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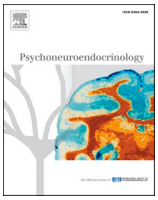

Late-life depression, allostatic load, and risk of dementia: The AGES-Reykjavik study

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ABSTRACT

Background: The current study aimed to assess if the relation between depression and dementia could be explained by allostatic load (AL) profiles, as well as assessing their risk on incident all-cause dementia, Alzheimer's disease (AD), and non-AD dementias.
Methods: The study included individuals without dementia at baseline from the population-based AGES-Reykjavik Study. Depressive symptoms assessed with the Geriatric Depression Scale-15 and AL markers were collected at baseline. Latent profile analysis (LPA) was performed on the AL markers. Incident dementia was measured during 12-years of follow-up. Cox regressions adjusted for AL profiles were performed to evaluate if AL could explain the relation between depressive symptoms and incident dementia. Additional Cox regressions exploring the interaction with depressive symptoms and AL profiles were also performed.
Results: LPA revealed four profiles based on AL factors: 'Low cardiovascular dysregulation' (43 %), 'Average' (42 % prevalence), 'High cardiovascular dysregulation' (11 %), and 'Multisystem dysregulation' (4 %). Cox regression analyses found an increased risk for dementia in the 'Multisystem dysregulation' group (HR 1.72; 95 % CI 1.26–2.33), as well as for AD (HR 1.75; 95 % CI: 1.12–2.71) and non-AD dementias (HR 1.87; 95 % CI: 1.23–2.84). AL profiles did not mediate the risk of all-cause dementia with depressive symptoms; however, there was evidence of additive interaction with depressive symptoms and the 'Multisystem dysregulation' profile and all-cause dementia (RERI 0.15; 95 % CI 0.03–0.26).
Conclusion: AL profiles and depressive symptoms were independently related to dementia. Individuals with multisystem dysregulation could be more susceptible to the negative effects of depressive symptomology on incident dementia.

1. Introduction

Dementia is characterized by debilitating cognitive impairment that increases the risk of mortality (Dewey and Saz, 2001). Today, 50 million people in the world have dementia, which is expected to triple by 2050 (Hebert et al., 2013; Livingston et al., 2020). The etiology is still not completely known, and no effective treatment is available (Tisher and Salardini, 2019). Further research on modifiable risk factors is crucial to better understand the biological underpinnings of dementia, allowing for the development of new interventions and prevention strategies, which would better the outcome for those at risk.

One of the most consistent determinants for dementia is depression (Bellou et al., 2017), yet the mechanistic relationship between the two is still not fully understood (Bennett and Thomas, 2014). Two main hypotheses regarding the relation between depression and dementia are the neurotoxicity and the vascular hypotheses. The neurotoxicity hypothesis stipulates that depression is related to dementia through increased cortisol due to dysregulation of the

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hypothalamic-pituitary-adrenal axis (Belvederi Murri et al., 2014; Byers and Yaffe, 2011; Jacobson and Sapolsky, 1991), whereas the vascular hypothesis states that depression may precede dementia through small vessel changes in mood-regulating areas (Taylor et al., 2013). In a recent study, we found that the neurotoxicity hypothesis did not explain the relation, while the vascular hypothesis did in part (Gerritsen et al., 2022). However, many risk factors overlap both depression and dementia, not only vascular and glucocorticoid factors, but also metabolic and inflammatory factors. We hypothesize that using a multisystem approach may better explain the relation between depression and dementia. An umbrella term encompassing all these biological risk factors is allostatic load (AL), which refers to the long-term, damaging physiological actions the body performs in response to stressful stimuli. While these biological factors are adaptive in response to acute stress (i.e., 'allostasis'), chronic stress over time leads to wear and tear on the body (McEwen, 2007), which can be measured by dysregulation in multiple physiological systems.

Depression has been linked to AL factors through two depressive subtypes (Lamers et al., 2010): atypical and melancholic depression. Atypical depression is characterized by altered energy intake, increased weight, female sex, and immune-metabolic physiological factors (e.g., high c-reactive protein [CRP], triglycerides, and blood pressure) (Glaus et al., 2018; Lamers et al., 2020). Whereas melancholic depression, characterized by symptoms of decreased appetite, lower body mass index, and smoking, is associated with increased cortisol levels (Lamers et al., 2013; Stetler and Miller, 2011). Further, hyperactivity in the hypothalamic-pituitary-adrenal (HPA) axis due to excess cortisol has been linked to depression (Stetler and Miller, 2011).

