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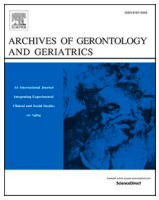

Associations of individual chronic diseases and multimorbidity with multidimensional frailty

Robbert J.J. Gobbens [a,b,c,d,*], Sandra Kuiper [d,e], Henriëtte Dijkshoorn [f], Marcel A.L.M. van Assen [g,h]

[a] Faculty of Health, Sports and Social Work, Inholland University of Applied Sciences, Amsterdam, the Netherlands
[b] Zonnehuisgroep Amstelland, Amstelveen, the Netherlands
[c] Department of Family Medicine and Population Health, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium
[d] Tranzo, Tilburg University, Tilburg, the Netherlands
[e] Department of Research, Public Health Service of West-Brabant, Breda, the Netherlands
[f] Department of Healthy Living, Public Health Service of Amsterdam, Amsterdam, the Netherlands
[g] Faculty of Social and Behavioral Sciences, Tilburg University, Tilburg, the Netherlands
[h] Faculty of Social and Behavioural Sciences, Utrecht University, Utrecht, the Netherlands

HIGHLIGHTS

- Chronic diseases had the strongest associations with total and physical frailty.
- The effects of chronic diseases on frailty differed strongly across diseases.
- Urinary incontinence and severe back disorder impaired frailty most.
- Cancer and hypertension had the weakest associations with frailty.
- Different weight should be given to individual chronic diseases in a measure of multimorbidity.

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ABSTRACT

Objective: To examine the associations between individual chronic diseases and multidimensional frailty comprising physical, psychological, and social frailty.
Methods: Dutch individuals ($N = 47{,}768$) age ≥ 65 years completed a general health questionnaire sent by the Public Health Services (response rate of 58.5 %), including data concerning self-reported chronic diseases, multidimensional frailty, and sociodemographic characteristics. Multidimensional frailty was assessed with the Tilburg Frailty Indicator (TFI). Total frailty and each frailty domain were regressed onto background characteristics and the six most prevalent chronic diseases: diabetes mellitus, cancer, hypertension, arthrosis, urinary incontinence, and severe back disorder. Multimorbidity was defined as the presence of combinations of these six diseases.
Results: The six chronic diseases had medium and strong associations with total (($f^2 = 0.122$) and physical frailty ($f^2 = 0.170$), respectively, and weak associations with psychological ($f^2 = 0.023$) and social frailty ($f^2 = 0.008$). The effects of the six diseases on the frailty variables differed strongly across diseases, with urinary incontinence and severe back disorder impairing frailty most. No synergetic effects were found; the effects of a disease on frailty did not get noteworthy stronger in the presence of another disease.
Conclusions: Chronic diseases, in particular urinary incontinence and severe back disorder, were associated with frailty. We thus recommend assigning different weights to individual chronic diseases in a measure of multimorbidity that aims to examine effects of multimorbidity on multidimensional frailty. Because there were no synergetic effects of chronic diseases, the measure does not need to include interactions between diseases.

* Corresponding author at: Faculty of Health, Sports and Social Work, Inholland University of Applied Sciences, De Boelelaan 1109 1081 HV, Amsterdam, the Netherlands.
E-mail address: robbert.gobbens@inholland.nl (R.J.J. Gobbens).

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1. Introduction

By 2050, 1 in 6 people worldwide will be age 65 years or older, an increase from 1 in 11 people in 2019 (United Nations Population Division, 2019). As the population worldwide ages, people suffering from individual chronic diseases, multimorbidity, and frailty will increase (Collard et al., 2012). The term *chronic disease* refers to a disease that is permanent, is caused by nonreversible pathological alteration, or requires rehabilitation or a long period of care (Villacampa-Fernandez et al., 2017); recently, the denomination *noncommunicable disease* is often used (Hunter & Reddy, 2013). Several single chronic diseases have been shown to be associated with frailty in community-dwelling older people. For example, a systematic review and meta-analysis of observational studies showed that older people with chronic obstructive pulmonary disease have a two-fold increase of frailty (Marengoni et al., 2018). Moreover, diabetes mellitus was associated with a 32 % increase in the odds of a higher level of frailty among Mexican American older people (Howrey et al., 2018). A study of a sample of 1271 Japanese people age ≥65 years showed that those with diabetes mellitus and frailty had a higher risk of disability and mortality compared with non-frail people without diabetes mellitus (Kitamura et al., 2019). There are also several studies that have demonstrated that heart failure is associated with frailty (Denfeld et al., 2017; Uchmanowicz et al., 2019).

Multimorbidity is defined as the co-occurrence of several chronic diseases in the same person (Marengoni et al., 2011). However, there is an ongoing debate about the operationalization of multimorbidity (Calderon-Larranaga et al., 2017) as a simple and weighted count of chronic diseases and comorbidity indexes (de Groot et al., 2003), for example, the Charlson Comorbidity Index (Needham et al., 2005). The prevalence figures, which range from 55 % to 98 % (Marengoni et al., 2011), are strongly affected by differences in operationalization. In addition, these figures are influenced by several other factors, such as female gender, greater age, and low socioeconomic status (Abad-Diez et al., 2014; Marengoni et al., 2011; Orueta et al., 2013). Multimorbidity has a great impact on mortality, decline in physical functioning, the use of four or more medications among community-dwelling older people, and lower quality of life (Fortin et al., 2004; Rizzuto et al., 2017; Woo & Leung, 2014). The prevalence of multimorbidity was 70.4 % in a sample of 1099 Swedish people age 78 or older, causing 7.5 years of life lost and 81 % of the sample to live their remaining years of life with disability (Rizzuto et al., 2017). In a cohort of 4000 Chinese people age 65 years or older, multimorbidity was present in 68.4 % of this population and appeared to be associated with polypharmacy and a decrease in physical function after 4 years of follow-up (Woo & Leung, 2014).

