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Frailty measures in immuno-metabolic subtypes of late-life depression; A two-year prospective study

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ABSTRACT

Background/Objectives – Frailty is highly prevalent with increasing age. Based on the concept of depression as a disorder of accelerated aging and its association with inflammation and metabolic dysregulation, we examined whether frailty measures at baseline and over time differed between immuno-metabolic subtypes of late-life depression.

Methods – Clinical cohort study in primary and secondary mental health care with two-year follow-up. In total 359 depressed older patients (≥ 60 years) classified in four immuno-metabolic subgroups by latent profile analysis. We compared frailty measures at baseline and two-year follow-up adjusted for confounders between immuno-metabolic based depressed subgroups. Frailty measures included the frailty index, physical frailty phenotype, and two proxies (handgrip strength, gait speed).

Results – At baseline, the relatively healthy depressed subgroup (n = 181) performed best on all frailty markers. While frailty markers worsened over time, the two-year course did not differ between the subgroups for any of these markers.

Conclusion – The more severe immuno-metabolic dysregulation present in late-life depression, the more frail. Nonetheless, as trajectories over time did not differ between subgroups, the difference probably emerged at midlife. Future studies should examine whether geriatric assessment might become relevant at earlier ages in specialized mental health care.

1. Introduction

Late life depressive disorder and frailty are both geriatric syndromes and associated with aging. These conditions are bidirectionally associated (Soysal et al., 2017), which may be explained by common pathophysiological mechanisms, reinforcing the onset and progression of both conditions. The relationship with frailty may (at least partly) explain why late life depression (LLD) is associated with a more chronic course and higher relapse rates compared to younger adults (Brown et al., 2020; Collard et al., 2015, 2017). One putative mechanism underlying this association may be metabolic and inflammatory dysregulation (Cleasby, Jamieson & Atherton, 2016; Köhler et al., 2017; Marijnissen et al., 2013). Immuno-metabolic dysregulation usually starts in midlife, becomes more common with increasing age (Domiguez & Barbagallo, 2016; Franceschi, Garagnani, Parini, Giuliani & Santoro, 2018), and influences the course of depression negatively (Au, Smith, Gariépy & Schmitz, 2015; Gallagher, Kiss, Lanctot & Herrmann, 2017). Immuno-metabolic dysregulation is not only considered an important physiological aging mechanism (Clegg, Young, Iliffe, Rikkert & Rockwood, 2013), it is also one of the major physiological mechanisms for conceptualizing LLD as a disorder of accelerated biological aging (Alexopoulos, 2019). Using a data-driven approach, we previously identified four subgroups of patients suffering from LLD based on different levels of immuno-metabolic dysregulation (Kokkeler et al., 2020). We identified a large subgroup of depressed older patients with no or very minimal immuno-metabolic dysregulation and a large

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subgroup with mild metabolic and inflammatory dysregulation, with a more severe depression and worse prognosis (Kokkeler et al., 2020). We additionally identified two smaller subgroups with specific inflammatory dysregulations.

Frailty is highly prevalent with increasing age and is conceptualized as a decrease of homeostatic mechanisms of multiple physiological systems beyond normal aging. This results in a vulnerability to negative health outcomes (e.g. falls, hospitalization, disability, mortality) triggered by minor stressors (Hoogendijk et al., 2019). LLD may lead to the onset of frailty due to lifestyle-related behaviours like less physical activity, reduced social contacts, and medication non-compliance (Buigues et al., 2015; Soysal et al., 2017). Conversely, frailty may lead to disability and functional dependence, eventually leading to depression (Soysal et al., 2017). Furthermore, frailty often co-exists with chronic diseases which are also associated with LLD including diabetes, vascular disease, and congestive heart failure (Walston, 2015).

LLD is a very heterogenic disorder (regarding both phenotype and etiology) with a worse prognosis compared to younger adults (Schaakxs et al., 2018). To optimize the treatment of LLD, it may be essential to identify more etiologic homogenic subtypes of depressed patients based on underlying pathophysiological mechanisms. We hypothesize that subtypes based on immuno-metabolic dysregulation may have differential levels of frailty which in turn may point to specific treatment strategies. Especially geriatric interventions like exercise interventions, nutritional interventions, treatment of cardiovascular risk factors, less polypharmacy may be relevant (Clegg et al., 2013; Dent et al., 2019; Hoogendijk et al., 2019).

In the present study we investigated whether severity and course of frailty differed between the immuno-metabolic based depression subtypes identified in our previous study (Kokkeler et al., 2020). Because immuno-metabolic dysregulation is one of the physiological mechanisms of frailty, we hypothesized that the metabolic inflammatory dysregulated subgroup would be most frail and would have the steepest increase of frailty measures over time.

2. METHODS

2.1. Study design and sample

The study is embedded in the Netherlands Study of Depression in Older persons (NESDO), an ongoing multi-site cohort study designed to examine the course and consequences of depressive disorders in older persons ($\geq$ 60 years) (Comijs et al., 2011, 2015). The study protocol of the NESDO study was approved by the Ethical Review Board of the VU University Medical Center and the ethical review boards of the participating institutes. All participants provided written informed consent.