Dementia has also been attributed to AL factors. Cardiovascular factors, such as hypertension and Framingham vascular risk factors (e.g., total cholesterol, high-density lipoprotein [HDL] cholesterol), increase the risk for dementia (Viticchi et al., 2017; Walker et al., 2017). A recent systematic review also highlighted type 2 diabetes as one of the top modifiable risk factors for dementia, emphasizing the role of metabolic factors as well (Bellou et al., 2017). Additionally, chronically-raised high-sensitivity CRP, an inflammatory marker, has been associated with an increased risk of vascular dementia (Schmidt et al., 2002). Lastly, regarding glucocorticoids, a recent review has outlined the relationship between higher levels of cortisol and increased risk for cognitive decline and dementia (Ouanes and Popp, 2019). While these markers have been linked individually to both dementia and depression, there has been increased need to explore multisystem etiological models.

While many studies have used sum scores to assess AL, there has been an increasing need to look at possible subsystems of biomarkers to account for the complex interactions that may exist between them (D'Amico et al., 2020; Juster et al., 2010) and to assess if one subsystem (e.g., immune-metabolic) may be more of a driving factor for disease risk than another system (e.g., cardiovascular). Additionally, by utilizing latent profile analysis (LPA) over latent class analysis (LCA), using continuous data rather than dichotomizing, we allow for more variation within and between the profiles. By using a profile-based technique that can unravel these subsystems, one can link the use of studying individual biomarkers and cumulative scores by looking at possible AL subsystems. Previous research has explored profiling individuals based on AL biomarkers, highlighting increased risk for mortality based on AL profiles (Goldman et al., 2006a, 2006b; Gruenewald et al., 2006). Further research has also found associations between higher AL and lower cognitive functioning (D'Amico et al., 2020; Goldman et al., 2006a; Karlamangla et al., 2002; Seeman et al., 1997; Seplaki et al., 2006), as well as with increased depressive symptoms (Goldman et al., 2006a; Kobrosly et al., 2013; Maloney et al., 2009; Seplaki et al., 2006). However, to our knowledge, assessing if AL profiles may explain the relationship between depression and dementia has yet to be done.

The current study aimed to explore the role of AL in the known relation between depression and dementia by assessing: 1) the relationship between AL profiles and risk of dementia; 2) the relationship between depressive symptoms and these AL profiles; 3) whether AL mediates the relationship between depression and dementia; and 4) if there is additive or multiplicative interaction between depression and AL profiles on dementia risk. Based on previous research, we hypothesized to find at least one AL profile characterized by metabolic and inflammatory criteria, one by cardiovascular factors, and one without any increased AL qualities (Forrester et al., 2019). We further hypothesized that the metabolic-inflammatory and cardiovascular profiles will be associated with depressive symptoms as well as an increased risk for dementia. We had no a-priori hypothesis regarding possible mediation or interaction of AL on the relation between depression and dementia.

2. Methods

2.1. Participants

The Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study is a population-based cohort study comprised of individuals aged 65 years and older living in the Reykjavik area. It is explained in-depth elsewhere (Harris et al., 2007). Briefly, the AGES-Reykjavik Study stems from the Reykjavik Study, which was initiated in 1967 by the Icelandic Heart Association. Between 2002 and 2006, 5764 participants were included in the study, randomly selected from survivors from the Reykjavik Study. All participants underwent baseline cognitive and biometric assessments at the Reykjavik research center. Participants were followed up until 2014 to identify incident dementia diagnoses.

2.2. Standard protocol approvals, registrations, and patient consents

The Icelandic National Bioethics Committee (VSN: 00–063), the Icelandic Data Protection Authority, and the Institutional Review Board for the National Institute on Aging, NIH approved this study. Written informed consent was obtained from all participants.

2.3. Depression assessment

The Geriatric Depression Scale-15 (GDS-15) (Yesavage et al., 1982) was used to assess depressive symptoms at baseline. The GDS-15 consists of items such as apathy (e.g., 'Have you dropped many of your activities or interests?'), feelings of helplessness and hopelessness, and life satisfaction. The answer categories are binary (i.e., either present or absent), and the internal consistency has been shown to be high, with a Cronbach's alpha of 0.80 (D'Ath et al., 1994). For sensitivity analyses, a cut-off of 6 or higher was also explored to define high depressive symptomology. We chose a cut-off of 6 or higher as it has been highlighted to have a higher sensitivity and specificity in community-based settings (Pocklington et al., 2016). A diagnosis of major depressive disorder (MDD) was also assessed using the Mini-International Psychiatric Interview. For more information on depression assessment, refer to (Geerlings et al., 2013).

2.4. Dementia assessment

Ascertainment of dementia was done using a three-step procedure based on international criteria and is described in detail elsewhere (Qiu et al., 2010; Saczynski et al., 2009; Sigurdsson et al., 2017). The total sample underwent cognitive assessment, and further neuropsychological testing was done in screen positives. In step 2, persons who were positive on test results, received further neurologic and proxy examinations. Next, a multidisciplinary panel consisting of a neurologist, geriatrician, neuroradiologist, and neuropsychologist diagnosed dementia according to international guidelines (Harris et al., 2007) at baseline for exclusion and at follow-up (between 2007 and 2011) for incident dementia. All participants were also continuously followed up for incident dementia using medical and nursing home records and

death certificates for less misclassification bias of cases as controls. When an individual moved into a nursing home, all-cause dementia and Alzheimer's disease (AD) diagnoses were based on an intake exam. Additional cases within a nursing home were done by a standardized procedure done by all Icelandic nursing homes (Jørgensen et al., 1997). For the current study, all-cause dementia, AD, and non-AD dementias were defined.