Multimorbidity is also associated with frailty; this was clearly demonstrated by a systematic review and meta-analysis that included 48 and 25 studies, respectively (Vetrano et al., 2019). As with multimorbidity, there are many operational definitions of frailty in circulation, which can roughly be divided into definitions that consider frailty to be a medical concept (physical frailty) and those that consider it to be a biopsychosocial concept (multidimensional frailty; Gobbens et al., 2010b). An example of a definition of physical frailty is this: Frailty is a biologic syndrome of decreased reserve and resistance to stressors resulting from cumulative declines across multiple physiologic systems, causing vulnerability to adverse outcomes (Fried et al., 2001). A measure of frailty appropriate to physical frailty is the phenotype of frailty, which includes five criteria: unintentional weight loss, weakness, poor self-reported endurance, slowness, and low physical activity (Fried et al., 2001).

Because psychological and social functioning in older people are neglected in physical frailty, multidimensional definitions are being used more and more often in research and practice. *Multidimensional frailty* is defined as a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, and social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes (Gobbens, Luijkx et al., 2010a, 2010b). Frailty has a major impact on the lives of older people. It is known to lead to an increased risk of disability while performing activities of daily living, hospitalization, institutionalization, lower quality of life, and mortality, independent from the operationalization (Fried et al., 2001; Gobbens & van Assen, 2012, 2014; Rockwood et al., 2005; Shamliyan et al., 2013). Examples of measures based on a multidimensional approach of frailty are the Frailty Index (Mitnitski et al., 2001), the EASY-Care Two step Older people Screening (van Kempen et al., 2014), and the Tilburg Frailty Indicator (TFI; Gobbens, van Assen et al., 2010b). Greater age, sex (being a woman), low socioeconomic status, an unhealthy lifestyle, and dissatisfaction with one's living environment are all factors that influence frailty (Gobbens, van Assen et al., 2010a).

Multimorbidity and frailty are related but different concepts (Cesari et al., 2017; Fried et al., 2004; Villacampa-Fernandez et al., 2017; Wong et al., 2010; Woo & Leung, 2014). Multimorbidity and frailty individually or in combination have a different impact on health outcomes, such as polypharmacy (Woo & Leung, 2014). Both multimorbidity and frailty are used to assess the risk profile of an older person with the aim of supporting clinical decisions and designing and carrying out interventions (Cesari et al., 2017) that focus on preventing or delaying adverse outcomes, such as lower quality of life and mortality (Kojima et al., 2016; Makovski et al., 2019; Nunes et al., 2016; Vermeiren et al., 2016). Multimorbidity can be considered a determinant of frailty (Gobbens, van Assen et al., 2010a).

In the present study, we examined the associations between individual chronic diseases and multidimensional frailty. This study is distinct from previous studies in several aspects. First, many studies focusing on these associations have used a physical operationalization of frailty, in particular the aforementioned phenotype of frailty (Vetrano et al., 2019; Weiss, 2011), disregarding the psychological and social domains of frailty. In addition, to examine these associations we used a much larger sample (>45,000 older people) than previous studies, which was also meant to be representative. By using this large sample, we increased our odds of detecting even small effects (i.e., statistical power to detect small effects approaches (1). Finally, we not only selected six chronic diseases whose prevalences in the sample were the highest, but we also examined synergetic effects of diseases, that is, the effect of combinations of these six individual self-reported chronic diseases in pairs. Here, too, we controlled for the effects of confounders (sex, age, marital status, ethnicity, education, income) to exclude alternative explanations of the associations between individual chronic diseases, multimorbidity, and multidimensional frailty.

2. Methods

2.1. Study population and data collection

We used data gathered by Public Health Services in the Netherlands in 2012. These data were part of a general health questionnaire, including information concerning not only chronic diseases, frailty, and sociodemographic characteristics but also lifestyle, disability, living environment, and social relations. Samples of community-dwelling older people age ≥65 years were randomly drawn by Statistics Netherlands from the registers of the municipalities in the city of Amsterdam, a large city including around 800,000 inhabitants, and the provinces Zeeland and Noord-Brabant (denoted "Zeebra"; small cities and rural areas), including around 381,000 and 2470,000 inhabitants, respectively. As mentioned in a previous article about a study that used the same samples (van Assen et al., 2016), people were excluded if they met at least one of the following criteria: older persons in long-term care facilities, prisoners, and older people staying in refugee asylum centers, or if they had participated in other research by Statistics Netherlands. In addition, a maximum of one older person per household was included in the sample.

In total, 81,644 older people—4542 living in Amsterdam and 77,102

living in Zeebra—were invited by letter to fill in a questionnaire, on paper or on the internet. These individuals received a reminder twice. Of these people, 47,768 decided to participate in our study (Amsterdam = 2432, Zeebra = 45,336): the total number corresponds to a response rate of 58.5 %.

2.2. Measurements

2.2.1. Multidimensional frailty

Multidimensional frailty was assessed with the Tilburg Frailty Indicator (TFI). The TFI is, a self-report questionnaire split into two parts. Part A contains 10 questions about determinants of frailty, and Part B contains 15 questions on the basis of which a health care professional can determine whether frailty is present. For this study, we used only Part B. The 15 questions refer to physical frailty (8 questions), psychological frailty (4 questions), and social frailty (3 questions). The score for total multidimensional frailty ranges from 0 (*not frail*) through 15 (*maximum frail*). The ranges of the scores for physical, psychological, and social frailty are 0 through 8, 0 through 4, and 0 through 3, respectively. Many studies have demonstrated that the TFI has good psychometric properties for assessing frailty among community-dwelling older people in the Netherlands (Gobbens et al., 2020; Gobbens, van Assen et al., 2010b, 2012a) and other countries e.g. China (Dong et al., 2017), Brazil (Santiago et al., 2013) and Portugal (Coelho et al., 2015).