In brief, the cohort consists of 378 depressed and 132 non-depressed older persons aged 60–93 years, recruited in primary and secondary mental health care between 2007 and 2010. Participants with a (suspected) diagnosis of dementia, a Mini Mental State Examination (MMSE) score of <18 (out of 30 points) (Folstein, Folstein & McHugh, 1975), a primary psychotic or bipolar disorder, or insufficient command of the Dutch language were excluded.

Inclusion was based on a diagnosis of depression according to the Diagnostic and Statistical Manual of Mental Disorders-IV-R (DSM-IV-R) criteria assessed with the Composite International Diagnostic Interview (CIDI; WHO version 2.1). The CIDI is a structured clinical interview with high validity for depressive and anxiety disorders (Kessler et al., 2010; Wittchen et al., 1991). Questions were added to diagnose current minor depression according to the research criteria of the DSM-IV-R (Comijs et al., 2011). Depression was defined as a past 6-months major depressive disorder (MDD, 95%), dysthymic disorder (26.5%), or past-month minor depression (5%). Severity of depression was measured with the well-validated 30-item Inventory of Depressive Symptomatology Self Report (IDS-SR; Hegeman et al., 2012, Rush, Gullion, Basco, Jarrett & Trivedi, 1996).

Baseline assessments included face-to-face interviews, medical examinations, cognitive tests, written questionnaires, and collection of fasten blood samples in the morning. Information was gathered about mental health outcomes, demographic characteristics and psychosocial, biological, cognitive and genetic determinants. At two-year follow up, all measures open to change were administered again Comijs et al., (2015).

For the present study, we included four immuno-metabolic based subgroups of depressed older patients identified in our previous study (Kokkeler et al., 2020). In this previous study Latent Class Analysis based on baseline metabolic and inflammatory biomarkers was performed in a sample of 359 depressed older patients. The baseline biomarkers included were; waist circumference, levels of triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose level, as well as systolic, and diastolic blood pressure, high-sensitive C-reactive protein (hsCRP), interleukin-6 (IL-6), Growth Differentiation Factor-15 (GDF-15) and Neutrophil Gelatinase-Associated Lipocalin (NGAL).

- Class A, “healthy” subgroup (n = 181, 49.7%), characterized by low scores across all metabolic and inflammation markers. This depressed subgroup was characterized by comparatively lower measures of waist circumference, triglyceride, glucose, and BMI, a lower frequency of diabetes and the metabolic syndrome, and higher levels of HDL cholesterol whereas inflammation markers were not elevated.
- Class B, “metabolic and inflammatory dysregulation” subgroup (n = 137, 37.6%), characterized by the presence of the Metabolic Syndrome reflected by higher waist circumference, triglyceride-levels and systolic and diastolic blood pressure and slightly elevated inflammatory markers compared to the other subgroups.
- Class C, “severe inflammation” subgroup (n = 27, 7.4%), characterized by higher levels of inflammation markers, mostly hsCRP and IL-6 compared to the other subgroups.
- Class D, “moderate inflammation” subgroup (n = 14, 3.8%), characterized by moderately elevated inflammatory markers with specifically high levels of GDF-15 and NGAL compared to the other subgroups.

Of the total 359 patients, 273 (76%) participated in the two-year follow-up visit. See Fig. 1 for an overview of inclusion and reasons for drop-out of study participants.

2.2. Frailty measures

Several frailty measures were examined, including the frailty index (FI), the physical frailty phenotype (PFP), and two proxies for frailty namely handgrip strength and gait speed (also components of the PFP).

The FI was used as our primary outcome because it is more sensitive to change due to its continuous score compared to the categorical score of the PFP (Clegg et al., 2013; Kulminski et al., 2008). Furthermore, the FI is a more accurate predictor of mortality compared to the PFP (Kojima, Iliffe & Walters, 2018).

2.2.1. Frailty index (FI)

The frailty index is the ratio of health deficits present to the total number of deficits considered. Irrespective of the specific health deficits and the number of health deficits taken into account, the FI is a better predictor of adverse health outcomes than chronological age and other indices of biological age (Mitnitski et al., 2015). In general, patients scoring $\geq$0.25 are considered frail.

The NESDO-FI was constructed according to the guidelines by Searle, Mitnitski, Gahbauer, Gill and Rockwood (2008) and was based on 41 non-depression related health deficits concerning chronic somatic diseases, objective and subjective measures of physical performance and cognitive performance, blood-born biomarkers, sensory functioning, subjective health measures, and cognitive functioning (see Oude

