significant attention in cost analyses, due to their tangible and immediate impact on healthcare budgets. The lack of understanding of the direct costs of morbidity combinations—or interaction of individual conditions and their impacts on costs—poses a challenge for policymakers in developing new models of integrated patient-centered care and evaluating their cost-effectiveness. Through this study, we hope to deliver a holistic health system perspective of healthcare costs for people with multimorbidity and provide formative evidence to inform the re-organization of healthcare delivery to support patients with multiple needs and promote the efficient use of healthcare resources.

This study aims to estimate the economic burden of multimorbidity in Belgium and to explore the interactions of co-existing chronic conditions in a person and how they influence healthcare costs.

Particularly, the research questions are:

1. How do the direct healthcare costs of multimorbidity vary across population sub-groups in Belgium?
2. What is the average annual direct healthcare cost per person per single chronic condition, dyad and triad?
3. Across dyads, is the direct cost more, less or equal to the expected combined direct costs of single conditions? Across triads, is the direct cost more, less or equal to the expected combined direct costs of the three associated dyads?
4. Which dyads/triads have the most economic impact on the individual and population level?

Methodology
Design

This is a retrospective longitudinal study using data from two linked databases. The study was reported in line with the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines(17) and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022(18).

Data sources

Data were obtained from two sources. The first database used was the 2018 Belgian Health Interview Survey (BHIS). The BHIS contains data on socio-demographic characteristics, health status, health behaviors, health care utilization, quality of life as well as other health determinants from a sample of over 10,000 people from approximately 6,000 households in Belgium(19). The BHIS is a cross-sectional design survey, which uses the national register as its sample frame. It is conducted every 4 to 5 years to allow for comparison of population changes over time, and serves as a basis to inform health service organization and policy. The BHIS aligns and follows the format of the European Health Interview Survey (EHIS). The sampling technique and implementation of the BHIS has been published elsewhere(20). The data used for this analysis is obtained from the BHIS 2018.

The second database is the Intermutualistic Agency (IMA) database, an administrative database that collects data on the usage and costs of healthcare on an individual level from all the public health insurance funds(21). Every legal resident in Belgium is obliged to join one of the seven Belgian health insurance funds, and is therefore included in the IMA database. Healthcare reimbursement data makes up the core of the database and data is updated twice every year from 2002 onwards. There are three sub-databases: (1) a population database containing limited socio-demographic data of all insured persons; (2) a healthcare database containing healthcare service utilization and cost data of both ambulatory and hospital care and (3) a pharmaceutical database containing prescription and cost of prescribed and reimbursed drugs purchased through public pharmacies. The IMA data utilized in this study spanned across four years, from 2017 to 2020. Data from the BHIS and IMA databases were linked using the national register number, forming the integrated HISLINK database.

Study participants

We included all community-living people in Belgium, aged 15 and older, who had complete profiles and successful data linkage, from the HISLINK database (N = 9,753). We analyzed participants’ sex (male/female), age group (10-year intervals), highest education level in the household (no diploma or primary education, lower secondary, higher secondary, higher education), annual household income in 2018 Euro (5 quintiles), region (Flemish, Wallonia, Brussels), and number of chronic conditions (0, 1, 2, 3, 4+).

Chronic conditions: The presence of chronic conditions was self-reported and was determined through the interviewee's response to the questions: "During the past 12 months, have you had any of the following diseases or conditions?". Information on 38 chronic conditions was collected in the BHIS, which was subsequently regrouped to 25 chronic conditions or morbidity groups as many conditions had shared or similar pathophysiology (Table 1). The mapping was adapted from Van Wilder et al(22), the International Statistical Classification of Diseases and Related Health Problems 10th Revision(23), and discussion among the team of authors.

Table 1 Classification of chronic conditions

Multimorbidity measures

We defined the existence of chronic condition(s) based on the respondents’ self-reported health status. We defined multimorbidity as "the co-existence of two or more (groups of) chronic conditions" based on our refined list of conditions(3). To determine multimorbidity, we summed the total number of (groups of) conditions of each respondent.

In order to report the specific types of multimorbidity combinations, we formed all possible dyads and triads from the list of 25 chronic conditions. However, after assessing the prevalence of single chronic conditions, we identified and excluded conditions that had a prevalence rate of 1% or lower, which are, gallstones, cirrhosis of the liver, kidney disease, stroke, hip fracture, and...
Parkinson’s disease. We focused on the more prevalent single chronic conditions, which subsequently formed the more prevalent dyads and triads to enhance robustness of results. With fewer observations, statistical fluctuations and random variations can have a more significant impact on the results. This can lead to increased uncertainty and a higher likelihood of producing results that are not representative of the true population characteristics. Moreover, the prevalent morbidity combinations contribute more to the burden of disease. In all, we included all 171 dyads and 969 triads formed by the list of 19 chronic conditions. The included single chronic conditions, dyads and triads are listed in Additional file 1.

**Timeframe**

Each participant’s self-reported health status applies to the 12-month timeframe prior to the date of the interview. In this study, we included the costs of all participants from 2017–2020.