2.2.2. Chronic diseases and multimorbidity

We assessed 19 self-reported chronic diseases: diabetes mellitus; cerebrovascular accidents; myocardial infarction; other serious cardiac disease; cancer; migraine; hypertension; peripheral arterial disease; chronic obstructive pulmonary disease; psoriasis; chronic eczema; dizziness with falls; serious intestinal disorders; urinary incontinence; arthrosis; rheumatoid arthritis; severe back disorder; severe neck or shoulder disorder; and severe disorder of the elbow, wrist, or hand. The participants were asked whether they had the chronic disease in the past 12 months. We defined multimorbidity as the presence of combinations of six individual chronic diseases that were most prevalent (>15 %) in the total sample (see penultimate column of Table 1 for prevalence figures). These diseases were diabetes mellitus, cancer, hypertension, arthrosis, urinary continence, and severe back disorder. However, it should be noted that urinary continence and severe back disorder should be considered chronic conditions instead of chronic diseases.

2.2.3. Sociodemographic characteristics

Sociodemographic characteristics of interest were sex, age, marital status, ethnicity, education, and income. See Table 1 for the response categories.

2.3. Statistical analyses

First, descriptive statistics (means and standard deviations, or frequencies) were calculated of all variables, for all respondents ("Complete Sample" column in Table 1) as well as for the group of participants with no missing data on any of the variables included in the regression analyses ("Regression Sample" in Table 1). We compared groups of respondents with and without missing data on all variables, using *t* tests with Cohen's *d* effect sizes (assuming equal group variances) and contingency tables with Cramer's *V* effect sizes, for continuous and discrete variables, respectively.

Each of the four frailty variables (total frailty and physical, psychological, and social frailty domain scores) was predicted using regression analyses. Each prediction of a frailty variable consisted of four steps that increased in model complexity. First, frailty was explained using background variables sex (women = 1), age (both linear and quadratic, centered and in lustrums, i.e., age = [X – 73.365]/5 and age^2 = age × age), marital status (married = 1, otherwise = 0), ethnicity (1 =

Table 1
Characteristics of the participants (total $N = 47{,}768$; in the regression analyses $N = 24{,}347$).

Characteristic	Number of observations (total N – missings)	*Complete sample M ± SD, range n (%)*	*Regression[1] sample M ± SD, range n (%)*	Comparison of total and regression sample (*t*, *p*, Cohen's *d* or χ^2, *p*, Cramer's *V*)
Age, mean ± SD, range		73.4 ± 6.6, 65–103	72.2 ± 6.3, 65–102	$t = 40.97$, $p < .001$, $d = 0.38$
Sex	47,768			$\chi^2 = 835.04$, $p < .001$, $V = 0.132$
Man		22,761 (47.6)	11,169 (45.9)	
Woman		25,007 (52.4)	13,178 (54.1)	
Marital status	46,300		*N = 24,186*	$\chi^2 = 728.26$, $p < .001$, $V = 0.125$
Married		30,537 (66.0)	17,313 (71.6)	
Cohabiting		1046 (2.3)	494 (2.0)	
Not married		1855 (4.0)	805 (3.3)	
Divorced		2776 (6.0)	1137 (4.7)	
Widowed		10,086 (21.8)	4437 (18.3)	
Ethnicity	47,768			$\chi^2 = 89.21$, $p < .001$, $V = 0.025$
Ethnic Dutch		42,902 (89.9)	21,944 (90.1)	
Morocco		137 (0.3)	67 (0.3)	
Turkey		136 (0.3)	72 (0.3)	
Surinam		226 (0.5)	77 (0.3)	
Other non-west		251 (0.5)	129 (0.5)	
Other west		4116 (8.6)	2069 (8.5)	
Education	44,935			$\chi^2 = 1657.95$, $p < .001$, $V = 0.192$
Low		8362 (18.6)	3299 (13.5)	
Middle-low		20,909 (46.5)	10,819 (44.4)	
Middle-high		7846 (17.5)	4817 (19.8)	
High		7818 (17.4)	5412 (22.2)	
Income	43,673			$\chi^2 = 379.38$, $p < .001$, $V = 0.093$
No, don't bother.		21,287 (48.7)	12,794 (52.5)	
No, no trouble, but I have to keep an eye on my expenses.		17,201 (39.4)	9110 (37.4)	
Yes, some effort		4236 (9.7)	2027 (8.3)	
Yes, great difficulty		949 (2.2)	416 (1.7)	
Chronic diseases			$N = 22{,}072$	
Number of chronic diseases, mean ± SD, range	28,898	2.2 ± 2.0, 0–15	2.5 ± 2.1, 0–15	$t = 12.43$, $p < .001$, $d = 0.18$
Multimorbidity,% yes	28,898	12,677 (43.9)	12,014 (54.4)	$\chi^2 = 109.79$, $p < .001$, $V = 0.062$

(*continued on next page*)

Table 1 (*continued*)