2.5. AL measures

Based on previous research (Seeman et al., 2010), we included the following *cardiovascular factors* as indicative of AL: systolic blood pressure and pulse pressure (Carbone, 2020; Rodriquez et al., 2019); *lipids* as HDL, low-density lipoprotein (LDL) (Forrester et al., 2019), and triglycerides (Seeman et al., 2010); *metabolic factors* as abdominal circumference (Mauss et al., 2016) and fasting glucose (Forrester et al., 2019); an *inflammatory factor* as high-sensitivity CRP (Smith et al., 2009), and *stress factors* as morning and evening salivary cortisol (Forrester et al., 2019). Two consecutive measurements of blood pressure were taken with a mercury sphygmomanometer, with the mean systolic blood pressure value being used. Pulse pressure was defined as diastolic blood pressure subtracted from systolic blood pressure. Fasting glucose, HDL cholesterol, triglycerides, and CRP were measured on a Hitachi 912, using reagents from Roche Diagnostics. Salivary cortisol samples were collected the night before visiting the research center and the next morning 45 min after waking with Salivette® devices (Sarstedt, Rommelsdorf, Germany) and analyzed with a time-resolved immunoassay with fluorescence detection (Delfia; PerkinElmer, Waltham, MA) (Geerlings et al., 2015). Inter-assay and intra-assay variabilities were below 12 % and 10 %, respectively. The lower detection limit was 0.43 nmol/L (Geerlings et al., 2015). Salivary cortisol, CRP, triglycerides, and fasting glucose were natural log-transformed due to skewed distribution.

2.6. Other measures

At baseline, age, sex, education, and lifestyle variables were assessed via questionnaires. Education was categorized as primary, secondary, college, or university degree. Smoking was characterized as current, former, or never smoker. Alcohol use was quantified as grams per week. Physical activity (moderate-vigorous intensity) was classified by a self-reported questionnaire as never, rarely, occasionally (weekly but <1 h), moderate (1–3 h per week), or high (>4 h per week) (Mijnarends et al., 2016) and included in the model as a nominal variable. Antihypertensive or antidepressant medication was classified as none or any. Mild cognitive impairment was defined by scoring less than 1.5 standard deviations below a cut-point determined from the cohort on memory or two other domains (e.g., language, visuoperceptual/visuoconstructional, psychomotor speed, executive functions, fine motor control) (Lopez et al., 2006) and was diagnosed by a multidisciplinary panel of specialists (see above with dementia diagnosis). Metabolic syndrome was defined based on WHO criteria (Alberti and Zimmet, 1998; Auðunsson et al., 2021) as having insulin resistance (i.e., type 2 diabetes or impaired fasting glucose or tolerance), as well as any two of the following: 1) hypertension or taking antihypertensive medications, 2) dyslipidemia, or 3) obesity accompanied by a high albumin excretion rate. Prevalent stroke was defined through self-assessment or from hospital registries. Presence of APOE ε4 genotype was assessed via microplate array diagonal gel electrophoresis (MADGE) (Gudnason et al., 1993). APOE ε4 was characterized as dichotomous, classifying those with ε2/4, ε3/4, and ε4/4 genotypes as APOE ε4 positive and those with ε2/2, ε2/3, and ε3/3 genotypes as APOE ε4 negative.

2.7. Data analysis

Excluding those with dementia at baseline, 5343 individuals were included in the current analysis. To address missing values (max: 12 %) at baseline, multiple imputation (10 datasets) was performed in Mplus (v. 6.12, Muthen and Muthen, 2004). Multiple imputation in Mplus is based on Bayesian Markov chain Monte-Carlo estimation. The outcome, incident dementia, was also used as a predictor in the imputation process, but it was not imputed itself. Results from the 10 datasets were then pooled for the rest of the analyses. Chi-square tests and ANOVAs were performed to assess differences in demographic and AL variables in those with high and low depressive symptomology.

First, we created profiles based on AL variables using LPA. LPA was performed using Mplus (v. 6.12, Muthen and Muthen, 2004) with AL items as indicators. LPA uses covariance across the indicator variables to find relationships amongst individuals (Ferguson et al., 2020). All AL factors were treated as continuous in the model. To determine the number of profiles, we used the Bayesian information criterion (BIC) and Akaike information criterion (AIC) with lower values indicating a better fitting model, the Vuong-Lo-Mendell-Rubin Likelihood Ratio test (VLMR), entropy with higher values indicating a better fit, and that at least 1 % of the cohort fitting into one profile. We estimated 2–6 profiles to assess best model fit. Participants were classified based on their most likely latent profile membership for further analyses. ANOVAs were performed to assess differences between profiles on AL markers and depressive symptomology.