**Cost measures**

A health system costing perspective was applied in this study. Total cost of healthcare as recorded in the IMA database included the amount reimbursed by insurance and copayments/supplements paid by the patient. The extracted costs represent all-cause direct health care costs on a per-patient basis, but the precise health reason for which medical acts were performed, was not directly retrievable from the data.

The costs that are considered are mainly direct medical costs. To a smaller extent direct nonmedical costs are also included, more specifically those which are partially reimbursed and for which information is available in the IMA database. The estimation and reporting of the indirect cost of multimorbidity is conducted in a distinct study, as the data source for addressing this specific research question varies from the one utilized in the current study.

Direct costs include direct medical cost (PROCEDURE_GROUP code 1–31, 35–41, 43–83, 85) and direct nonmedical cost (code 32–34, 42, 84). The list of value labels is presented in the (Additional file 2).

Direct medical costs may include:

- Outpatient (medical acts by GPs, specialists and outpatient clinics, physiotherapy, occupational therapy, speech therapy, rehabilitation clinics, etc)
- Inpatient (stays in general hospitals, specialized psychiatric and neurological hospitals (including day-patient treatment), procedures taking place in the hospital such as dialysis, surgery,...)
- Emergency care (ICU, ambulance, oxygen, etc)
- Pharmacy (drugs)
- Others (equipment, etc)

Direct nonmedical cost may include:

- Food supplement
- Parking fees

**Data preparation**

we summed all-cause healthcare costs by individual per year. The IMA database exclusively contained data concerning variable costs associated with hospital care, which encompass costs related to the specific interventions conducted during the hospitalization. The IMA dataset did not incorporate hospital fixed cost, which is a fixed amount that covers the cost of the stay (e.g. infrastructure provided) and care in the hospital. The amount of fixed cost depends on the type of hospital, the services received, and the number of nights/days hospitalized. This amount is usually paid out directly to hospitals by health insurance funds, therefore hospital fixed costs were additionally added on for individuals that were hospitalized during each year. To estimate the fixed portion of the total cost of hospital care, the number of hospitalizations per patient per year was multiplied
by the publicly available average annual 100% per diem cost according to the type of hospitalization(24, 25). The resulting fixed costs were then added to the available variable hospital costs to obtain the total hospitalization costs used in this analysis. To enable comparison, all costs from 2017–2020 were inflated to 2022 Euro using the consumer price index(26).

### Statistical analyses

Unadjusted sub-group differences were assessed using t-tests. Generalized linear models with quasipoisson distribution and log link function were built to estimate the effects of dyads/triads on healthcare costs. Statistical analyses were performed in R through RStudio (2023.03.0)(27). The complex survey design schemes of the BHIS and sampling weights were accounted for in our survey design object to ensure representativeness of data on the population level. Confidence intervals were calculated using the profile likelihood method(28).

To contain the number of independent parameters, only chronic conditions with a prevalence rate greater than 2.5% were included. Interaction terms are additional variables that are created by multiplying two or more predictor variables together – in this case they are variables that signify the chronic conditions. Interaction terms were introduced for the most prevalent dyads and triads. A prevalence cut-off of 2.0% and 1.5% was used, respectively, to ensure parameter identifiability. This strategy was implemented to ensure sufficient observations, as the selection of prevalence cut-offs followed a progressive pattern for single conditions, dyads, and triads, reflecting the progressively changing prevalence of participants with one, two, and three concurrent conditions.

Variable selection was facilitated by the filter method which mitigates the risk of overfitting while striking a balance between selecting major predictors of interest, maintaining accuracy, and ensuring computational efficiency(29). Filter methods first assess the significance of predictors independently of the predictive models and then proceed to build models using only the predictors that meet a certain criterion(30). The relationship between each predictor and the outcome was determined through receiver operating characteristics (ROC) curves. If a linear model was fitted, then the absolute value of the t-value for the predictor’s slope was examined(31, 32). Otherwise, a loess smoother was fitted to the predictor and the resulting R^2 statistic was calculated to determine variable importance relative to the intercept-only null model(32).

We constructed three mixed models to separately assess the effects of single chronic conditions, dyads and triads on healthcare costs. The model for single conditions consisted of 19 chronic conditions and six established important determinants of healthcare costs; i.e., age, sex, highest education level in the household, financial burden of medical treatment (i.e., a heavy burden/somewhat a burden/not a burden at all/no one in the household needed medical examinations or treatments), number of comorbidities and year. The dyad model replicated the single condition model structure while incorporating 58 additional dyad interaction terms. Similarly, the triad model mirrored the dyad and included 41 triad interaction terms. A list of the included chronic conditions, dyad and triad interaction terms is supplied in Additional file 1. Model outputs are presented in Additional file 3.