Chronic diseases in the regression				
Diabetes mellitus	44,492	6994 (15.7)	3530 (14.5)	$\chi^2 = 60.51$, $p < .001$, $V = 0.037$
Cancer	45,229	7681 (17.0)	4146 (17.0)	$\chi^2 = 0.08$, $p = .777$, $V = 0.001$
Hypertension	36,448	14,625 (40.1)	9339 (38.4)	$\chi^2 = 95.38$, $p < .001$, $V = 0.051$
Arthrosis	36,476	12,707 (34.8)	7578 (31.1)	$\chi^2 = 444.34$, $p < .001$, $V = 0.110$
Urinary incontinence	36,225	5495 (15.2)	3163 (13.0)	$\chi^2 = 273.66$, $p < .001$, $V = 0.087$
Severe back disorder	36,245	5784 (16.0)	3447 (14.2)	$\chi^2 = 179.23$, $p < .001$, $V = 0.070$
Chronic diseases not in the regression				
Rheumatoid arthritis	35,874	4062 (11.3)	$N = 24,040$	$\chi^2 = 249.86$, $p < .001$, $V = 0.083$
Cerebrovascular accidents	45,058	3678 (8.2)	2276 (9.5) $N = 24,167$	$\chi^2 = 55.91$, $p < .001$, $V = 0.035$
Myocardial infarction	44,955	4621 (10.3)	1756 (7.3) $N = 24,158$	$\chi^2 = 9.94$, $p = .002$, $V = 0.015$
Other serious cardiac disease	44,856	2676 (6.0)	2382 (9.9) $N = 24,131$	$\chi^2 = 72.94$, $p < .001$, $V = 0.040$
Migraine	35,786	2549 (7.1)	1226 (5.1) $N = 23,776$	$\chi^2 = 42.93$, $p < .001$, $V = 0.035$
Peripheral arterial disease	36,250	3112 (8.6)	1543 (6.5) $N = 24,173$	$\chi^2 = 222.75$, $p < .001$, $V = 0.078$
Chronic obstructive pulmonary disease	36,340	4637 (12.8)	1700 (7.0) $N = 24,168$	$\chi^2 = 131.31$, $p < .001$, $V = 0.060$
Psoriasis	35,943	1606 (4.5)	2740 (11.3) $N = 24,131$	$\chi^2 = 4.32$, $p = .038$, $V = 0.011$
Chronic eczema	36,187	1460 (4.0)	1040 (4.3) $N = 24,173$	$\chi^2 = 32.37$, $p < .001$, $V = 0.030$
Dizziness with falls	36,009	2557 (7.1)	875 (3.6) $N = 24,112$	$\chi^2 = 238.727$, $p < .001$, $V = 0.081$
Serious intestinal disorders	36,349	2029 (5.6)	1658 (8.1) $N = 24,240$	$\chi^2 = 119.033$, $p < .001$, $V = 0.057$
Severe neck or shoulder disorder	36,270	4911 (13.5)	1128 (4.7) $N = 24,190$	$\chi^2 = 181.16$, $p < .001$, $V = 0.071$
Severe disorder of elbow, wrist or hand	36,146	3624 (10.0)	2862 (11.8) $N = 24,115$	$\chi^2 = 200.24$, $p < .001$, $V = 0.074$
			2037 (8.4)	

Table 1 (*continued*)

Frailty				
Total, mean (SD), range	35,276	2.7 ± 2.8, 0–15	2.5 ± 2.8,0–15	$t = 12.58$, $p<.001$, $d = 0.15$
Physical, mean (SD), range	39,275	1.4 ± 1.8, 0–8	1.3 ± 1.8, 0–8	$t = 11.31$, $p < .001$, $d = 0.12$
Psychological, mean (SD), range	43,488	0.8 ± 1.1, 0–4	0.7 ± 1.0, 0–4	$t = 16.80$, $p < .001$, $d = 0.16$
Social, mean (SD), range	41,020	0.6 ± 0.8, 0–3	0.5 ± 0.8, 0–3	$t = 25.54$, $p < .001$, $d = 0.27$

[1] The number of observations in the regression sample is also provided for variables that were not in the regression analysis. This number equals 24,347 minus the number of missings in that sample.

otherwise, 0 = native), education (four categories ranging from low to high), and income (four categories; see Table 1). We included marital status only in the models for the prediction of physical and psychological frailty domains because this background variable corresponds too much to the frailty component living alone. In our regression analyses, we incorporated linear effects of education and income on multimorbidity, because these linear effects approximated their effects on frailty well in other analyses of the same dataset (van Assen et al., 2016).

In the second step of our regression analyses we added multimorbidity to the model, with multimorbidity being the sum of six dummies: diabetes mellitus, cancer, hypertension, arthrosis, urinary continence, and severe back disorder. This model assumes that all effects of the individual chronic diseases on frailty are equal, estimated by its regression coefficient. Third, we replaced the multimorbidity predictor by six disease dummies (having [1] or not having [0]: diabetes mellitus, cancer, hypertension, urinary continence, arthrosis, severe back disorder), allowing us to test different effects of these chronic diseases on frailty. We tested the null hypothesis of equal effects of these diseases on frailty by comparing the R^2s of the models in Step 2 and Step 3.

Finally, in Step 4 we added a block of 5 two-way interactions of one disease with all the other five diseases to the model. By comparing the model fit (R^2) of Step 3 with Step 4, we tested whether the effect of a disease on frailty is synergetic or not, that is, if the effect of a disease on frailty depends on whether one has other disease(s) or not. In Step 4, six analyses were conducted, each one focusing on the synergetic effects of one disease. We conducted these six analyses rather than one analysis with all 15 two-way interactions to avoid multicollinearity because of multiple interactions involving the same predictors, which would interfere with testing our hypothesis.

The effect of multimorbidity in Step 2 and of individual predictors on frailty of Step 3 and their tests are reported in a table. The effects and tests of Step 4 (interactions) are reported in a separate table. Because we conducted many statistical tests and the sample size is very large (N = 24,347), we used a statistical significance level of 0.001 in all our tests, still achieving a statistical power to detect a small effect larger than 0.9999 for all our tests.

3. Results

3.1. Descriptive statistics

The characteristics of the participants are described in Table 1. The average age of our regression sample was 72.2 years, with men comprising 45.9 %. Most participants were married (71.6 %) and ethnic Dutch (90.1 %). Compared with the total sample, the regression sample was, on average, younger (1.2 years), had fewer men (1.7 %) and more ethnic Dutch people (0.2 %), had higher education (V = 0.192), and seemed to have fewer income issues (V = 0.093). These sample differences are on the small side (V around 0.1), with the education difference being small to medium.

On average, participants in the regression sample (N = 24,347) had

2.5 chronic diseases; 54.4 % had more than one chronic disease. Of the chronic diseases, hypertension was most prevalent in the total sample (40.1 %), followed by arthrosis (34.8 %) and cancer (17.0 %). Relative to the total sample, participants in our regression sample had, on average, more chronic diseases (d = 0.18), and higher multimorbidity (V = 0.062), but prevalence figures of the six most chronic diseases were lower in the regression sample ($Vs \leq 0.11$). Frailty was also lower in the regression sample ($ds \leq 0.27$).