Next, we determined the risk of these AL profiles on developing all-cause dementia, AD, and non-AD. Univariate Cox regression analyses were performed in IBM SPSS Statistics (version 25) to estimate the hazard ratio (HR) of the association between AL profiles and all-cause dementia, AD and non-AD with follow-up years on the time scale. Model 1 corrected for age, sex, and education, and model 2 added history of stroke, smoking, alcohol use, antihypertensive and antidepressant medication, physical activity, and APOE e4 genotype as covariates. The Cox proportional hazards, influential observations, and nonlinearity assumptions were tested and met.

Finally, we estimated the risk of depression with developing all-cause dementia, AD, and non-AD, with the AL profiles as covariates. Cox regression analyses first were done with depressive symptoms as main predictor and compared to joint models adding the AL profiles to assess their individual and joint contributions to dementia risk. Next, we also assessed multiplicative interaction with depressive symptoms and AL profiles by adding product terms between depressive symptoms and AL profiles into the model. We also calculated the relative excess risk due to interaction (RERI) to assess additive interaction (Knol et al., 2007) and used the delta method to calculate the confidence interval (Hosmer and Lemeshow, 1992). Model 1 correcting for age, sex, and education, and model 2 for additional correction (see above) were also performed. Sensitivity analyses were done to explore differences in models 1 and 2 when using a clinical cut-off of the GDS-15 (6 or higher) or using a clinical diagnosis of MDD. To explore the robustness of the RERI, a sensitivity analysis exploring interaction using standardized depressive symptom scores was also performed. Lastly, a competing risk model was performed with all-cause mortality and dementia-free mortality as separate outcomes in Cox regression models.

3. Results

Of the 5343 participants (mean age at baseline: 77 years), 58 % were women (Table 1). During a 12-year follow-up (M = 8.43 years; SD = 3.43 years), 1099 individuals developed dementia with 492 cases having AD diagnosis. Most individuals (n = 900) were diagnosed via assessment in nursing homes, and an additional (n = 160) were diagnosed by the Icelandic Heart Association, and 39 by death certificates. Internal consistency of the GDS-15 was quite high with a Cronbach's alpha of 0.71.

The LPA on AL variables showed that four profiles were determined as the best-fitting model (see Supplemental Table 1). According to BIC and AIC criteria, more profiles resulted in a better fitting model. Additionally, based on the VLMR, four profiles compared to five profiles resulted in a better model fit (p = 0.047). Lastly, entropy was higher in

Table 1
Baseline characteristics in the study sample and stratified by high depressive symptomology (n = 5343).

	Total population (n = 5343)	GDS < 6 (n = 4933)	GDS 6 + (n = 410)
Age, years	77 ± 6	77 ± 6	78 ± 6
Women	58 %	57 %	65 %
Education, college + university	27 %	28 %	19 %
Current smoker	12 %	12 %	16 %
Alcohol use, gr/week	15 ± 32	15 ± 32	11 ± 24
Physical activity, moderate/high	32 %	33 %	21 %
Stroke/blood clot in brain	7 %	6 %	12 %
MCI at baseline	10 %	10 %	18 %
Metabolic syndrome	32 %	31 %	33 %
Diabetes	13 %	12 %	16 %
Antihypertensive medication	48 %	48 %	47 %
Antidepressant medication	14 %	13 %	34 %
APOE e4 genotype	28 %	28 %	28 %
Depression (M ± SD)			
GDS-15, total	2 ± 2	2 ± 1	8 ± 2
Allostatic load indicators (M ± SD)			
Systolic blood pressure (mmHg)	143 ± 21	143 ± 21	142 ± 23
Diastolic blood pressure (mmHg)	74 ± 10	74 ± 10	73 ± 11
Pulse pressure (mmHg)	69 ± 18	69 ± 18	68 ± 20
High-density lipoprotein (mmol/L)	1.6 ± 0.5	1.6 ± 0.5	1.6 ± 0.4
Low-density lipoprotein (mmol/L)	3.5 ± 1.0	3.5 ± 1.0	3.4 ± 1.0
Abdominal circumference (cm)	101 ± 12	101 ± 12	101 ± 12
Fasting glucose (mg/dL)	5.8 ± 1.2	5.8 ± 1.2	5.8 ± 1.4
Triglycerides (mg/dL)	1.2 ± 0.7	1.2 ± 0.7	1.3 ± 0.6
C-reactive protein (mg/L)	3.8 ± 6.8	3.7 ± 6.4	5.2 ± 10.7
Morning cortisol (nmol/L)	20 ± 13	20 ± 14	18 ± 15
Evening cortisol (nmol/L)	4 ± 7	4 ± 7	5 ± 6

NOTE: Diastolic blood pressure was not used in the latent profile analysis, only systolic blood pressure and pulse pressure. Missings were less than 1 % for all indicators except: 9 % for evening cortisol, 10 % for morning cortisol, and 12 % for GDS-15 sum score.
GDS = Geriatric Depression Scale-15; MCI = mild cognitive impairment.

the four profile model (0.829 v. 0.777). Therefore, we chose a four profile model. A figure of the five profile model is shown in Supplemental Fig. 1.