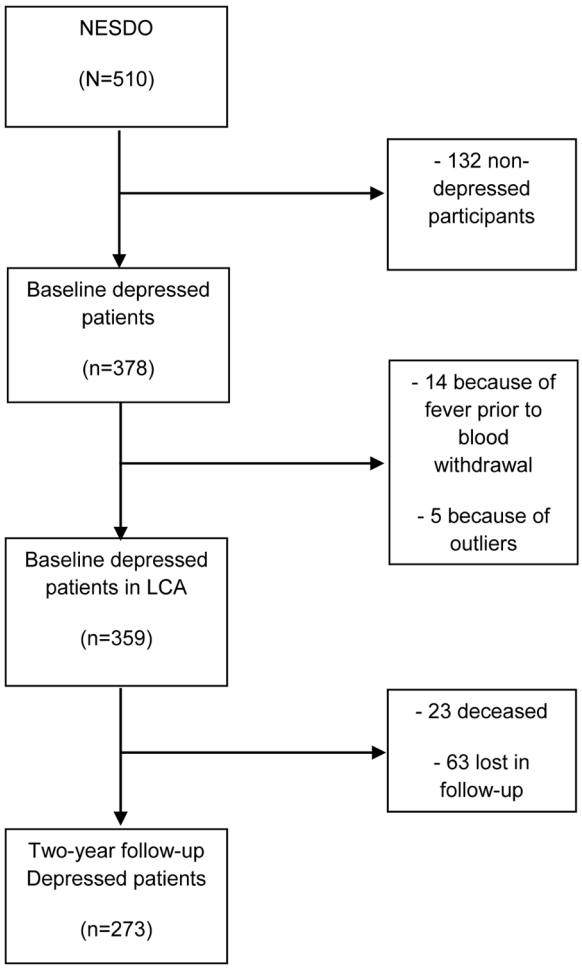

Fig. 1. Flow Chart of inclusion and drop-out study participants.

Voshaar et al., 2021).

Because of its continuous nature, the FI is sensitive to change and makes it possible to study trajectories of frailty over time (Hoogendijk, van Kan, Guyonnet, Vellas & Cesari, 2015).

2.2.2. Physical frailty phenotype (PFP)

The PFP was operationalized according to the five criteria of Fried et al., 2001 as described previously (Collard, Comijs, Naarding, Voshaar & R., 2014). Frailty was defined as presence of three or more criteria. In addition, a severity score (0–5) was computed, based on the number of criteria met. We chose the continuous PFP severity score instead of the dichotomized PFP score of Fried et al. as outcome for the analyses on course of frailty, beside the continuous FI score, because continuous outcomes are much more sensitive to change than dichotomous outcomes.

Unintentional weight loss was defined as either unwanted (self-report) weight loss of 1 kg/week or more during two or more consecutive weeks, or a body mass index (BMI) less than 18.5 kg/m2.

Weakness was defined as the maximum handgrip strength of the dominant hand assessed using a handgrip dynamometer. The best of two trials was classified depending on sex and BMI according to Fried et al., 2001 Participants unable to perform the test were also considered weak.

Exhaustion was defined as a score of 3 or 4 points on one or both of the Inventory of Depressive Symptoms (Rush et al., 2003) questions about energy level and leaden paralysis / physical energy.

Slow gait was measured using the 6-m walking test, using sex- and body height–cutoffs as extrapolated from Fried et al., 2001 (9 s for men ≤173 cm and women ≤159 cm tall; 8 s for men >173 cm and women >159 cm).

Low physical activity was determined by daily activities such as walking, and gardening, and sports activity less than once weekly, as assessed according to the short form of the International Physical Activities Questionnaire (Craig et al., 2003).

2.3. Covariates

Demographics - Demographics included age, sex, and educational level (in years).

Lifestyle and physical health indicators – Baseline indicators included current smoking (yes/no), use of alcohol, global cognitive functioning, and number of chronic diseases.

The number of alcoholic drinks per day was based on the first two items of the Alcohol Use Disorders Identification Test (AUDIT) (Aalto, Alho, Halme & Seppä, 2011; Babor, Kranzler & Lauerman, 1989). Global cognitive functioning was assessed by the Mini Mental State Examination (MMSE) (Folstein et al., 1975). The number of chronic diseases was assessed by self-report questions with high accuracy compared to general practitioner information (Kriegsman, Penninx, van Eijk, Boeke & Deeg, 1996). We asked for cardiac disease (including myocardial infarction), peripheral atherosclerosis, stroke, diabetes mellitus, COPD (asthma, chronic bronchitis or pulmonary emphysema), arthritis (rheumatoid arthritis or osteoarthritis), cancer, or any other disease.

Clinical characteristics – The diagnosis of depression or dysthymia at baseline (and two-year follow-up) according to the DSM-IV-R criteria was assessed using the Composite International Diagnostic Interview (CIDI; WHO version 2.1). The CIDI is a structured clinical interview with high validity for depressive and anxiety disorders (Wittchen et al., 1992; Kessler et al., 2010). Questions were added to diagnose current minor depression according to the research criteria of the DSM-IV-R (Comijs et al., 2011). Severity of depression was measured with the well-validated 30-item Inventory of Depressive Symptomatology Self Report (IDS-SR) (Hegeman et al., 2012; Rush et al., 1996).

The course of depression severity during the two-year follow-up was assessed using the repeated IDS-SR scores taken at baseline and every six-months until two-year follow-up. Patients were instructed to bring their medication containers, in order to check the use of medication. For the present study, we considered the baseline use of antidepressants (yes/no, as well as differentiated into categories SSRI/ TCA/ MAO/ other (e.g. Venlafaxine, Duloxetine and Mirtazapine)) of interest.

2.4. Statistical analysis

First, baseline demographics and clinical characteristics of the immuno-metabolic based subgroups identified in our previous study (Kokkeler et al., 2020) were compared using one-way ANOVA for continuous variables, and Chi^2- test for categorical variables.

Next, we compared the level of frailty between the different subgroups.