3.2. Regression analyses without interactions (step 1 to step 3)

The background variables explained 23.0 %, 20.7 %, 9.5 %, and 11.8 % of the variance of total, physical, psychological, and social frailty, respectively (see Table 2). Controlling for the effects of chronic diseases, nonnatives, women, and older people were, on average, more frail, married people had higher physical and psychological frailty, education was negatively associated with frailty, and income was positively associated with frailty.

Multimorbidity was associated with more frailty, with increased explained variances equal to 0.084 (f^2 = 0.122) for total, 0.115 (f^2 = 0.170) for physical, 0.02 (f^2 = 0.023) for psychological, and 0.007 (f^2 = 0.008) for social, corresponding to small effects for social and psychological frailty, a small to medium effect for total, and a medium effect for physical frailty. Effects of chronic diseases on frailty were different (see penultimate row of Table 2) for total frailty (ΔR^2 = 0.021, f^2 = 0.032), physical frailty (ΔR^2 = 0.026, f^2 = 0.04), psychological frailty (ΔR^2 = 0.009, f^2 = 0.01), and social frailty (ΔR^2 = 0.003, f^2 = 0.003), all corresponding to small effects. A comparison of effects of chronic diseases revealed that these effects on total and physical frailty were all stronger than their effects on psychological frailty, which were all stronger than their effects on social frailty. Controlling for all other predictors, urinary incontinence and severe back disorder impaired frailty most, followed by arthrosis and diabetes mellitus, and cancer and hypertension had the weakest effects.

Table 3 shows the results regarding synergetic effects of chronic diseases on frailty. No synergetic effects were found for psychological and social frailty; that is, the effect of a chronic disease on these frailty domains did not depend on the effects of other diseases (statistically nonsignificant values of ΔR^2, with all $\Delta R^{2s} <$ s0.001). The effect of each chronic disease on physical frailty depended on the effect of the other chronic diseases, but effect sizes were all (very) small ($\Delta R^2 \leq .003$), practically irrelevant, one could argue. Most noticeable is that the effect of arthrosis on physical frailty got stronger in combination with diabetes mellitus, urinary incontinence, and severe back disorder, a pattern that was also found for total frailty.

4. Discussion

Previous studies have shown that individual chronic diseases and multimorbidity are associated with frailty (Vetrano et al., 2019; Weiss, 2011). However, in these studies frailty was predominantly operationalized as a biological concept, focusing exclusively on physical limitations that older people may have. An added value of the present study is that we used a multidimensional operationalization of frailty, the Tilburg Frailty Indicator (TFI), a user-friendly self-report questionnaire for assessing physical, psychological, and social frailty (Gobbens, van Assen et al., 2010b). The aim of our study was to examine the associations of six individual common chronic diseases (diabetes mellitus, cancer, hypertension, arthrosis, urinary incontinence, and severe back disorder), and the combinations of these chronic diseases in pairs, with multidimensional frailty. We conducted this study in the Netherlands, using a sample of 47,768 community dwelling older people age 65 years or older.

With regard to the background characteristics of the sample, the regression analyses showed that age, ethnicity, lower education, and income (great financial difficulty) were associated with total (multidimensional) frailty, and all three frailty domains (physical, psychological, and social), after controlling for chronic diseases. These findings are confirmed by many previous studies that also have used the TFI to determine multidimensional frailty and its domains (van Assen et al., 2016). For three of the four frailty variables, the association with income was the largest. The exception was social frailty, with which sex had the largest association; this can possibly be explained by the fact that more women are living alone and therefore may also struggle more with feelings of loneliness. A previous study of Dutch community-dwelling older people age 75 years or older demonstrated that 28.0 % of men and 62.8 % of women lived alone, and 51.2 % of men and 64.9 % of women indicated feelings of loneliness (Gobbens, van Assen et al., 2010a).

Our first main finding is that diseases were medium and strongly

Table 2
Effect of background characteristics and diseases on total frailty and domains of frailty[1].