3.1. Description of AL profiles

The profile with the highest prevalence (i.e., 43 %) was named the 'Low cardiovascular' profile due to lower blood pressure compared to the total sample (mean systolic blood pressure: 130 mmHg vs. in the total sample: 143 mmHg) and generally average levels on all other AL markers (Fig. 1). The profile with the second highest prevalence (i.e., 42 %) was distinguished by average values across all AL domains and therefore called 'Average'. This profile was defined as the reference group for all remaining analyses. A third profile was described by high pulse pressure (mean pulse pressure: 103 mmHg vs. in the total sample: 69 mmHg) with a prevalence of 11 %, and therefore termed the 'High cardiovascular dysregulation' profile due to high levels on only cardiovascular AL markers. Lastly, a profile containing 4 % of the sample, was characterized by higher values across multiple AL domains, with higher triglycerides (2.0 mg/dL vs. 1.2 mg/dL), higher abdominal circumference (109 cm vs. 101 cm), higher glucose (10 mg/dL vs. 5.8 mg/dL), higher evening cortisol (6 nmol/L vs. 4 nmol/L), and higher CRP (5.4 mg/L vs. 3.8 mg/L). Average levels were seen regarding cardiovascular AL markers. Therefore, it was named 'Multisystem dysregulation' (Table 2, Fig. 1). ANOVAs on the AL markers reported significant differences amongst all AL markers between the profiles. Briefly, the 'High cardiovascular dysregulation' profile had the highest mean age (79 years), highest proportion of women (62 %), and lowest proportion of individuals with high education (26 %). Whereas the 'Multisystem dysregulation' profile had the lowest proportion of women (44 %) and the highest proportion of individuals with high education (30 %). Demographic and covariate information per AL profile is shown in Supplemental Table 2.

3.2. Depression and AL profiles

When comparing those with high vs. low depressive symptomology, a one-way ANOVA showed that CRP was higher in those with high depressive symptoms ($F(1, 5341) = 16.33$, $p < 0.001$), as well as higher evening cortisol ($F(1, 5341) = 14.18$, $p < 0.001$). No other AL variables differed between those with low or high depressive symptomology. When comparing the AL profiles, depressive symptoms were slightly higher in the 'High cardiovascular dysregulation' and 'Multisystem dysregulation' profiles (Supplemental Info 1).

3.3. AL profiles and dementia risk

Cox regression analyses for the first model, adjusting for age, sex, and education, showed no association between the 'High cardiovascular dysregulation' profile (HR 1.09; 95 % CI 0.89–1.32) or the 'Low cardiovascular' profile (HR 1.04; 95 % CI 0.86–1.26) compared to the 'Average' profile with all-cause dementia. There was a 59 % increased risk for all-cause dementia in the 'Multisystem dysregulation' profile (HR 1.59; 95 % CI 1.17–2.15) compared to the 'Average' profile (Table 3, model 1). Estimates and confidence intervals slightly changed in the second model after further correction for additional lifestyle factors (Table 3, model 2).

For AD dementias, there was an increased risk in the 'Multisystem dysregulation' group with full adjustment for covariates (HR 1.75; 95 %

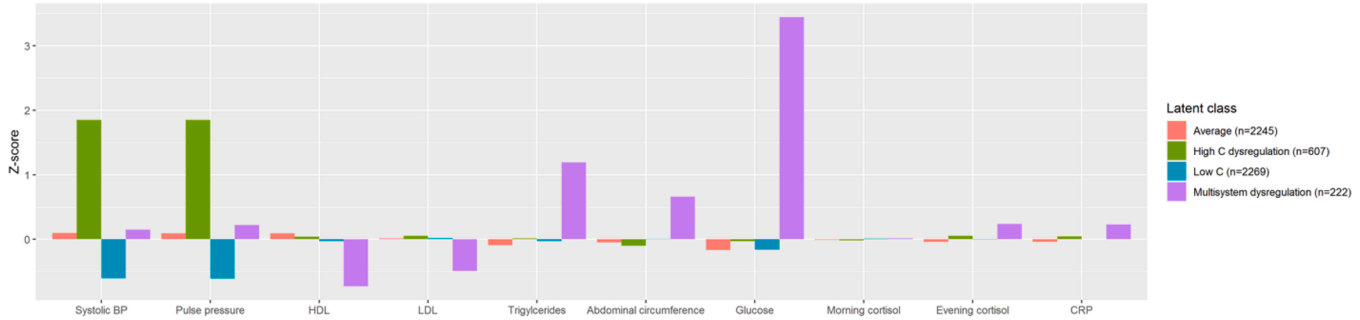

Fig. 1. Average allostatic load factor value per profile. Note: z-scores are represented here for visualization purposes. However, the variables are used in their non-standardized format in the latent profile analysis.

