Characterization of depression subtypes and depression chronicity in middle aged and older adults: An Analysis of the Canadian Longitudinal Study on Aging (CLSA)

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ABSTRACT

Depression has heterogeneous symptom presentations and long-term courses, but little effort has been made to categorize depressive symptoms more finely among middle-aged and older adults, despite the increased tendency for chronic course of depression in older adults compared to younger adults. Adverse childhood experiences (ACE) and allostatic load (AL) are known to be associated with depression, but there is no comprehensive research linking these stressors to depression subtypes and its chronicity. The objectives of this research are: 1) to identify symptom-based depression subtypes at baseline among participants in the Canadian Longitudinal Study on Aging; 2) to assess their relationships with profiles of stress-related biological markers and early life adversities; and 3) to assess depression chronicity, its relationships with baseline depression subtypes, and its prognostic risk factors at three-year follow up. Participants with a baseline score of 10 or more on the Center for Epidemiological Studies Depression-10 item scale (CESD-10) were included in the analyses, and chronic depression was defined as a CESD-10 score of 10 more at both time points. Latent profile analyses were applied to baseline data on depressive symptoms, AL biomarkers and ACE, within the cross-sectional (n=3966) and longitudinal (n=3473) samples. In the cross-sectional study, multinominal logistic regression was used to determine the relationships between depression subtypes, stressors and other covariates. In the longitudinal study, chronic depression was regressed based on baseline variables using logistic regression. We identified four distinct depression subtypes, named positive affect, melancholic, typical and atypical, as well as three profiles of ACEs (low, moderate, physical abuse) and three profiles of AL (average, high-cardiovascular, low-cardiovascular). Depression subtypes had unique significant associations with stressor profiles. The strongest associations were observed for the atypical subtype (versus positive affect subtype) including a significantly lower relative risk (RRR 0.73, 95% CI: 0.57-0.93) for physical abuse-ACE, a higher risk for low-cardiovascular AL (RRR 1.31, 95%CI: 1.02-1.68), and a lower risk of high-cardiovascular AL (RRR 0.64, 95% CI: 0.49, 0.85), compared with the positive affect subtype. The prevalence of chronic depression was (46.6%), and was significantly associated with increased age group, total annual household income category, and chronic conditions score; decreased perceived social standing score; and current smoker status. Depression heterogeneity was identified, regarding symptom-based subtypes, their relationships with stress-related biological markers and early life adversities, and their relative risks for

chronicity at three-year follow-up. Additionally, we characterized the prevalence of depression chronicity, relative to baseline factors including depression subtypes, which fills a gap in the literature regarding binary courses of depression subtypes within middle-aged and older adults. We found that prognostic factors for chronic depression are consistent with commonly identified depression incidence risk factors, and that stress profiles had distinct relationships with chronicity. Important factors for chronicity include baseline depressive symptom profiles, as well as ACE profile exposures and some AL profiles. Depression subtypes had distinct associations with stress-related biological markers and early life adversity profiles, as well as distinct risks for a more chronic course. Moreover, stressor exposures may not only have an impact on the profile of depressive symptoms experienced, but may also be significantly associated with depression chronicity. Such findings have implications for personalized clinical depression management strategies, earlier identification of depression, and potential primary and secondary intervention strategies.

RÉSUMÉ

Les symptômes de la dépression et ses évolutions à long termes sont hétérogènes, mais peu d'efforts ont été faits pour catégoriser les symptômes dépressifs chez les adultes d'âge moyen et les adultes plus âgés, malgré la tendance accrue d'une évolution chronique de dépression chez les adultes plus âgés par rapport à ceux plus jeunes. Les associations des expériences négatives de l'enfance (ACE) et de la charge allostatique (AL) à la dépression sont bien connues, mais il n'existe aucune recherche approfondie reliant ces facteurs de stress aux sous-types de dépression et à sa chronicité. Les objectifs sont: 1) identifier les sous-types de dépression basés sur les symptômes des participants à l'Étude longitudinale canadienne sur le vieillissement (CLSA) à la phase initiale; 2) évaluer leurs relations avec les profils de marqueurs biologiques liés au stress et les adversités d'enfance; et 3) évaluer la chronicité de la dépression au premier suivi (3 ans), sa relation avec les sous-types de dépression initiaux et ses facteurs pronostiques. Les participants ayant un score de 10 ou plus sur l'échelle «Center for Epidemiological Studies Depression-10 Item» (CESD-10) à la phase initiale ont été inclus dans les analyses. La chronicité de la dépression a été définie comme un score CESD-10 de 10 ou plus aux deux collectes de données. Des analyses de profil latent ont été appliquées aux données du phase initiale (les symptômes dépressifs, les' ACE, les biomarqueurs AL), dans les échantillons transversaux (n = 3966) et