Finally, we examined the course of frailty by assessing the course of the FI, the PFP, gait speed, and handgrip strength, in separate analyses, using mixed model analysis (Twisk, de Boer, de Vente & Heymans, 2013). Models with random coefficients for intercept and/or slope per subject were compared, and the following elements were subsequently tested to determine the best fitting model, using the likelihood ratio test: (1) a general linear change in all classes (i.e. a main effect of time), (2) stable differences between the classes (i.e. a main effect of class), and (3) differences in course between the classes (i.e. an interaction between class and time). All models were adjusted for baseline covariates; age, sex, years of education, smoking, alcohol use, number of chronic diseases, global cognitive functioning, and use of antidepressants. In addition, we adjusted for the course of depression severity, as a time-varying covariate.

Analyses were conducted in SPSS, version 25. We considered p-values less than 0.05 as significant.

3. RESULTS

3.1. Characteristics of the study sample

The mean age was 70.8 (standard deviation 7.4) years (range 60–90 years) and 66.6% were females. Table 1 shows the baseline characteristics of the four immuno-metabolic based subgroups (A through D), a detailed description can be found in Kokkeler et al., 2020.

3.2. Frailty at baseline

Table 2 shows baseline parameters of frailty across subgroups. The overall prevalence of frailty in our sample according to the FI and the PFP are 45.3% and 29.4%, respectively.

The mean FI was higher in the *moderate inflammation* subgroup (class D, 0.33), the *severe inflammation* subgroup (class C, 0.29), and the *metabolic and inflammatory dysregulation* subgroup (class B, 0.29) compared to the *healthy* depressed subgroup (class A, 0.19). Based on the cut-off (FI $\geq$0.25) 23.3% of the patients in the *healthy* depressed subgroup (class A) were considered frail, which is significantly less than in the other subgroups, where 65% or more were considered frail.

According to the PFP, frailty was present in 29.4% of the patients. Here too, the *moderate inflammation* subgroup (Class D, 57.1%), the *severe inflammation* subgroup (Class C, 44.0%), and the *metabolic inflammatory* subgroup (class B, 33.6%) had a higher percentage of patients suffering from frailty than the *healthy* depressed subgroup (class A, 21.8%). Furthermore, less patients in this *healthy* depressed subgroup met the criteria for slow gait (demonstrated by a faster six meter walking time) and less met the criteria for low handgrip strength compared to all the other subgroups.

3.3. Course of frailty over two years

The two-year follow-up data were missing for 86/359 patients (24.0%). The attrition rate did not differ between subgroups ($\chi^2 = 28.3$, df=24, p=.249). The *moderate inflammation* subgroup (class D) had the highest number of dropouts (50%, including 21.4% deceased), followed by *severe inflammation* subgroup (class C) with 29.6% dropouts (11.1% deceased), and the *metabolic and inflammatory dysregulation* subgroup (class B) with a 27.7% dropouts (8.0% deceased). The healthy depressed subgroup had the least number of dropouts (18.2%, including 3.3% deceased).

To compensate for a healthy survivor effect (drop-out due to frailty, especially death), we added the number of deceased to the number of frail at the two-year follow-up assessment. Fig. 2 presents the development of the frailty percentage according to the frailty index, both excluding, and including the number of deceased at follow-up, for the four subgroups. As depicted, the number of patients suffering from frailty increased over time, and this is especially evident in the *moderate inflammation* subgroup (class D), which already had the highest percentage of frailty at baseline.

The course of frailty was further examined by Linear Mixed Models for the outcomes FI, the PFP severity score, handgrip strength, and gait speed, respectively. For all the four outcomes (in both the models adjusted and unadjusted for covariates), inclusion of a main effect of time and a main effect of class improved the fit of the models, as indicated by the likelihood ratio tests at each step. At all steps, a random intercept provided to be the best fitting model, as indicated by the likelihood ratio test. Adding a random slope did not improve the fit of the models.

Additional inclusion of an interaction effect of class by time did not improve the fit of the models any further (neither the unadjusted, nor

Table 1
Baseline differences between the immuno-metabolic depressed subgroups.

	Total sample(n 359)	Class A(n 181)	Class B(n 137)	Class C(n 27)	Class D(n 14)	P-value ANOVA/ Chi^2	F/ Chi^2	Post hocHochberg†/ Chi^2
Demographics:								
• Sex, female (%)	66.6	79.0	53.3	66.6	35.7	<0.001	29.4	*A* > B, D
• Age mean (SD), years	70.8 (7.4)	70.3 (6.9)	70.4 (7.7)	71.4 (6.3)	78.4 (8.3)	.001	5.6	*D* > A, B, C
• Years of education, mean (SD), years	10.4 (3.4)	10.8 (3.3)	10.0 (3.5)	10.5 (3.5)	9.2 (3.8)	.088	2.2	–
Mental/ physical health:								
• Current smoker (%)	25.6	23.0	27.7	25.9	35.7	.637	1.7	–
• # alcohol consumptions/ day, mean (SD)	0.55 (0.89)	0.54 (0.89)	0.58 (0.93)	0.58 (0.80)	0.38 (0.76)	.862	5.7	–
• MMSE, mean (SD)	27.7 (2.0)	27.8 (1.9)	27.6 (2.2)	28.0 (1.8)	26.8 (1.9)	.197	1.6	–
• # chronic disease, mean (SD)	2.5 (1.7)	2.2 (1.7)	2.9 (1.6)	2.7 (1.5)	3.2 (1.9)	.001	5.7	*B* > *A*
Clinical characteristics:								
• Major depressive disorder past 6 months (%)	94.7	94.5	95.6	92.6	92.9	.900	0.6	
• Dysthymia past 6 months (%)	26.2	21.0	36.5	11.1	21.4	.004	13.4	*B* >*A, C*
• Minor depression past month (%)	5.6	6.1	2.9	14.8	7.1	.095	6.4	-
• Depression severity (IDS), mean sum score (SD)	29.8 (12.9)	27.7 (12.6)	32.7 (13.1)	29.6 (11.5)	30.4 (14.2)	.009	3.9	*B* > *A*
Antidepressant use:								
• Any (%)	71.9	70.7	75.2	70.4	57.1	.495	2.4	–
• SSRI (%)	27.7	32.0	24.3	25.9	7.1	.138	5.5	–
• TCA(%)	22.1	22.2	25.5	11.1	7.1	.198	4.7	–
• MAO (%)	0.6	0.6	0.7	0.0	0.0	.959	0.3	–
• Other (%)	27.7	21.5	31.6	37.0	50.0	.028	9.1	*A* < B, D