The mixed models for single chronic conditions, dyads and triads were constructed based on these equations, respectively:

$$\log (\text{cost})_{ij} = \beta_{0,\text{single}} + \sum_{m=1}^{M} \beta_{ijm} \text{chronicdiseases}_{ijm} + \sum_{q=1}^{Q} \beta_{ijq} \text{covariates}_{ijq} + (u_{ij} + \epsilon_{i})$$

And:

$$\log (\text{cost})_{ij} = \beta_{0,\text{dyads}} + \sum_{m=1}^{M} \beta_{ijm} \text{chronicdiseases}_{ijm} + \sum_{n=1}^{N} \beta_{ijn} \text{dyadinteractions}_{ijn} + \sum_{q=1}^{Q} \beta_{ijq} \text{covariates}_{ijq} + (u_{ij} + \epsilon_{i})$$

And:

$$\log (\text{cost})_{ij} = \beta_{0,\text{trads}} + \sum_{m=1}^{M} \beta_{ijm} \text{chronicdiseases}_{ijm} + \sum_{n=1}^{N} \beta_{ijn} \text{dyadinteractions}_{ijn} + \sum_{p=1}^{P} \beta_{ijp} \text{triadinteractions}_{ijp} + \sum_{q=1}^{Q} \beta_{ijq} \text{covariates}_{ijq} + (u_{ij} + \epsilon_{i})$$
Where:

\[ \log (\text{cost})_{ij} \] denotes the estimated log transformed value of the cost variable for individual \( i \) in household \( j \);

\[ \beta_{\text{single}} \] and \( \beta_{\text{dyads}} \) and \( \beta_{\text{triads}} \) represent the overall fixed effect mean of \( \log (\text{cost})_{ij} \) across all households \( j \) for individuals \( i \) of the reference category, for single conditions, dyads and triads, respectively;

\( \text{chronicdiseases}_{ijm} \) is a vector representing individual-level chronic conditions and \( \beta_{ijm} \) are their respective estimated fixed slope coefficients;

\( \text{dyadinteractions}_{ijn} \) is a vector representing all interaction terms of the 58 most prevalent dyads and \( \beta_{ijn} \) are their respective estimated fixed slope coefficients;

\( \text{triadinteractions}_{ijp} \) is a vector representing all interaction terms of the 41 most prevalent triads and \( \beta_{ijp} \) are their respective estimated fixed slope coefficients;

\( \text{covariates}_{ijq} \) is a vector representing the six individual-level confounding factors of interest and \( \beta_{ijq} \) are their respective estimated fixed slope coefficients;

The random part between brackets contains: \( u_{ij} \) and \( \epsilon_i \). The first allows the intercept to vary between households, accounting for the household specific deviations from the overall intercepts \( \beta_{\text{single}} \) or \( \beta_{\text{dyads}} \) or \( \beta_{\text{triads}} \). The second is the idiosyncratic error term, which accounts for the individual deviations in \( \log (\text{cost})_{ij} \) from the household specific intercept.

For the assessment of interaction effects, the main goal was to observe the true interaction effects (i.e. interaction term coefficients) of co-existing conditions in a dyad/triad and how they influenced healthcare costs. A 95% confidence level was used to assess whether the costs of dyads and triads significantly differed from those of single conditions. P-values < 0.05 were reported. A significant p-value shows that the predicted sum cost is different when conditions co-exist compared to when they exist independently. The interaction effect is multi-directional in that each condition simultaneously influences, and is influenced by, the other condition(s).

In the case of dyads, a negative coefficient signals a sub-additive (antagonistic) interaction, implying that the combined effect of the two conditions was associated with an estimated mean healthcare cost that is lower than the summed cost of the same conditions existing in different individuals. A positive coefficient shows a super-additive (synergistic) interaction, revealing that the combined effect of the two conditions was associated with an estimated mean healthcare cost that is higher than the summed cost of the same conditions existing in different individuals. The expected mean increase is based on the additive effect of each of the conditions individually.

In the case of triads, we interpreted the results slightly differently. Given that a triad comprises three concurrent conditions, it gives rise to three potential combinations of dyads originating from those three conditions. Consequently, a negative coefficient indicates a sub-additive interaction. This suggests that the combined influence of the three conditions is linked to an average healthcare cost estimate that is lesser than the combined costs of the three associated dyads present in separate individuals. Conversely, a positive coefficient signifies the opposite scenario.

**Risk assessment and ethical consideration:** The BHIS 2018 has been approved by the ethics committee of the University Hospital of Ghent on December 21, 2017 (opinion EC UZG 2017/1454). Participation in the BHIS is voluntary, and no formal requirement for written and signed consent was established. Participation itself was considered tantamount to providing consent. This approach aligns with the principles of Good Epidemiological Practice as outlined by the International Epidemiological Association (IEA) Guidelines, which emphasize that formal written consent may be unnecessary when the research takes place in non-threatening settings and where voluntary participation carries no risk of losing potential benefits(33). Data linkage was authorized by the Information Security Committee (local reference: Deliberation No. 17/119 of December 19, 2017, amended on September 3, 2019).
This study was granted ethical approval on 26th July 2021 by the Ethics Committee at the University of Antwerp Hospital (Ethisch Comité UZA/UA), ID 2021 – 0405.

Results

Overview of multimorbidity in Belgium

In Fig. 1, the prevalence of individual conditions, dyads, and triads is depicted, along with the pattern of dyad and triad combinations. The outer ring of the figure displays dot sizes reflecting the prevalence of individual chronic conditions, while the orange lines in the center denote dyads and triads, with color intensity indicating their respective prevalence. Notably, the more prevalent morbidity clusters are denoted by the darker-stroked curves. The diverse morbidity labels are color-coded based on their respective categories. A comprehensive list of all potential morbidity combinations and their corresponding prevalence rates is presented in Additional file 4.