longitudinaux (n = 3473). Dans l'étude transversale, la régression logistique multinomiale a déterminé les relations entre les sous-types de dépression et les facteurs de stress ci-dessus. Dans l'étude longitudinale, la dépression chronique a été régressée en fonction des variables de la phase initiale par régression logistique. Nous avons identifié quatre sous-types de dépression distincts (affect positifs, mélancolique, typique et atypique), trois profils d'ACE et trois profils d'AL . Les sous-types de dépression avaient des associations uniques avec les profils de stress. Les associations les plus fortes ont été observées pour le sous-type atypique par rapport au sous-type affect positifs, y compris un risque plus faible d'abus physique-ACE (RRR 0,73; IC à 95%: 0,57-0,93), un risque plus élevé d'AL cardiovasculaire-faible (RRR 1,31; IC95%: 1,02-1,68), et un risque plus faible d'AL cardiovasculaire-élevé (RRR 0,64; IC95%: 0,49-0,85). La prévalence de la dépression chronique (46,6%) était significativement associée aux groupes plus âgés, ainsi qu'au revenu et au score des maladies chroniques plus élevés, au score de statut social perçu diminué et au statut de fumeur actuel. Nous avons caractérisé la prévalence de la chronicité de la dépression, par rapport aux facteurs initiaux, y compris les sous-types de dépression. Ceci comble une lacune dans la littérature concernant les cours binaires des sous-types de dépression chez les adultes d'âge moyen et plus âgés. Les facteurs pronostiques sont cohérents avec les facteurs de risque pour la dépression couramment identifiés, et les profils de stress montrent avoir eu des relations distinctes avec la chronicité. Les facteurs importants pour la chronicité incluaient les profils de symptômes dépressifs initiaux, les profils ACE et certains profils AL. Les sous-types de dépression avaient des associations distinctes avec des marqueurs biologiques de stress et d'ACE, ainsi que des risques distincts pour une évolution chronique. De plus, les facteurs de stress pouvaient non seulement avoir un impact sur le profil de symptômes dépressifs ressentis, mais pouvaient également être associées à la chronicité de la dépression. Ces résultats ont des implications pour les stratégies personnalisées de gestion clinique de la dépression, l'identification précoce de la dépression et les stratégies d'intervention primaires et secondaires.

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PREFACE & CONTRIBUTION OF AUTHORS

This manuscript-based thesis consists of two manuscripts (Manuscript 1 and Manuscript 2) that have been prepared for submission for publication in peer-reviewed journals. The two manuscripts represent original scholarship and distinct contributions to the body of knowledge regarding the epidemiology of depressive symptom-based subtypes and their chronicity in relation to stress.

Collaborative efforts were fundamental to the composition of the manuscripts included in this thesis. While Gabriella Spiegler is the primary author, the specific contributions of each party are as follows:

M.Sc. thesis (excluding Manuscript 1 and Manuscript 2)

Gabriella Spiegler: Drafting and revision of the thesis

Xiangfei Meng: Revision of the thesis

Norbert Schmitz: Revision of the thesis

Manuscript 1: Characterization of depression subtypes and their relationships to stressor profiles among middle-aged and older adults: An analysis of the Canadian Longitudinal Study on Aging (CLSA)

Gabriella Spiegler: Study design, drafting of ethics board and dataset application, drafting study funding applications, all analyses, interpretation of the results, drafting and revision of the manuscript

Xiangfei Meng: Study design, revision of ethics board and dataset applications, revision of the analyses, revision of interpretation of the results, and revision of the manuscript

Norbert Schmitz: Study design, and revision of the manuscript

Christina Wolfson: Revision of study design and revision of the manuscript

Muzi Li: Guidance pertaining to data processing, coding and analyses best-practices

Yingying Su: Guidance pertaining to data processing, coding and analyses best-practices

Manuscript 2: Identification of factors associated with chronicity of depression: An analysis of the Canadian Study on Aging (CLSA)

Gabriella Spiegler: Study design, drafting of ethics board and dataset application, all analyses, interpretation of the results, drafting and revision of the manuscript
Xiangfei Meng: Study design, revision of ethics board and dataset applications, revision of the analyses, revision of interpretation of the results, and revision of the manuscript
Norbert Schmitz: Study design, and revision of the manuscript
Muzi Li: Guidance pertaining to data processing, coding and analyses best-practices
Yingying Su: Guidance pertaining to data processing, coding and analyses best-practices