Class A Healthy depressed subgroup.
Class B Metabolic and inflammatory dysregulation subgroup.
Class C Severe inflammation subgroup.
Class D Moderate inflammation subgroup.
† Hochberg post hoc analysis was chosen because of differences in class-size.
SD = Standard Deviation.
MMSE = Mini Mental State Examination.
IDS = Inventory of Depressive Symptomatology.
SSRI = Selective Serotonin Reuptake Inhibitor.
TCA = Tricyclic Antidepressant.
MAO = Monoamine Oxidase Inhibitor.

Table 2
Frailty at baseline in the immuno-metabolic depressed subgroups.

	Total(N 359)	Class A(n 181)	Class B(n 137)	Class C(n 27)	Class D(n 14)	P-value ANOVA/ Chi²	F/ Chi²	Post hoc Hochberg/ Chi²
Frailty								
• Frailty index, mean (SD)	0.24 (0.11)	0.19 (0.09)	0.29 (0.10)	0.29 (0.08)	0.33 (0.08)	**<.001**	37.9	A < B, C, D
• Frail according to Frailty index (%)	45.3	23.3	65.0	74.1	78.6	**<.001**	71.7	A < B, C, D
• Frail according to Frailty phenotype (%)	29.4	21.8	33.6	44.0	57.1	**.004**	13.3	A < B, C, D
• # Frailty phenotype criteria (%)						**.015**	29.3	A ≠ B, D
◦ 0	15.2	18.8	12.6	12.0	0.0			
◦ 1	31.0	35.8	28.6	20.0	14.3			
◦ 2	24.5	23.6	25.2	24.0	28.6			
◦ 3	18.6	13.3	24.4	24.0	21.4			
◦ 4	7.7	4.2	8.4	16.0	28.6			
◦ 5	3.1	4.2	0.8	4.0	7.1			
Frailty phenotype criteria								
• Low handgrip strength (%)	25.6	17.8	29.6	37.0	64.3	**<.001**	19.8	A < B, C, D D > A, B
• Handgrip strength, mean (SD) †	27.0 (10.7)	26.1 (9.7)	28.7 (11.8)	25.1 (9.9)	24.4 (10.0)	**.037**	2.9	-§
• Slow gait (%)	26.7	19.0	30.6	40.0	64.3	**<.001**	18.8	A < B, C, D B < D
• Six meter walking time, mean (SD) ‡	6.88 (1.52)	6.33 (1.45)	7.27 (1.58)	7.52 (1.08)	10.06 (1.15)	**<.001**	7.7	A < B < D

Class A Healthy depressed subgroup.
Class B Metabolic and inflammatory dysregulation subgroup.
Class C Severe inflammation subgroup.
Class D Moderate inflammation subgroup.
† corrected for thee outliers to obtain normal distribution.
‡ Ln-transformation was performed, the values listed are the retransformed mean and SD of the Ln values.
§ With the Hochberg post-hoc analysis no significant differences were found between the classes. With the less strict LSD post-hoc analyses class A was significantly different from class B.
SD = Standard Deviation.