	Total frailty			Physical frailty			Psychological frailty			Social frailty		
	B	SE	p	B	SE	P	B	SE	P	B	SE	p
Sex (women)	0.476	0.031	**<0.001**	0.042	0.019	0.031	0.175	0.013	**<0.001**	0.210	0.009	**<0.001**
Age	0.532	0.013	**<0.001**	0.316	0.008	**<0.001**	0.064	0.005	**<0.001**	0.123	0.004	**<0.001**
Age^2	0.135	0.008	**<0.001**	0.080	0.005	**<0.001**	0.018	0.003	**<0.001**	0.026	0.002	**<0.001**
Marital status (married)				0.151	0.022	**<0.001**	0.169	0.014	**<0.001**			
Ethnicity	0.366	0.049	**<0.001**	0.212	0.030	**<0.001**	0.075	0.020	**<0.001**	0.093	0.015	**<0.001**
Education	−0.224	0.016	**<0.001**	−0.137	0.010	**<0.001**	−0.066	0.006	**<0.001**	−0.023	0.005	**<0.001**
Income	0.587	0.021	**<0.001**	0.309	0.013	**<0.001**	0.191	0.008	**<0.001**	0.111	0.006	**<0.001**
ΔR^2	0.230 F(6, 24,340) = 1214.371, **p < 0.001**			0.207 F(7, 26,157) = 977.357, **p < 0.001**			0.095 F(7, 27,626) = 414.167, **p < 0.001**			0.118 F(6, 27,085) = 605.695, **P < 0.001**		
Multimorbidity	0.740	0.014	**<0.001**	0.552	0.008	**<0.001**	0.133	0.005	**<0.001**	0.059	0.004	**<0.001**
ΔR^2	0.084 F(1, 24,339) = 2980.361 **p < 0.001**			0.115 F(1, 26,156) = 4450.531, **p < 0.001**			0.020 F(1, 27,625) = 632.296, **p < 0.001**			0.007 F(1, 27,084) = 220.925, **P < 0.001**		
Diabetes mellitus	0.631	0.043	**<0.001**	0.534	0.026	**<0.001**	0.028	0.017	0.090	0.061	0.013	**<0.001**
Cancer	0.343	0.039	**<0.001**	0.267	0.024	**<0.001**	0.086	0.016	**<0.001**	−0.003	0.012	0.781
Hypertension	0.198	0.031	**<0.001**	0.145	0.019	**<0.001**	0.034	0.012	**0.005**	0.035	0.009	**<0.001**
Urinary incontinence	1.330	0.046	**<0.001**	0.831	0.028	**<0.001**	0.347	0.018	**<0.001**	0.140	0.014	**<0.001**
Arthrosis	0.920	0.034	**<0.001**	0.758	0.020	**<0.001**	0.137	0.013	**<0.001**	0.033	0.010	**0.001**
Back disorder	1.264	0.044	**<0.001**	0.901	0.027	**<0.001**	0.228	0.017	**<0.001**	0.119	0.013	**<0.001**
ΔR^2	0.021 F(5, 24,334) = 156.405, **P < 0.001**			0.026 F(5, 26,151) = 2051.916, **p < 0.001**			0.009 F(5, 27,620) = 57.954, **p < 0.001**			0.003 F(5, 27,079) = 17.907, **P < 0.001**		
R^2 *total*	0.336, p < 0.001			0.348, p < 0.001			0.124, p < 0.001			0.128, p < 0.001		

[1] Shown are the effects of multimorbidity in step 2, and for all other predictors the effects in the final model including all predictors (except the multimorbidity predictor).

Table 3
Synergetic effects of chronic diseases on total frailty and domains of frailty[1].

	Total frailty			Physical frailty			Psychological frailty			Social frailty		
	B	SE	p	B	SE	p	B	SE	p	B	SE	p
Diabetes mellitus												
Cancer	−0.060	0.108	0.580	0.003	0.066	0.964	−0.010	0.043	0.824	−0.023	0.032	0.473
Hypertension	0.038	0.085	0.652	0.019	0.051	0.710	0.031	0.033	0.349	0.013	0.025	0.604
Urinary incontinence	0.115	0.112	0.306	0.133	0.067	0.047	−0.032	0.043	0.461	0.005	0.033	0.880
Arthrosis	0.390	0.091	**<0.001**	0.396	0.055	**<0.001**	−0.017	0.036	0.629	−0.014	0.027	0.608
Back disorder	0.214	0.115	0.062	0.060	0.069	0.389	0.057	0.045	0.204	0.059	0.034	0.082
ΔR^2	0.001 F(5, 24,329) = 6.419,			0.002 F(5, 26,146) = 14.389,			<0.001 F(5, 27,615) = 0.618,			<0.001 F(5, 27,074) = 0.792,		
	***p* < 0.001**			***p* < 0.001**			*p* = 0.686			*p* = 0.555		
Cancer												
Diabetes mellitus	−0.018	0.109	0.866	0.043	0.066	0.513	0.001	0.043	0.973	−0.028	0.033	0.395
Hypertension	−0.103	0.081	0.204	−0.038	0.049	0.438	−0.062	0.032	0.056	0.013	0.024	0.590
Urinary incontinence	−0.182	0.105	0.083	−0.244	0.064	**<0.001**	−0.088	0.041	0.034	0.050	0.031	0.109
Arthrosis	0.182	0.087	0.035	0.191	0.053	**<0.001**	0.036	0.034	0.299	−0.029	0.026	0.260
Back disorder	0.104	0.112	0.350	0.036	0.068	0.597	0.059	0.044	0.181	0.006	0.033	0.861
ΔR^2	<0.001 F(5, 24,329) = 1.926,			0.001 F(5, 26,146) = 5.224,			<0.001 F(5, 27,615) = 2.127,			<0.001 F(5, 27,074) = 0.838,		
	p = 0.086			***P* < 0.001**			*p* = 0.059			*p* = 522		
Hypertension												
Diabetes mellitus	0.056	0.085	0.509	0.037	0.051	0.473	0.037	0.033	0.271	0.009	0.025	0.722
Cancer	−0.108	0.080	0.178	−0.039	0.049	0.432	−0.057	0.032	0.077	0.005	0.024	0.830
Urinary incontinence	0.140	0.090	0.119	0.085	0.054	0.119	−0.020	0.035	0.564	0.048	0.027	0.071
Arthrosis	0.086	0.067	0.202	0.114	0.041	0.005	−0.050	0.027	0.061	0.015	0.020	0.443
Back disorder	0.159	0.088	0.069	0.111	0.053	0.038	−0.026	0.034	0.452	0.058	0.026	0.027
ΔR^2	<0.001 F(5, 24,329) = 2.481,			0.001 F(5, 26,146) = 4.401,			<0.001 F(5, 27,615) = 2.073,			<0.001 F(5, 27,074) = 2.419,		
	p = 0.030			***p* < 0.001**			*p* = 0.066			*p* = 0.034		
Urinary incontinence												
Diabetes mellitus	0.187	0.110	0.090	0.206	0.066	0.002	−0.020	0.043	0.645	−0.006	0.032	0.847
Cancer	−0.128	0.103	0.214	−0.191	0.063	0.002	−0.081	0.041	0.046	0.047	0.031	0.126
Hypertension	0.114	0.089	0.204	0.056	0.054	0.296	−0.033	0.035	0.349	0.055	0.026	0.036
Arthrosis	0.310	0.092	**<0.001**	0.255	0.055	**<0.001**	−0.002	0.036	0.954	0.064	0.027	0.019
Back disorder	0.099	0.109	0.362	0.197	0.066	0.003	−0.053	0.042	0.211	0.006	0.032	0.851
ΔR^2	0.001 F(5, 24,329) = 4.713,			0.002 F(5, 26,146) = 13.073,			<0.001 F(5, 27,615) = 1.403,			<0.001 F(5, 27,074) = 2.698,		
	***p* < 0.001**			***p* < 0.001**			*p* = 0.220			*p* = 0.019		
Arthrosis												
Diabetes mellitus	0.403	0.088	**<0.001**	0.383	0.053	**<0.001**	0.001	0.034	0.987	−0.013	0.026	0.630
Cancer	0.136	0.083	0.102	0.136	0.051	0.007	0.032	0.033	0.338	−0.027	0.025	0.274
Hypertension	0.064	0.065	0.328	0.084	0.040	0.034	−0.058	0.026	0.024	0.030	0.020	0.130
Urinary incontinence	0.267	0.090	0.003	0.236	0.054	**<0.001**	−0.016	0.035	0.642	0.066	0.027	0.012
Back disorder	0.393	0.087	**<0.001**	0.296	0.053	**<0.001**	0.040	0.034	0.249	0.041	0.026	0.109
ΔR^2	0.002 F(5, 24,329) = 12.835,			0.003 F(5, 26,146) = 27.628,			<0.001 F(5, 27,615) = 1.469,			<0.001 F(5, 27,074) = 2.629,		
	***p* < 0.001**			***P* < 0.001**			*p* = 0.196			***p* = 0.022**		
Back disorder												
Diabetes mellitus	0.298	0.112	0.008	0.147	0.068	0.030	0.061	0.044	0.164	0.043	0.033	0.194
Cancer	0.110	0.108	0.310	0.043	0.066	0.518	0.059	0.043	0.165	0.001	0.032	0.987
Hypertension	0.132	0.086	0.124	0.104	0.052	0.046	−0.050	0.034	0.140	0.060	0.025	0.019
Urinary incontinence	0.086	0.107	0.424	0.204	0.065	0.002	−0.068	0.042	0.104	0.012	0.032	0.695
Arthrosis	0.399	0.088	**<0.001**	0.295	0.054	**<0.001**	0.045	0.035	0.192	0.039	0.026	0.135
ΔR^2	0.001 F(5, 24,329) = 7.639,			0.002 F(5, 26,146) = 12.652,			<0.001 F(5, 27,615) = 1.797,			<0.001 F(5, 27,074) = 2.371,		
	***p* < 0.001**			***p* < 0.001**			*p* = 0.110			***p* = 0.037**		