In 2018, multimorbidity affected approximately 48% (95%CI: 46–49) of the population aged 15 and over in Belgium. Circulatory system-related diseases and musculoskeletal-related diseases were the largest morbidity groups. The most frequent single chronic conditions included: arthropathies, dorsopathies, hypertension, high cholesterol and allergy. The most common dyad was Arthropathies + Dorsopathies, accounting for 14.1% (95%CI: 13.1–15.1) of cases. The most prevalent triad was Arthropathies + Dorsopathies + Hypertension, accounting for 5.2% (95%CI: 4.6–5.8) of cases.

Characteristics of the study population

Table 2 presents the characteristics of the study population and the average annual healthcare expenditures in 2022 Euro, per number of co-existing conditions. The overall mean age of the study population was 49 years old. The mean age increased in sub-groups with a higher number of chronic conditions. Amongst the study population (N = 9,753), 16% had two chronic conditions, 11% had three chronic conditions and 21% had four or more chronic conditions – with these categories being mutually exclusive. Healthcare expenditure also increased with age, and with the number of co-existing conditions.

The population under study is composed of various age groups, among which individuals aged 70 and above make up approximately 17%, and their healthcare cost accounted for around 43% of the total healthcare cost of the studied population. People with multimorbidity constituted nearly half of the studied population and their total healthcare cost constituted 74% of the healthcare cost of the studied population. From here, we also observed that people aged 70 + with multimorbidity accounted for 27% of the multimorbidity population, and around 13% of the general studied population. It is noteworthy that the healthcare expenses associated with individuals aged 70 and above, who are also grappling with multiple health conditions, contributed to 50% of the total healthcare cost of the multimorbidity population, and 37% of the total healthcare cost of the general studied population.

The study population consisted more of females than males (53% vs 48%) and more females had multimorbidity than males. On average, female participants incurred higher healthcare expenditure than their male counterparts (p = 0.003). However, in the subgroups of people with three or more chronic conditions, the average healthcare expenditure per person was higher for male than female participants (not statistically significant). We assessed the highest level of education attained in the household, as a determinant of health expenditure. Around half of all participants came from households with at least one family member with higher education. Participants from households with a lower level of education incurred higher healthcare costs than those from households with a higher level of education (p < 0.0001). This is consistent across all numbers of co-existing conditions. Similar to household education, lower household income quintiles were associated with a higher level of health spending and this was observed across all numbers of co-existing conditions. Across regions, the overall average healthcare expenditure per person was higher in Flanders, followed closely by Wallonia, and then Brussels. However, this difference is not statistically significant and there are also no clear trends amongst the subgroups of numbers of conditions.

The average annual direct costs of single chronic conditions
The estimated average direct cost per person per year for all single chronic conditions, dyads, and triads are presented in Additional file 5. Figure 2 represents the costs associated with the 19 chronic conditions. The color choices are employed solely for a visually appealing representation and do not serve any classification purpose. The average annual direct cost per person with one chronic condition was €2,438 (95% CI: 2,141-2,734). Among the single conditions with the lowest costs, stomach ulcer and allergy stood out, averaging €2,035 (95% CI: 1,524-2,546) and €2,096 (95% CI: 1,713-2,478) per person per year, respectively. Conversely, the highest-cost single conditions included cancer, chronic fatigue, diabetes, and genitourinary problems, with average costs of €4,979 (95% CI: 3,629-6,329), €3,599 (95% CI: 2,680-4,517), €3,416 (95% CI: 2,768-4,063), and €3,260 (95% CI: 2,551-3,968) per person per year, respectively. Among the most prevalent conditions, dorsopathies and arthropathies exhibited average costs of €2,301 (95% CI: 1,818-2,783) and €2,849 (95% CI: 2,342-3,355) per person per year, respectively.

The average annual direct costs of dyads

The average yearly cost per person for dyads was €3,515 (95% CI: 3,093 – 3,937).

The dyads with the highest costs frequently included cancer, diabetes, chronic fatigue, and genitourinary problems (Fig. 3). The top ten most expensive dyads had costs ranging from €5,753 (95% CI: 3,509-7,997) for Bowel disorder + Diabetes to €8,345 (95% CI: 4,998 – 11,691) for Cancer + Chronic fatigue.

The low-cost group comprised the ten least expensive dyads—frequently including allergy, stomach ulcer, and osteoporosis—with costs ranging from €1,518 (95% CI: 912-2,124) for Eye disease + High cholesterol to €1,816 (95% CI: 1,247-2,384) for Skin disease + Stomach ulcer.

The top ten most prevalent dyads—frequently including arthropathies, dorsopathies, hypertension, and high cholesterol levels—had costs ranging from €1,928 (95% CI: 1,408-2,448) for Allergy + Dorsopathies to €5,666 (95% CI: 3,044 – 8,288) for Dorsopathies + Chronic fatigue. The most prevalent dyad of Arthropathies + Dorsopathies had a cost of €3,044 (95% CI: 2,296-3,792). The dyad of Dorsopathies + Paroxysmal disorders was not only one of the most prevalent but also among the least expensive in terms of cost.