Table 2
Baseline characteristics of the indicators in the latent profile analysis with four profiles.

	Average n = 2245 (42 %)	High Cardiovascular Dysregulation n = 607 (11 %)	Low Cardiovascular n = 2269 (43 %)	Multisystem Dysregulation n = 222 (4 %)
Allostatic load indicators (M ± SD)				
Systolic blood pressure (mmHg)	145 ± 10	181 ± 14	130 ± 10	146 ± 17
Diastolic blood pressure (mmHg)	74 ± 9	78 ± 12	73 ± 10	73 ± 11
Pulse pressure (mmHg)	71 ± 9	103 ± 13	58 ± 9	73 ± 14
High-density lipoprotein (mmol/L)	1.6 ± 0.4	1.6 ± 0.4	1.6 ± 0.5	1.3 ± 0.4
Low-density lipoprotein (mmol/L)	3.5 ± 1.0	3.6 ± 1.1	3.5 ± 1.0	3.0 ± 1.1
Abdominal circumference (cm)	100 ± 12	100 ± 12	101 ± 12	109 ± 13
Fasting glucose (mg/dL)	5.6 ± 0.7	5.8 ± 0.8	5.6 ± 0.6	10.0 ± 2.5
Triglycerides (mg/dL)	1.2 ± 0.6	1.2 ± 0.6	1.2 ± 0.6	2.0 ± 1.2
C-reactive protein (mg/L)	3.6 ± 7.0	4.1 ± 7.4	3.8 ± 6.1	5.4 ± 9.2
Morning cortisol (nmol/L)	20 ± 16	19 ± 15	20 ± 14	20 ± 14
Evening cortisol (nmol/L)	4 ± 7	4 ± 6	4 ± 5	6 ± 10
Depressive symptoms (GDS-15 sum score)	2 ± 2	3 ± 2	2 ± 2	3 ± 2

Note: GDS-15 = Geriatric Depression Scale-15.

Table 3
HRs and 95 % CIs from the Cox regression on all-cause dementia, AD, and non-AD with allostatic load profiles.

	No. of cases	All-cause dementia (n = 1099) HR (95 % CI)	No. of cases	Alzheimer's disease (n = 492) HR (95 % CI)	No. of cases	Other dementias (n = 607) HR (95 % CI)
Model 1						
Average	459	1 (reference)	216	1 (reference)	242	1 (reference)
High Cardiovascular Dysregulation	153	1.09 (0.89; 1.32)	50	0.83 (0.61; 1.13)	102	1.34 (1.04; 1.72)
Low Cardiovascular	438	1.04 (0.86; 1.26)	203	1.01 (0.83; 1.23)	236	1.06 (0.80; 1.40)
Multisystem Dysregulation	49	1.59 (1.17; 2.15)	23	1.49 (0.96; 2.31)	27	1.81 (1.19; 2.76)
Model 2						
Average	459	1 (reference)	216	1 (reference)	242	1 (reference)
High Cardiovascular Dysregulation	153	1.19 (0.97; 1.44)	50	0.87 (0.64; 1.19)	102	1.40 (1.09; 1.79)
Low Cardiovascular	438	1.03 (0.86; 1.24)	203	1.00 (0.82; 1.22)	236	1.03 (0.82; 1.31)
Multisystem Dysregulation	49	1.72 (1.26; 2.33)	23	1.67 (1.08; 2.59)	27	1.85 (1.21; 2.81)

Model 1 is adjusted for age, sex, and education.
Model 2 is adjusted for age, sex, education, smoking, alcohol, physical activity, stroke at baseline, antihypertensive medication, antidepressant medication, and APOE e4 genotype.

CI 1.12–2.71). For non-AD dementias, an increased risk was found in the 'High cardiovascular dysregulation' group (HR 1.34; 95 % CI 1.04–1.72) and in the 'Multisystem dysregulation' group (HR 1.81; 95 % CI 1.19–2.76) in model 1 and remained with further adjustment for covariates in model 2 (Table 3).