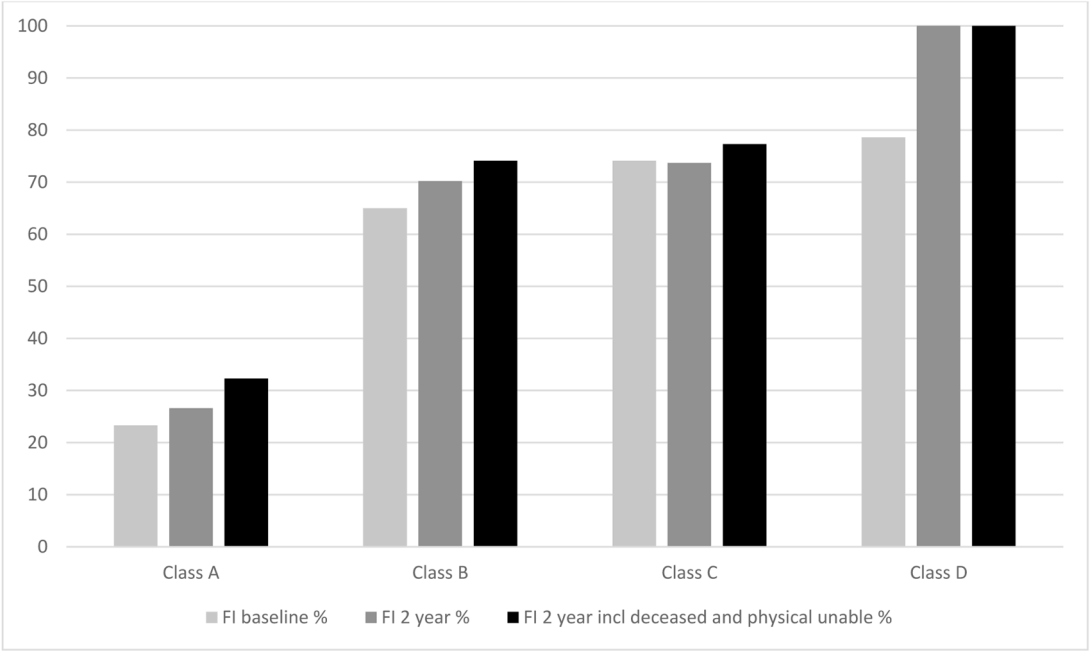

Fig. 2. Course of percentage frail on FI, including deceased, in the immuno-metabolic subgroups, FI = Frailty Index.

the adjusted model, for the latter; for FI: $F = 1.58$, p=.194, for PFP: $F = 0.68$, p=.568, for six meter walking time: $F = 0.17$, p=.918, and for handgrip strength: $F = 0.79$, p=.500). This indicates that the increase of frailty over time did not differ between the four subgroups. Table 3 presents the best fitting models for the course of frailty over the follow-up period for the four outcomes examined by linear mixed models.

3.3.1. *Course of frailty index*

The optimal mixed model showed that for all classes, the FI increased linearly from baseline with (after adjustment for covariates) 0.02 per year. The *healthy* depressed subgroup (Class A) consistently had a significantly lower FI overall compared to the other subgroups.

Table 3
Optimal models of course of frailty on four outcomes.

	Frailty index						**# Frailty Phenotype criteria**					
	Unadjusted			**Adjusted†**			**Unadjusted**			**Adjusted†**		
Effects:	**B (SE)**	**F/t**	**P**	**B (SE)**	**F/t**	**P**	**B (SE)**	**F/t**	**P**	**B (SE)**	**F/t**	**P**
• Time (years since baseline)	0.01 (0.00)	24.77	**<.001**	0.02 (0.00)	51.71	**<.001**	-0.14 (0.04)	11.83	**.001**	0.01 (0.04)	0.03	.871
• Class:		41.25	**<.001**		33.28	**<.001**		8.45	**<.001**		3.27	**.022**
○ Class A	Reference‡	-	-	Reference‡	-	-	Reference§	-	-	Reference¶	-	-
○ Class B	0.10 (0.01)	9.96	**<.001**	0.07 (0.01)	9.17	**<.001**	0.31 (0.13)	2.42	**.016**	0.02 (0.10)	0.15	.880
○ Class C	0.10 (0.02)	5.22	**<.001**	0.08 (0.01)	6.27	**<.001**	0.63 (0.23)	2.75	**.006**	0.41 (0.16)	2.46	**.014**
○ Class D	0.15 (0.03)	5.78	**<.001**	0.06 (0.02)	3.43	**.001**	1.37 (0.32)	4.28	**<.001**	0.50 (0.25)	2.01	**.045**
	Six meter walking time						**Handgrip strength**					
	Unadjusted			**Adjusted†**			**Unadjusted**			**Adjusted†**		
Effects:	**B (SE)**	**F/t**	**P**	**B (SE)**	**F/t**	**P**	**B (SE)**	**F/t**	**P**	**B (SE)**	**F/t**	**P**
• Time (years since baseline)	0.26 (0.12)	5.16	**.024**	0.45 (0.12)	13.20	**<.001**	-0.53 (0.18)	8.55	**.004**	-0.72 (0.20)	12.92	**<.001**
• Class:		6.36	**<.001**		2.83	**.039**		2.77	**.042**		2.30	.078
○ Class A	Reference±	-	-	Reference‡	-	-	Reference‡	-	-	Reference¥	-	-
○ Class B	1.36 (0.50)	2.73	**.007**	1.20 (0.47)	2.57	**.011**	2.72 (1.19)	2.29	**.023**	0.26 (0.86)	0.31	.758
○ Class C	1.41 (0.91)	1.56	.121	1.01 (0.77)	1.30	.194	-1.19 (2.16)	-0.55	.583	-1.88 (1.40)	-1.34	.180
○ Class D	4.67 (1.25)	3.74	**<.001**	2.17 (1.14)	1.90	.058	-2.90 (2.92)	-0.99	.322	-4.26 (2.05)	-2.08	**.039**

† Adjusted for age, sex, years of education, smoking, alcohol use, number of chronic diseases, global cognitive functioning, use of antidepressants, and course of IDS.
‡ No other significant differences ($p \leq .05$) between classes were found.
§ In addition: Class D differs significantly from Class B (p=.001), and marginally significant from Class C (p=.051).
¶ In addition: Class B differs significantly from Class C (p=.020), and from Class D (p=.047).
± In addition: Class D differs significantly from Class B (p=<0.001), and from Class C (p=.028).
¥ In addition: Class B differs significantly from Class D (p=.024).