The average annual direct costs of triads

The annual average cost per person for each triad was €4,592 (95% CI: 3,920-5,264). Figure 4 shows the expenses associated with the top 10 high-cost triads, the top 10 low-cost triads, and the top 10 prevalent triads, along with their respective prevalence rates. Notably, all triads within the top 10 high-cost and low-cost categories displayed low prevalence rates, each falling under 1%.

The high-cost group had triads ranging from €12,966 (95% CI: 6,947 – 18,985) for Cancer + Cardiovascular disease + Chronic fatigue to €20,244 (95% CI: 11,397 – 29,090) for Cancer + Diabetes + Chronic fatigue.

In contrast, the low-cost group had triads ranging from €1,083 (95% CI: 503-1,663) for Dorsopathies + Paroxysmal disorders + Stomach ulcer to €1,435 (95% CI: 817-2,054) for Eye disease + High cholesterol + Stomach ulcer.

Triads in the prevalent group had cost ranging from €1,824 (95% CI: 1,010 – 2,638) for Dorsopathies + High cholesterol + Hypertension to €7,437 (95% CI: 2,966 – 11,908) for Arthropathies + Dorsopathies + Chronic fatigue, placing it in between the low- and high-cost groups. The most prevalent triad of Arthropathies + Dorsopathies + Hypertension had a cost of €3,894 (95% CI: 2,725-5,063).

Total costs of multimorbidity on the population level

The dyad with the highest prevalence, Arthropathies + Dorsopathies, incurred an annual treatment cost exceeding €4 billion (representing 11% of total national health expenditure). In contrast, the cost of treating the most expensive dyad, Cancer + Chronic Fatigue, was merely 2%. For triads, the treatment cost of the most prevalent combination, Hypertension + Arthropathies + Dorsopathies, accounted for 5% of national health expenditure. Conversely, the most expensive triad, Cancer + Diabetes + Chronic fatigue, carried a cost of just 1%.
Interaction effects of dyads and triads on healthcare expenditure

Of the 58 most prevalent dyads, six dyads showed significant interaction. Figure 5 presents the coefficients of these six dyads on the log-scale. Amongst dyads with significant effects,

most dyads produced a sub-additive effect indicating a reduced overall average cost compared with single conditions. The four dyads with sub-additive interaction effects were Diabetes + Hypertension, Allergy + Hypertension, Arthropathies + Diabetes, and Chronic fatigue + Hypertension. The two dyads with super-additive interaction effects were Depression + Paroxysmal disorders and Eye disease + Hypertension.

Of the 41 most prevalent triads, eight triads showed significant interactions (Fig. 6). Contrary to the interaction patterns seen in dyads; in triads, most had super-additive effects (five triads). Sub-additive effects were found in three triads. The top three triads with super-additive interaction effects were Dorsopathies + Genitourinary problems + High cholesterol, Diabetes + High cholesterol + Hypertension, and Allergy + Depression + Dorsopathies. The three triads with sub-additive interaction effects were Arthropathies + Dorsopathies + Osteoporosis, Arthropathies + Genitourinary problems + High cholesterol, and Depression + Dorsopathies + High cholesterol.

Overall, with these model specifications and amongst prevalent morbidity combinations, many of the multimorbidity interaction coefficients were insignificant, indicating that the predicted cost of a patient with multimorbidity did not differ significantly from the summed costs of the same conditions existing in different patients.

Discussion

Summary of findings

This study provides insights into numerous multimorbidity profiles in Belgium. In addition to examining the cost by the number of co-existing conditions as well as demographic and socioeconomic subgroups, the study explored the costs of a large number of dyads (171) and triads (969) associated with a list of 19 of the most prevalent chronic conditions. People with multimorbidity constituted nearly half of the studied population and their total healthcare cost constituted around three-quarters of the healthcare cost of the studied population. The cost of multimorbidity increased with age and with the number of co-existing conditions, and individuals with lower socioeconomic status were more prone to higher healthcare costs than those of higher socioeconomic status. The most common dyad, comprising Arthropathies + Dorsopathies with a prevalence rate of 14%, accounted for 11% of the total national health expenditure. Similarly, the most frequent triad, encompassing Arthropathies + Dorsopathies + Hypertension at a prevalence rate of 5%, contributed 5%. Prevalent morbidity combinations, rather than high-cost ones, made a greater contribution to total national health expenditure. The average annual direct cost per person for dyads was €3,515 (95%CI: 3,093 – 3,937), while the annual average direct cost per person for triads was €4,592 (95%CI: 3,920-5,264). Dyads and triads associated with cancer, diabetes, chronic fatigue, and genitourinary problems had the highest costs. In most cases, the cost associated with an individual having multimorbidity is lower or not substantially different from the combined costs of the same conditions observed in separate patients.

General trend of multimorbidity and cost

In 2018, multimorbidity affected approximately 48% of the population aged 15 years and over in Belgium. This rate surpasses the findings of a recent Lancet review that reported an overall global multimorbidity prevalence of 37.2% (95% CI: 34.9–39.4%) in the community setting, as well as a regional rate for Europe at 39.2% (95% CI: 33.2–45.2%)(35). However, it is important to approach these comparative statements with caution. The presence of heterogeneity in study methodologies, sample selections, data collection approaches, definitions of multimorbidity, and the scope of included chronic conditions introduces challenges in directly comparing prevalence rates of multimorbidity.