3.4. Depression and incident dementia and the role of AL profiles

Cox regression analyses found an increased risk for incident dementia in relation to the sum-score on the GDS-15 (HR per point increase 1.12; 95 % CI 1.09–1.15) which remained in model 2. An increased risk for AD dementia (HR 1.07; 95 % CI 1.03–1.12) and non-AD dementias (HR 1.16; 95 % CI 1.12–1.21) was also found in relation to depressive symptoms, which also remained in model 2. However, when adding the AL profiles into the Cox regression to assess mediation, the effect estimates of depressive symptoms on incident dementia remained increased (Fig. 2). Further, HRs and confidence intervals were similar in the AL profiles for all-cause dementia, AD, and non-AD dementias in the joint model with depressive symptoms compared to a model with AL profiles alone (Supplemental Table 3, Table 3). Sensitivity analyses based on the GDS-15 cut-off of 6 or higher or using current MDD diagnosis showed similar results as well (Supplemental Table 4). Evidence for possible additive interaction with depressive symptoms and the 'Multisystem dysregulation' profile was found for all-cause dementia (RERI 0.15; 95 % CI 0.04–0.26), as well as non-AD dementia (RERI 0.17; 95 % CI 0.01–0.33) in model 1 (Table 4). That is, the combined effect of depressive symptoms and the 'Multisystem dysresgulation' profile on all-cause dementia and non-AD dementia was larger than the sum of the individual effects. Results stayed similar for all-cause dementia after further correction for covariates (Table 4) and when standardizing depressive symptoms (Supplemental Table 5). No evidence for interaction on the multiplicative scale was found with depressive symptoms and any AL profile (Table 4; Supplemental Table 5).

The competing risk model did not find a difference in risk when looking at dementia-free mortality compared to all-cause dementia (Supplemental Table 6).

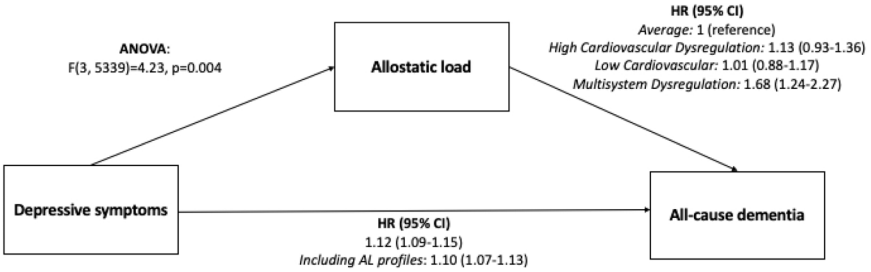

Fig. 2. Schematic diagram of the relations between depressive symptoms, allostatic load profiles, and all-cause dementia. Hazard ratios (HRs) and 95% confidence intervals are shown for the relationships between allostatic load and all-cause dementia, as well as between depressive symptoms and all-cause dementia (also adjusted for allostatic load profiles), adjusted for age, sex, education, smoking, alcohol, physical activity, stroke at baseline, antihypertensive medication, antidepressant medication, and APOE e4 genotype. AL = allostatic load.

Table 4
Additive and multiplicative interaction between depressive symptoms and AL profiles on all-cause dementia, AD, and non-AD.

	No. of cases	All-cause dementia (n = 1099)	No. of cases	Alzheimer's disease (n = 492)	No. of cases	Other dementias (n = 607)
Model 1		**HR (95 % CI)**		**HR (95 % CI)**		**HR (95 % CI)**
Multiplicative interaction						
Depressive symptoms x High cardiovascular dysregulation	153	0.99 (0.91; 1.08)	50	0.97 (0.84; 1.13)	102	0.99 (0.89; 1.10)
Depressive symptoms x Low cardiovascular	438	1.01 (0.94; 1.09)	203	1.00 (0.92; 1.10)	236	1.01 (0.93; 1.10)
Depressive symptoms x Multisystem dysregulation	49	1.10 (0.97; 1.24)	23	1.09 (0.88; 1.35)	27	1.06 (0.92; 1.23)
Additive interaction		**RERI (95 % CI)**		**RERI (95 % CI)**		**RERI (95 % CI)**
Depressive symptoms x High cardiovascular	153	0.00 (−0.07; 0.08)	50	-0.03 (−0.16; 0.09)	102	0.04 (−0.07; 0.14)
Depressive symptoms x Low cardiovascular	438	0.01 (−0.05; 0.07)	203	0.00 (−0.08; 0.08)	236	0.01 (−0.05; 0.08)
Depressive symptoms x Multisystem dysregulation	49	**0.15 (0.04; 0.26)**	23	0.13 (−0.07; 0.33)	27	**0.17 (0.01; 0.33)**
Model 2		**HR (95 % CI)**		**HR (95 % CI)**		**HR (95 % CI)**
Multiplicative interaction						
Depressive symptoms x High cardiovascular dysregulation	153	0.97 (0.89; 1.05)	50	0.95 (0.82; 1.10)	102	0.95 (0.85; 1.05)
Depressive symptoms x Low cardiovascular	438	1.08 (0.96; 1.21)	203	0.99 (0.91; 1.08)	236	1.04 (0.90; 1.20)
Depressive symptoms x Multisystem dysregulation	49	1.01 (0.95; 1.07)	23	1.09 (0.89; 1.35)	27	1.00 (0.93; 1.08)
Additive interaction		**RERI (95 % CI)**		**RERI (95 % CI)**		**RERI (95 % CI)**
Depressive symptoms x High cardiovascular	153	-0.02 (−0.10; 0.06)	50	-0.05 (−0.19; 0.08)	102	-0.01 (−0.14; 0.11)
Depressive symptoms x Low cardiovascular	438	0.01 (−0.05; 0.06)	203	-0.01 (−0.09; 0.07)	236	0.00 (−0.06; 0.06)
Depressive symptoms x Multisystem dysregulation	49	**0.15 (0.03; 0.26)**	23	0.16 (−0.05; 0.37)	27	0.15 (−0.01; 0.32)

Model 1 is adjusted for age, sex, and education.
Model 2 is adjusted for age, sex, education, smoking, alcohol, physical activity, stroke at baseline, antihypertensive medication, antidepressant medication, and APOE e4 genotype.
For information on calculation of the additive RERI by using a product term in a regression model, please see (Knol et al., 2007).
AL = allostatic load; AD = Alzheimer's disease.