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CHAPTER 3: Manuscript I

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LIST OF ABBREVIATIONS

ACEs: Adverse childhood experiences

AIC: Akaike's information criterion

AL: Allostatic load

BIC: Bayesian information criterion

CLSA: Canadian Longitudinal Study on Aging

CRP: high-sensitivity C-reactive protein

CESD-10: Center of Epidemiological Studies for Depression-10 item questionnaire

eGFR: estimated glomerular filtration rate

HbA1c: Glycated hemoglobin A1c

LLD: Late-life depression

LPA: Latent profile analysis

MD: Major depression

OR: Odds ratio

RRR: Relative risk ratio

WBC: White blood cell count

95% CI: 95% confidence interval

CHAPTER 1: INTRODUCTION

The World Health Organization has identified depression as the single largest contributor to global disability (Smith and De Torres, 2014). An estimated 300 million people globally suffer from depression (Smith and De Torres, 2014). Although major depression (MD) is less common in later life compared to younger adults, it has a more chronic course, putative differences in clinical presentations (Haigh et al., 2018), and older adults with subclinical depression have reported functional impairments similar to those of MD (Blazer, 2003). Given the importance of MD and depressive symptoms as a public health concern, especially as the population age (Chang et al., 2019) research on etiology, and effective prevention and treatment is imperative.

The heterogeneity of depression (in terms of variability in risk factors, symptomatology and courses) is well documented, and has long been considered a barrier to treatment and etiological research (Ulbricht et al., 2018). Depression has been further classified according to age of onset, gender, and etiological factors (Harald and Gordon, 2012), but clinically relevant categorizations of depression remain elusive (Ulbricht et al., 2018). Data-driven methods, such as latent profile analysis, are increasingly used to classify depression, as they provide opportunities to identify latent groups and to classify observations into exclusive profiles, characterized by their responses to selected indicators items (Beijers et al., 2019; Ulbricht et al., 2018; van Loo et al., 2012; Veltman et al., 2017). To date, the indicators used in these approaches are predominantly symptom-based(Ulbricht et al., 2018). Notably, however, there is still a lack of consistent findings on identified depression subtypes, likely at least in part due to the heterogeneity of methodologies across studies (i.e. sample population, definition of depression, type and number of depression indicators used) (Ulbricht et al., 2018). Most findings have identified two to seven subtypes that are predominantly symptom and/or severity based, with three identified subtypes being the most common (Ulbricht et al., 2018). Commonly identified subtypes of depression in the literature include those named after “melancholic” and “atypical” specifiers, despite sometimes incomplete overlap with the corresponding Diagnostic and Statistical Manual of Mental Disorders (DSM)-specifier criteria (Beijers et al., 2019). Finer characterization of depression remains a relevant topic for depression research, and given the lack of consistent findings to date, deeper investigations of known factors associated with depression are needed.

The stress-vulnerability model is widely accepted for understanding the etiology of depression because it explains how biopsychosocial factors are related to depression. It argues that an individual's susceptibility to depression depends on their individual predispositions, such as genetics, which interact with contextual stressors to influence the risk of depression (Monroe and Simons, 1991). Research on the interplay between genetic vulnerability and stress for subsequent depression has been inconclusive. For instance, one study found that the effect of polygenetic risk scores (a measure of disease risk based on many genes) on depression was increased in the presence of childhood trauma (Peyrot et al., 2014), whereas another study observed that life stressors but not polygenetic risk score had independent and cumulative effects on subsequent depression (Su et al., 2022). What has been consistent is the role of stress in depression. Within context, stressful exposures may be counterbalanced by protective factors, such as social support (Atkinson et al., 2021). The perception of stress is highly relevant to depression (Cristóbal-Narváez et al., 2022), but remains subjective in nature. Accordingly, allostatic load (AL) biomarkers provide objective measures of the effects of cumulative physiological 'wear-and-tear', resulting from excessive stress and stress responses (Andreescu et al., 2019a; McEwen and Gianaros, 2011). AL is measured by a number of biomarkers that have yet to be standardized, and which span multiple physiological systems (cardiovascular, immune, metabolic, neuroendocrine). Various methods have been used to assess allostatic load, including the common method of calculating the sum of dichotomous 'high-risk' biomarkers established by clinical cut-offs or statistical means (i.e. top quartile of standardized values) (Howard and Sparks, 2016). Although elevated AL score has been associated with increased depression severity (Andreescu et al., 2019b; Kobrosly et al., 2014), few studies have investigated AL biomarkers profiles in relation to symptom-based subtypes or course of depression in middle-aged and older adults. Moreover, there is a large body of evidence linking adverse childhood experiences (ACEs) to depression (Dobson et al., 2021; Tan and Mao, 2023; Wilson-Genderson et al., 2022). Allostatic load may be one of explanations for the negative impact of ACEs on later depression(Finlay et al., 2022). There is a lack of research on the specific relationships between profiles of ACEs and depression subtypes (Dias et al., 2015; Iob et al., 2020; Li et al., 2022b).