[1] Shown are the interaction effects of one chronic disease with all other chronic diseases, controlled for all (main) effects shown in Table 2 (these main effects are not shown in the table). As interaction effects were tested for each chronic disease separately and there are six chronic diseases, the table contains six blocks of results.

ΔR^2 corresponds to the increase in explained variance after adding the interaction effects of one chronic disease to the model in Table 2.

associated with total and physical frailty, respectively, and had a small association with psychological and social frailty. Many other studies have confirmed the association between diseases and physical frailty. For instance, in two community health centers in China, a high prevalence of physical frailty, determined with the phenotype of frailty (Fried et al., 2001), was found among people age ≥65 years with type 2 diabetes mellitus (Kong et al., 2021). In addition, in a longitudinal study of 2455 people age 65 to 85 years conducted in six European countries (Spain, Sweden, the United Kingdom, Germany, Italy, and the Netherlands) arthrosis was associated with pre-frailty and frailty, assessed with the phenotype of frailty (Castell et al., 2015). Finally, a systematic review and meta-analysis based on five studies with a total sample of 7656 people with a mean age ≥70 years that had the objective to review the association between hypertension and frailty verified the association of hypertension and physical frailty (Vetrano et al., 2018).

Our second main finding is that the associations of the six most prevalent chronic diseases with the frailty variables differed across diseases. This finding has implications for determining multimorbidity with regard to multidimensional frailty. Often a summation of the chronic diseases present was used, in particular when the TFI was the measurement tool (Gobbens et al., 2015; Gobbens, van Assen et al., 2012b). On the basis of this study, one can conclude from the different association strengths of diseases with frailty that a different weight should be given to individual chronic diseases in a measure of multimorbidity that aims to examine associations with multidimensional frailty. Such a measure does not yet exist but may be developed in part on the basis of this study, using the regression weights of Table 2 as a starting point.

Four out of six individual chronic diseases (hypertension, urinary incontinence, arthrosis, and severe back disorder) were associated with all four frailty variables (total, physical, psychological, and social), after controlling for all other variables in the model. Diabetes mellitus and cancer were both associated with total and physical frailty; however, diabetes mellitus was not associated with psychological frailty, and

cancer was not associated with social frailty. This may be due to the operationalization of these frailty domains, but more research is needed to explain why these associations were not found. Qualitative research, including interviews with people with diabetes mellitus and cancer, may also be appropriate to gain more insight into this subject.

Our regression analyses showed that urinary incontinence had the largest association with multidimensional frailty, followed by severe back disorder and arthrosis. A systematic review and meta-analysis focusing on the association between urinary incontinence and frailty, including 11 studies (3784 participants; mean age = 78.2 years) observed that urinary incontinence is twice as common in older people with frailty (odd ratio [OR] 2.28, 95 % confidence interval [CI] 1.35–3.86; Veronese et al., 2018). A more recent retrospective cohort study showed that stress and urge urinary incontinence were associated with a 13.3 % (95 % CI [7.2–19.7]) and 18.4 % (95 % CI [8.3–29.4]) increase in score on the Frailty Index, respectively (Matta et al., 2020). The finding that urinary incontinence had a relatively strong association with frailty is also related to the fact that urinary incontinence is included as a component in several operational definitions of frailty. For example, urinary incontinence belongs to the nine frailty markers identified by Puts et al. (2005), the Edmonton Frail Scale (Rolfson et al., 2006), and the 70-item Canadian Study of Health and Aging Frailty Index (Rockwood et al., 2005). In more recent operationalizations of frailty, urinary incontinence seems to be less frequently included. This may indicate that urinary incontinence, like other chronic diseases, is increasingly viewed as a component of frailty, as this has been indicated in previous studies (Cesari et al., 2017; Fried et al., 2004; Gobbens, Luijkx et al., 2010a).