The five most commonly occurring chronic conditions in dyads and triads were found to be arthropathies, dorsopathies, hypertension, high cholesterol, and allergy. Some of these results are consistent with findings from the United States, England...
and France(36–38). In the United States, arthritis, high cholesterol and hypertension were also found to be the most common in multimorbidity dyads and triads, alongside diabetes(36, 37). Hypertension was reported as the most common condition in morbidity combinations in England, alongside diabetes, chronic kidney disease and asthma(16). However, chronic kidney disease had low prevalence in Belgium. Diabetes and asthma (as part of the respiratory disease group) were also common but secondary to the five prevalent conditions mentioned earlier.

The results of this study support previous research indicating that the cost of multimorbidity increases with age and the number of concurrent conditions(39–44). However, after adjusting for the number of conditions, adding age to the analysis did not significantly improve the ability to explain the variation in costs(45). Nevertheless, individuals aged 70 and above who were affected by multimorbidity played a significant role in terms of healthcare costs. Despite constituting a smaller portion of the total population, this group accounted for a substantial share of healthcare expenditures. Specifically, their healthcare costs were notably higher, contributing significantly to the overall financial burden of healthcare. This underscores the importance of addressing the unique healthcare needs and challenges faced by the elderly population, particularly those dealing with multiple health conditions simultaneously.

Further, our study confirms that multimorbid individuals of lower socioeconomic status had higher healthcare costs compared to those of higher status. Similar research in the UK also showed that healthcare costs increased with greater levels of deprivation; conversely, individuals from higher socioeconomic backgrounds were more likely to experience better health, leading to lower care needs(46–48).

**Cost of multimorbidity in Belgium in comparison with other countries**

In comparison to the few other high-income countries for which data are available, the average cost of multimorbidity per person in Belgium appears to be lower, with dyads and triads costing an average of €3,515 and €4,592 per person per year, respectively. A study conducted in England revealed that the average cost per person per year for dyads was £5,013 (£3,717) and for triads was £7,116 (£5,276), but it only accounted for secondary care costs and excluded primary care and pharmaceutical expenses – the actual cost may be much higher(16). Similarly, in the United States, the median costs for dyads and triads were $6,751 ($6,208) and $8,892 ($8,177), respectively(36, 49–51). The most expensive dyad in our study was Cancer + Chronic Fatigue, with an estimated cost of €8,345; which was lower than the estimate of €11,381 for Cancer + Neurological diseases in New Zealand(52). The most prevalent dyad in our study, Arthropathies + Dorsopathies, costed £3,044; which was lower than the cost of treating Osteoarthritis + Back pain in Sweden (€5,358)(53). One of the most prevalent triads in our study was Dorsopathies + High cholesterol + Hypertension (€1,824), the cost of which was significantly lower than the estimated cost of treating Low back pain + Hypertension + Hyperlipidemia (€22,906) in the United States(54). Comparing our findings with that of other studies is challenging because few other studies have a comparable scope. Further, it should be noted that comparing costs between countries is difficult due to variations in the disease burden, methodology, data collection, sample representativeness, and differences in healthcare systems(2). Despite this, on average, the cost of multimorbidity in Belgium was found to be notably lower than that of other countries with similar economic contexts.

In our study, the dyads associated with the highest costs predominantly consisted of cancer, diabetes, chronic fatigue, and genitourinary problems. These results are in part consistent with previous studies that have identified cancer and diabetes as standalone conditions associated with high costs, and dyads/triads that include these conditions are also costly to treat(2, 52, 55–57). However, the reasons why chronic fatigue and genitourinary problems frequently appeared in the top most expensive dyads/triads in our study are less obvious. Further investigation into literature found that chronic fatigue is a complex chronic illness that causes widespread pain, cognitive impairment, and can incapacitate individuals for a long period of time with a poor prognosis(58). Diagnosis relies on assessing patient-reported symptoms and extensive testing to exclude other illnesses or factors, as there is no specific laboratory-based diagnostic test(58). Extensive testing and the impact on quality of life leading to possible homecare service use to some extent explain the high cost of chronic fatigue. Genitourinary problems encompass a broad range of conditions, including urinary incontinence, kidney stones, chronic cystitis, and prostate problems. Studies have indicated that patients with genitourinary problems not only incurred high healthcare costs for testing and treatment, but also for behavioral therapy, devices, and routine care items(59, 60).
In the low-cost group, common chronic conditions within the combinations were allergy, stomach ulcer, and osteoporosis. Allergy is often excluded from multimorbidity studies, making it difficult to compare the cost of morbidity combinations involving allergy across countries. As the health outcomes data used in this study was self-reported by patients, it was uncertain whether the person received a clinical diagnosis and whether healthcare is sought. Furthermore, in many types of allergies, avoidance of the suspected allergen is the only treatment, and healthcare is typically only sought in the event of a reaction(61, 62). This may explain the relatively low healthcare costs associated with allergy. Regarding stomach ulcers, complications are uncommon and most cases are treated with pharmacotherapeutics(63, 64); thus it is reasonable that healthcare costs are relatively low. Regarding osteoporosis, a study conducted in Belgium in 2004 reported having osteoporosis cost €535 per person per year and the author recognized that this figure is low, possibly because osteoporosis remains under-treated in Belgium(65). Hence, factors like underreporting, limited healthcare utilization, and cost-effective management contribute partially to the lower costs observed in certain dyads and triads.