4. Discussion

The current study aimed to explore the role of AL in the relation between depressive symptoms and incident dementia. Using LPA, we identified four profiles: 'Low cardiovascular', 'Average', 'High cardiovascular dysregulation', and 'Multisystem dysregulation'. A 72 % increased risk of all-cause dementia was found in the 'Multisystem Dysregulation' group, and a 41 % increased risk of non-AD dementias was found for the 'High cardiovascular dysregulation' group. Depressive symptoms were associated with a 10% higher risk of all-cause dementia with each point increase on the GDS-15, which remained after further correction of the AL profiles. Therefore, no evidence for mediation was found. Evidence for additive interaction was found between depressive symptoms and the 'Multisystem dysregulation' profile for all-cause dementia, specifically for non-AD related dementias. No multiplicative interaction was found with depressive symptoms and any AL profile.

While AL profiles and dementia have yet to be assessed previously, the results of the AL profiles with incident dementia are in line with previous studies on depression and AL profiles. This suggests that AL profiles may show similar associations with both dementia and depression. The highest risk for incident dementia was found in the 'Multisystem Dysregulation' group, which was characterized by metabolic and inflammatory factors. Previous studies on AL and depression also found an association between depression and AL profiles characterized by dysregulation in metabolic and inflammatory subsystems (Beijers et al., 2019; Carbone, 2021; Kokkeler et al., 2022; van Haeringen et al., 2022). Further, this profile was associated specifically with AD dementia as well, whereas both the 'Multisystem Dysregulation' and the 'High cardiovascular dysregulation' were associated with AD and non-AD dementias. This could be due to vascular dementia cases in the non-AD dementia subgroup. This distinction in AL profiles between subtypes of dementia should be assessed further for more precise and individualized intervention implementation.

Previous research has highlighted the most consistent evidence for risk of dementia being depression (Bellou et al., 2017). Hypotheses regarding this association have included inflammatory, stress, and vascular mechanisms that all cumulatively represent AL (Gerritsen et al., 2022; Lupien et al., 2009; Perna et al., 2021; Tetsuka, 2021). We did find that there was an indication that the joint effect of the 'Multisystem dysregulation' profile and depressive symptoms was greater than the sum of the effects of the 'Multisystem dysregulation' profile alone and depressive symptoms alone. This implies those in the 'Multisystem dysregulation' profile could be more susceptible to the negative effects of late-life depressive symptoms on incident dementia. As this is the first study assessing the role of AL profiles and depressive symptoms on incident dementia, and we had no a-priori hypothesis regarding this finding, future studies need to replicate this finding.

Strengths of this study include a large, community-based population, extensive follow-up time to determine incident dementia and the monitoring of dementia diagnosis with virtually no loss to follow-up for dementia outcome. Multiple imputation was done to address missing data and HRs were corrected for potential confounders. Further, using LPA as the analytical method allowed for using empirically-based classification instead of arbitrary cut-offs.

One limitation of the current study was that a wide range of AL markers were not available for inflammatory and stress processes, such as interleukin-6 or D-HEAS. Additionally, subtyping of dementias other than AD was not done reliably in those diagnosed in nursing homes. Therefore, we were unable to examine vascular dementia as an outcome and infer with categorical certainty our results regarding AD and non-AD individuals. It is critical to note that the population of the AGES-Reykjavik study is ethnically homogeneous. These findings need to be replicated in other populations, especially in those who are marginally underrepresented. Further, we did not have the power to distinguish between those who had remitted or prior depressive symptoms and those who only experienced late-life depressive symptoms. Thus, these results need to be validated in those who also experience high depressive symptoms in early- to midlife. Lastly, our findings regarding the interaction between depressive symptoms and the 'Multisystem dysregulation' profile needs to be replicated, as this profile was less prevalent (i.e., 4 % of the study sample).

The current study found that both a profile specifically associated with metabolic and inflammatory dysregulation, as well as increased depressive symptoms, were independently associated with an increased risk of all-cause dementia. Further, this profile showed specific susceptibility to the effects of depressive symptoms on dementia risk. Future studies on dementia should take a multifaceted approach to guide awareness for subsequent individualized prevention and treatment efforts.

Conflict of interest

All authors declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105975.

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