Our third main finding is that associations of diseases with frailty are not, or hardly, synergetic; that is, the association of a disease with psychological and social frailty does not get stronger in the presence of another disease, and it hardly gets stronger (negligibly stronger in practice) for physical and total frailty. The implication of this finding is that a weighted sum of diseases, as discussed previously, is sufficient to model and predict frailty. Discussing one small but interesting synergetic association is the association of arthrosis with total and physical frailty that got slightly stronger in combination with diabetes mellitus, urinary incontinence, and severe back disorder. Arthrosis is the most frequent joint disease and one of the leading causes of disability (Courties & Sellam, 2016). A systematic review and meta-analysis, including 10 studies, showed that type 2 diabetes mellitus is associated with the development and presence of arthrosis (Williams et al., 2016). A cross-sectional study of a sample of 1399 community-dwelling Japanese women age 75 to 84 years showed that low-back disorder with pain, arthrosis, and urinary incontinence were associated with one another (Kim et al., 2015). Although their synergetic associations were very small, future studies may examine the joined associations of prevalent diseases arthrosis, diabetes mellitus, urinary incontinence, and severe back disorder.

Some limitations of the present study should be noted. First, as mentioned in an article about a previous study based on the same samples, there were relatively many missing values related to frailty. About one quarter of the participants had missing values on total frailty ($n = 12{,}492$), which is more than in other studies that have used the TFI to determine multidimensional frailty (Coelho et al., 2015; Freitag et al., 2015; Gobbens, van Assen et al., 2010b). An explanation for this finding is that the TFI was positioned at the end of the long general health questionnaire for older people living in Zeebra. Although we do not believe that the missing data affected our results on the associations between diseases and frailty, given that our comparison to the excluded participants (because of missing data) showed that our participants had, on average, a higher education than the total study sample, one may want to be careful with generalizing our results to older people with low education.

Second, all data were collected by self-report. The TFI, a self-report questionnaire, was used to assess multidimensional frailty (Gobbens, van Assen et al., 2010b). This instrument does not contain performance-based tests as the phenotype of frailty has (Fried et al., 2001). However, as demonstrated before, the domains of the TFI correlated as expected with performance-based tests (Gobbens, van Assen et al., 2010b), and these performance-based tests do not increase the explained variance of psychological and social frailty on top of what can be explained by the TFI (Gobbens & van Assen, 2012). Considering the measures of the diseases, the MultiCare Cohort Study showed that the agreement of self-reported and general practitioner–reported chronic diseases in a sample of community-dwelling older people depends on the type of chronic disease; very good agreement was found for diabetes mellitus, and moderate agreement was found for hypertension and cancer (Hansen et al., 2014). In addition, the level of agreement depended on patient characteristics (e.g., age, sex, education level, and income; Hansen et al., 2014). Differences in agreement can also be explained by communication challenges between general practitioner and patient, repression, avoidance, memory problems by the patient, and differences in the understanding of a disease between general practitioner and patient (Hansen et al., 2015).

Third, we examined the associations of multimorbidity by the sum of the six most prevalent chronic diseases and combinations of these six individual chronic diseases in pairs, ignoring the less prevalent diseases. Incorporating (some of) these less prevalent diseases could have led to different findings, for example, a less prevalent disease may have a large association with frailty or have a practically relevant synergetic association.

Finally, the cross-sectional design of our study does not allow strict cause–association interpretations of the relationships between the six chronic diseases, multimorbidity, and total frailty and the three frailty domains (physical, psychological, and social). Therefore, we recommend carrying out a longitudinal study that examines the associations of chronic disease with multidimensional frailty in the short and long term, for instance, a follow-up period of 1 and 10 years, respectively.

5. Conclusions

The present study demonstrates that six chronic diseases (diabetes mellitus, cancer, hypertension, urinary incontinence, arthrosis, and severe back disorder) had medium and strong associations with total and physical frailty, respectively, and had a small association with psychological and social frailty. Of these diseases, urinary incontinence and severe back disorder had the largest associations with frailty, followed by arthrosis and diabetes mellitus, and cancer and hypertension had the weakest associations, controlling for all other predictors, including background characteristics. In addition, our study shows that the associations of the six chronic diseases with the frailty variables differ across diseases. Finally, the association of a disease with psychological and social frailty did not get stronger in the presence of another disease and only slightly stronger for physical and total frailty. The implication of our findings is that different weight should be given to individual chronic diseases in a measure of multimorbidity that aims to examine associations with multidimensional frailty.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. The Medical Ethics Review Committee decided that medical-ethics approval was not necessary because particular treatments or interventions were not offered or withheld from respondents (W12_146 # 12.17.0163). The integrity of respondents was not encroached upon as a consequence of participating in the study, which is the main criterion in medical-ethical procedures in the Netherlands (Central Committee on Research Involving Human Subjects, 2010). Informed consent, in terms of information giving and maintaining confidentially, was respected.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the Dutch Health Services of the provinces Zeeland and Brabant and the city of Amsterdam (the Netherlands), 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 from the authors upon reasonable request and with permission of the Dutch Health Services of the provinces Zeeland and Brabant and the city of Amsterdam (the Netherlands).

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CRediT authorship contribution statement

Robbert J.J. Gobbens: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Sandra Kuiper:** Writing – review & editing, Writing – original draft, Data curation. **Henriëtte Dijkshoorn:** Writing – review & editing, Writing – original draft, Data curation. **Marcel A.L.M. van Assen:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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