**The importance of interaction effects in multimorbidity costing**

To ensure precise estimation in multimorbidity costing studies, it is essential to consider interaction effects to avoid the potential risks of overestimating or underestimating cost. Only a few other studies have explored the interaction of conditions on cost of multimorbidity(14, 38, 66). In our study, the cost of most dyads and triads did not differ significantly from the summed cost of the same conditions existing in different individuals. For those that differed significantly, more sub-additive effects were observed in dyads and super-additive effects in triads. For dyads, one out of two pairs with super-additive interaction effects are discordant conditions and one out of four pairs with sub-additive effects are concordant conditions. For triads, four out of five triads with super-additive interaction effects are discordant conditions and one out of three triads with sub-additive effects are concordant conditions. According to Piette and Kerr, concordant conditions share similar pathophysiologic risk or disease management plan, while discordant conditions are those with pathophysiologic risk and a disease management plan that are not directly related(67, 68). A third type – dominant conditions – are severe conditions that may limit life expectancy or require extensive medical treatment(67, 68). Based on this premise, the majority of our results are reasonable as they align with this classification. For example, having Eye disease + Hypertension (discordant) or Dorsopathies + Genitourinary problems + High cholesterol (discordant) increased spending, while having Diabetes + Hypertension (concordant) or Arthropathies + Dorsopathies + Osteoporosis (concordant) reduced spending. Although this study does not enable us to explain all of our findings, it serves as a foundation for investigating the healthcare-seeking behavior of individuals with dyads and triads that display either super or sub-additive healthcare expenditure. More frequent utilization, complex disease trajectories or complications, polypharmacy, and inadequate coordination between services are potential explanations for why some dyads/triads result in super-additive healthcare spending(7, 69, 70).

However, our study showed that most dyads and triads resulted in either lower or comparable healthcare costs than the summed cost of the same conditions in different individuals. Although this could be perceived as positive news from an economic perspective, it could also indicate that patients with multimorbidity are ‘backgrounding’ one condition for another and may not be receiving sufficient care for all their conditions. This phenomenon aligns with the Shifting Perspectives Model of Chronic Illness that suggests people living with multimorbidity may place illness in the foreground or the background of their “world”, depending on the context(71).

**Implications for future research, health system and policy**

This study provides a basis for identifying the morbidity combinations that are most expensive and most prevalent, which can help to understand where cost savings can be achieved through care reorganization and prevention. For those with super-additive health expenditure, it is recommended to conduct further research into the level of care integration and health seeking behavior. In the case of concordant diseases, it may be more efficient to seek efficiency gains for instance in appointing the concordant disease management to the same medical doctors, resulting in time and cost savings and more effective communication(72). For management of common concordant conditions, the first line could be the appropriate level of daily care, with a transmural component of – for instance – annual visits to a medical specialist(8). Such models are already in place for single disease care pathways(73). For those with sub-additive spending, it is suggested to conduct further research to
understand the health service utilization patterns. The results can serve as a case study for best practices or identify whether the patient is having unmet needs.

To support decision-makers and researchers to predict and monitor the costs of morbidity combinations, a multimorbidity costing tool can be built, embedding the model from this study to provide a user-friendly platform that can automatically generate the cost of different morbidity clusters with a lifetime time horizon, based on the user’s parameter inputs. The potential applications of this tool are extensive, ranging from policy-makers and practitioners to insurance companies, patients, and families. Its potential impact in informing health policy and decision-making processes cannot be overstated.

Strengths and limitations

This study represents the first of its kind in Belgium, at a time when population-level studies on the cost of multimorbidity remain scarce in Europe and globally(2). By including a large number of morbidity combinations, accounting for both dyads and triads, our study provides a comprehensive assessment of the cost of multimorbidity. While the list of 19 chronic conditions included in the study is not exhaustive, it encompasses the conditions most prevalent in the population, satisfying the criteria of including at least 12 chronic conditions suggested by Fortin et al, for an accurate measurement of multimorbidity(74).

Our use of linked longitudinal data from an exhaustive claim database, a reliable source of information for studying the cost of various conditions, increases the reliability of our findings(14, 45, 75). Notably, linked data is still not widely utilized in research on the cost of multimorbidity, highlighting the novelty of our approach(2). Furthermore, the use of health insurance claim databases has been endorsed for conducting cost-of-illness studies, further adding to the robustness of our study(76, 77).

Our sample size is relatively large and is representative of the population, providing a strong basis for generalization of our findings. Most importantly, we took into account interaction effects, providing more accurate estimations and avoiding the risk of over- or underestimating costs.

There are several limitations and challenges that should be taken into consideration when interpreting the findings of our study. Conducting multimorbidity research is inherently challenging due to the vast number of possible morbidity combinations and scenarios. This is further complicated by computational limitations and the need to strike a balance between model fit and parsimony.