3.3.2. Course of physical frailty phenotype

The unadjusted optimal mixed model showed that for all classes the PFP severity score significantly decreased linearly from baseline with 0.14 points per year. However, after adjustment for the baseline covariates and the course of depression (but not after solely correction for baseline covariates (i.e. baseline IDS score)) the PFP severity score did no longer show a significant change over time.

The *healthy* depressed subgroup (Class A) consistently showed a significantly lower PFP severity score compared to all the other classes. After adjustment for covariates this difference was maintained for the *severe inflammation* subgroup (Class C), and the *moderate inflammation* subgroup (Class D). In addition, in the adjusted model the *metabolic and inflammatory dysregulated* subgroup (Class B) showed a consistently lower PFP severity score compared to the *severe inflammation* subgroup (Class C), and the *moderate inflammation* subgroup (Class D) (not shown in the table).

3.3.3. Course of gait speed

For all classes, the six meter walking time increased linearly from baseline (after adjustment for covariates) with 0.45 s per year. The *healthy* depressed subgroup (Class A) showed a consistent significantly faster six meter walking time compared to the *metabolic and inflammatory dysregulated* subgroup (Class B), and the *moderate inflammation* subgroups (Class D). After adjustment for covariates, the difference with de *moderate inflammation* subgroup (Class D) lost its significance.

3.3.4. Course of handgrip strength

The unadjusted optimal model showed that for all classes the handgrip strength decreased with 0.53 points per year. The *healthy* depressed subgroup (Class A) consistently had a significantly lower mean handgrip strength compared to the *metabolic inflammatory dysregulated* subgroup (Class B). After adjustment for covariates, the optimal model showed a decreased handgrip strength for all classes with 0.72 point per year, and the differences between the classes were no longer significant (p=.078).

3.3.5. Post-hoc analyses

Since no difference was found in the course of frailty between the four subgroups, we did two analyses post-hoc. First, we compared the course of frailty between the two largest subgroups only, i.e. between the *healthy* depressed subgroup (Class A), and the *metabolic and inflammatory dysregulated* subgroup (Class B). Secondly, we compared the *healthy* depressed subgroup (Class A) to all the other subgroups (Class B, C, D) combined.

Both analyses did not demonstrate any significant difference in course of frailty between the classes (Class A vs Class B; PFP p=.663, Gait Speed p=.158, Handgrip strength p=.126; Class A vs Class B, C, D; PFP p=.646, Gait Speed p=.611, Handgrip strength p=.725). Regarding the FI, however, the class by time interaction approached significance (Class A compared to Class B: p=.066; and Class A compared to all other classes combined: p=.090). Interestingly, in these models the increase of FI in the *healthy* depressed subgroup (Class A), was faster compared to the *metabolic and inflammatory dysregulated* subgroup (Class B), and compared to the other subgroups (Class B, C, D) combined.

4. DISCUSSION

4.1. Main findings

The immuno-metabolic based subgroups of depressed older patients differed with respect to their level of frailty. In the relatively healthy depressed subgroup, frailty was less advanced than in the subgroups characterized by immuno-metabolic dysregulation. As expected, frailty increased over time. This was seen in the adjusted analyses of the course of FI as well as two performance-based proxies included as components in the PFP (gait speed and handgrip strength), but not of the PFP itself. This suggests that FI is more sensitive to small changes in frailty than the PFP. Furthermore, the FI was less influenced by the course of depression

compared to the PFP. In contrast with our hypothesis, the two-year course of frailty, irrespective of the specific frailty measure, did not differ between the subgroups.

4.2. Frailty in depressive subgroups

At baseline, the healthy depressed subgroup performed better on all frailty measures compared to the depressed subgroups with metabolic and/ or inflammatory dysregulation. Because of the cross-sectional observation, no causal relation can be determined, it remains unclear if the patients developed metabolic and/or inflammatory dysregulation and then became frail, or vice versa, and what role late life depression had in this process.

Frailty, and also pre-frailty is associated with inflammation, in particular elevated levels of CRP and IL-6, found in a recent meta-analysis (Soysal et al., 2016). The *severe inflammation* subgroup, characterized by depressed patients with specifically higher levels of hsCRP and IL-6, is more frail compared to the *healthy* depressed subgroup, but not compared to the other immuno-metabolic subgroups. This may be the result of the small group size.

Less research is done on the relation between metabolic dysregulation and frailty. A recent large cross-sectional study found an association between the metabolic syndrome and frailty (Buchmann et al., 2019). Obesity, the main characteristic of the metabolic syndrome, can lead to physical limitations resulting in frailty.

However, how can we explain why immuno-metabolic depressed subgroups had a different frailty level at baseline, while the increase over time did not differ between subgroups?