In addition, the health outcomes used in our study were derived from a cross-sectional national health survey, which may be limited by patients’ subjective reporting of their health status, unclear diagnoses, overlapping symptoms, and other factors that can affect the accuracy of the reported data. For practical reasons, we also assumed that patients had had the same chronic conditions over all four years, and excluded certain chronic conditions with low prevalence (stroke, cirrhosis of the liver, kidney diseases, Parkinson’s disease, hip fracture and gallstones) to increase the robustness of our findings. However, this may have led to an overestimation of the presented costs. Regarding covariates, data for proximity to death was insufficient for inclusion, despite its recognized significance as an explanatory factor for healthcare costs, even more so than age(78).

Additionally, diverse methodologies exist for the selection, inclusion, and classification of chronic conditions. The list of conditions incorporated in our study was formulated after numerous deliberations within the team, acknowledging that alternative approaches may also exist. For instance, some conditions could potentially be debated as symptoms or risk factors, rather than standalone chronic conditions. This is inevitable given the complex nature of chronic conditions and multimorbidity, and the lack of a consensus on definitions and terminologies(3, 74, 79). Moreover, some conditions were collapsed to form broader morbidity groups (Fig. 1) and there may be potential overlaps across groups. The limited number of included chronic conditions could potentially have resulted in an underestimated prevalence of multimorbidity. Nonetheless, our study aimed to capture all available conditions that could impact a person’s quality of life and incur healthcare expenditure over a long period. Indirect costs, estimated using a separate data source, are not presented here but are reported in a different study.

Conclusion
Prevalent morbidity combinations, rather than high-cost ones, made a greater contribution to total national health expenditure. Our research serves as a starting point for subsequent research on the healthcare-seeking behavior of individuals with super or sub-additive healthcare expenditure. The model developed in this study can be used to create a user-friendly costing tool for multimorbidity, which can inform health policy and decision-making processes. We draw upon this evidence as a stepping stone to enhance the healthcare system, with an aim to develop more accommodating and cost-effective care for patients with diverse needs. Our study contributes to the scarce literature on this topic in Europe and worldwide.

**Declarations**

**Statements and Declarations**

**Competing interests:** The authors declare that they have no competing interests.

**Acknowledgement:** We would like to express our sincere appreciation to the Intermutualistic Agency (IMA), whose dataset access and continuous support were indispensable for our research.

**Ethics approval:** The study was granted ethical approval on 26th July 2021 by the Ethics Committee at the University of Antwerp Hospital (Ethisch Comité UZA/UA), ID 2021-0405.

**Consent for publication:** Not applicable

**Availability of data and materials:** The data that support the findings of this study are available from the Intermutualistic Agency but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available upon reasonable request and with permission of the Intermutualistic Agency.

**Funding:** This research is a component of PBT’s doctoral project, which is funded through the BOF-DOCPRO grant from the University of Antwerp.

**Authors’ contributions:** PBT and JvO conceptualized the project. JVdH, FB, VG introduced access to the databases and provided guidance and support on the use of data. PBT conducted the analysis with statistical support from GN, EA, PBos; and JK, EMT, PBeutels provided health economics support and expertise. GVH contributed valuable epidemiological expertise, while JvO provided guidance and insights on health system aspects. PBT wrote the manuscript, performed all revisions and was responsible for the submission. JvO provided supervision throughout the entire process. All authors read and approved the final manuscript.

**Patient and public involvement:** Patient and public involvement (PPI) was not incorporated into the design, conduct, or reporting of our research due to practical constraints. Nevertheless, it’s worth noting that several of our co-authors are experienced medical practitioners, and their inclusion in the study provided valuable insights, allowing us to better align our findings with real-world clinical perspectives and healthcare practices.

For the dissemination phase of the study, we have a comprehensive plan that will involve a broader public engagement strategy. This will encompass patients and the public, health insurance agencies, policy makers, healthcare providers, and other stakeholders. Additionally, we are committed to developing a user-friendly tool for multimorbidity costing, which will be a valuable resource for patients and the public, providing them with access to important insights and information related to healthcare costs and multimorbidity management.

**References**


Tables
Tables 1–3 is available in the Supplementary Files section.

Figures
Figure 1

The prevalence and patterns of multimorbidity in 2018
Figure 2

The average annual direct cost per single chronic condition (in 2022 Euro)
Figure 3

The average annual direct costs of 171 dyads (in 2022 Euro)
Figure 4

The average annual direct costs of the top high-cost, low-cost, and prevalent triads

<table>
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Figure 5

Interaction effects of dyads

- Depression + Paroxysmal Disorders
- Eye disease + Hypertension
- Diabetes + Hypertension
- Allergy + Hypertension
- Arthropathies + Diabetes
- Chronic fatigue + Hypertension

Group:
* Super-additive effects
* Sub-additive effects
Interaction effects of dyads on healthcare expenditure

Figure 6

Interaction effects of triads on healthcare expenditure

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AF1Listofincludedtermssandinteractionterms.pdf
- AF2Costingredients.pdf
- AF3Modeloutputs.xlsx
- AF4Prevalenceofsinglebdyadstriads.xlsx
- AF5Costofsinglebdyadstriads.xlsx
- Table13.docx