First, despite that there was no difference in increase of frailty over time between the subgroups, in the subgroups different underlying biological pathways can be the cause of the increased frailty measures, with the same result. As described above, inflammation, mostly hsCRP and IL-6, and metabolic dysregulation may be drivers of frailty. In the metabolic and inflammatory dysregulated subgroup (Class B), the effect on frailty might be driven by the metabolic syndrome, as well as mild elevations of hsCRP and IL-6. In the severe inflammation subgroup (Class C), frailty might be more driven by severe elevations of hsCRP and IL-6, but less metabolic dysregulation, with eventually equal result on frailty. And finally, the moderate inflammation subgroup (Class D) which is characterized by inflammation parameters more specifically related to brain health might represent a pathway to cognitive frailty. These are solely hypothesis concerning differences in increase of frailty levels, our study might have been underpowered to detect differences.

Second, frailty is a clinical phenotype which is associated with aging. Nonetheless, numerous interrelated physiological systems are involved in frailty, among which the brain, endocrine system, immune system, skeletal muscles, respiratory system, cardiovascular system, and the renal system (Clegg et al., 2013; Fried et al., 2009; Khan, Hemati & Donovan, 2019). Since so many physiological systems are involved, it may be that focussing on differences in only one of these systems, e.g. immuno-metabolic dysregulation, cannot explain any difference in the overall course of frailty. Abnormalities in one particular system are indeed less predictive for frailty than the number of abnormal systems combined (Clegg et al., 2013; Fried et al., 2009).

Third, the baseline frailty differences between the four subgroups may reflect differences in either the age of onset or speed of frailty between the subgroups. In the metabolic and/or inflammatory dysregulated subgroups, frailty might, for example, have started at an earlier age compared to the healthy depressed subgroup, and when the healthy depressed subgroup started becoming frail later in life, the speed of frailty in the immuno-metabolic dysregulated subgroups may already have diminished somewhat. Although speculative, this latter hypothesis is also supported by the post-hoc analyses, showing that the healthy depressed subgroup experienced a faster increase of the FI compared to the other subgroups, albeit not statistically significant. Although our study does not provide any evidence for this latter explanation, it is in line with other studies. For example, telomere length, a molecular marker of aging, is consistently shorter in depressed patients when compared to a non-depressed comparison group, but this difference disappears in later life (Arts et al., 2018; Verhoeven et al., 2014; Wolkowitz, Epel, Reus & Mellon, 2010). Moreover, the association between immuno-metabolic dysregulation in depression is already present at middle age (Köhler et al., 2017). Based on admixture analyses, a first depressive episode after the age of 40 years was identified as an indication of a late-onset type (Zhu et al., 2012).

4.3. Strengths and limitations

A strength of our study is the inclusion of several frailty operationalisations, as no consensus exists on the best operationalisation (Yaksic et al., 2019). In contrast to the FI, which is considered the most sensitive measure, the PFP did not change significantly over time (Kulminski et al., 2008). The fact that the PFP decreased over time in the unadjusted and adjusted analyses, but not after correction for the course of depression as a time-varying covariate, suggests that the PFP is confounded by depression. This can be explained by overlapping criteria of the PFP and depressive disorder (Fried, Ferrucci, Darer, Williamson & Anderson, 2004). In particular, our operationalisation of weight loss criterion and the low physical activity criterion might have additionally contributed to this confounding (Theou et al., 2015). Nonetheless, the use of different frailty measures facilitates comparison with previous studies, especially as the prevalence of frailty widely differs based on the FI and PFP with 45.3% and 29.4%, respectively in our study.

A limitation is that our sample contains older patients (60 years or older). As stated above, the aging process starts at an earlier age. A sample aged 45 years and over, as recently chosen in the Canadian Longitudinal Study of Aging, might have been more relevant (Raina et al., 2009). Secondly, a longer duration of follow-up and more frequent assessments might have been relevant to detect non-linear changes of frailty over time. Nonetheless, this will not be possible in the present study regarding the sample size of the different subgroups and dropout rate. Moreover, the sample size of the severe inflammation and moderate inflammation subgroup as well as high attrition rates may have led to a lack of power, masking potential differences in the course of frailty over time. Lastly, in the NESDO study no information is gathered about Activities of Daily Living (ADL) which can act as a confounder in frailty data.

4.4. Conclusion

Patients with late-life depression consist of different subgroups regarding immuno-metabolic profiles. Among depressed patients with more severe immuno-metabolic dysregulation, frailty levels seem to be higher, most likely during midlife. In old age, no difference in the course of frailty could be established with even a converging tendency. Future studies should examine whether a comprehensive geriatric assessment and intervention strategies might become relevant at earlier ages in specialized mental health care to delay frailty in immuno-metabolic dysregulated depressed subgroups.

Conflict of interest

The authors have no financial or any other kind of personal conflicts with this paper.

Author contributions

All authors (KJEK, RCOV, DR, RHSB, JS, and RMM) satisfy the four conditions of the ICMJE for an authorship by having substantially contributed to the concept of the study, interpretation of the data, critical revision of the article, approval of the final version, and agreed to be accountable for all aspects of the work. KJEK, RCOV, and RHSB

have analysed the data. KJEK has drafted the first version. RMM and RCOV supervised the research.

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The authors maintained full independence in the conduct of this work. The sponsors had no role in design, methods, subject recruitment, data collections, analysis or preparation of the manuscript.

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Disclosures

K.J.E. Kokkeler, R.C. Oude Voshaar, D. Rhebergen, R.H.S. van den Brink, J. Spijker, and R.M. Marijnissen report no disclosures.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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