The overall goal of this M.Sc. Thesis is to thoroughly investigate the heterogeneity of depression by understanding its latent subtypes and their relationships with stress measures, as well as how these stress measures and latent subtypes shape depression chronicity. Specifically,

this M.Sc. Thesis aims to: 1) identify latent depression subtypes among middle-aged and older adults of the Canadian Longitudinal Study on Aging Comprehensive cohort; 2) assess their relationships to profiles of stress-related biological markers and early life adversities; and 3) assess depression chronicity, its relationships with baseline depression subtypes, and its prognostic risk factors at three-year follow up.

The thesis applies the stress-vulnerability model to deepen our understanding of the heterogeneity of depression, through two conceptually related manuscripts with different aims; the first manuscript focuses on what kind of depression subtypes are present and their links to stressors, while the second manuscript investigates the roles of stressors and depression subtypes in relation to the chronic course of depression. Ultimately, the research findings of the thesis could provide insight into a finer characterization of depression subtypes, and a deeper understanding of the specific relationships between depression subtypes and various stress profiles. These findings could help to identify and link appropriate clinical management strategies and intervention strategies (with primary and secondary targets) to the appropriate depression phenotype.

CHAPTER 2: MANUSCRIPT I

In this chapter, I present our cross-sectional study in which depression subtypes were characterized on the basis of their unique combinations of symptoms and symptom severities, and their relationships with stressor profiles were elucidated. In the Discussion section of this manuscript, I describe the observed subtypes in the context of existing findings, and highlight the observed differential associations between depression subtypes, stressor profiles and other covariates. Additionally, I describe the putative mechanism by which adverse childhood experiences may be related to allostatic load and depression subtypes. This manuscript is formatted for submission to the journal *Psychiatry Research*.

Characterization of depression subtypes and their relationships to stressor profiles among middle-aged and older adults:
An analysis of the Canadian Longitudinal Study on Aging (CLSA)

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Abstract

The heterogenous clinical presentations of depression are not sufficiently reflected by current diagnostic criteria. Associations between adverse childhood experiences (ACEs), allostatic load (AL), and depression subtypes have not been extensively studied. This study aimed to characterize depression subtypes based on their clinical presentations, and to elucidate the relationships between depression subtypes, AL biomarkers, and ACEs in a sample of middle-aged and older adults. Participants from the Canadian Longitudinal Study on Aging Comprehensive cohort with a score of 10 or more on the Center for Epidemiologic Studies Depression-10 item scale were included (n=3966). Latent profile analyses were used to determine depression subtypes and AL and ACE profiles. Multinomial logistic regression was used to determine associations between depression subtypes, stressor profiles and other covariates. Four distinct depression subtypes were identified, including positive affect (63.5%), melancholic (10.5%), typical (14.4%), and atypical (11.6%). Distinct associations between depression subtypes, ACE and AL profiles, and covariates of interest were observed. In particular, the atypical depression had the largest significant associations with stressors compared to the positive affect subtype; it was associated with an higher relative risk of low-cardiovascular AL profile (RRR 1.31, 95%CI: 1.02-1.68) and a lower risk of high-cardiovascular AL profile (RRR 0.64, 95% CI: 0.49, 0.85) and a lower relative risk of physical abuse ACE (RRR 0.73, 95% CI: 0.57,0.93). The melancholic subtype had an increased risk of low cardiovascular AL (RRR 0.72, 95%CI: 0.53-0.99), and the typical subtype had a lower risk of high-cardiovascular AL (RRR 0.63, 95% CI: 0.43, 0.92). Other significant covariates differentiating the subtypes included age, sex, smoking status, chronic condition score, marital status, and physical activity. The present study describes distinct associations between depression subtypes and objective and self-reported measures of stress, as well as related factors that differentiate subtypes. The findings may inform more targeted and integrated clinical management strategies for depression in individuals exposed to multiple stressors.

Keywords: CLSA, latent profile analysis, Adverse childhood experience, Allostatic load, late life depression

1. Introduction

Major depression (MD) is projected to rank as the top burden of disease worldwide by 2030 (Organization, 2008). The heterogeneity of depression includes symptoms, prognosis, treatment, suicide risk, and relationships with other disorders, and may be related to etiological differences (Hussain et al., 2022). In older adults, despite being associated with increased risk of morbidity and mortality (Blazer, 2003; Reynolds et al., 2022), MD may be inaccurately dismissed as part of the ageing process due to perceived differences in its presentation compared to younger populations (Zhang et al., 2022). However, the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) does not distinguish late-life depression (LLD) from MD (American Psychiatric, 2022). Furthermore, the diagnosis of depression does not adequately capture the broad heterogeneity of depressive symptoms (American Psychiatric, 2022; Zhang et al., 2022); therefore, finer categorizations of depressive symptoms are needed. Finer categorization of depression is essential for etiological and treatment research, as it could help identify and link appropriate clinical treatments and prevention strategies to depression subtypes (Reynolds et al., 2022).

While the heterogeneity of depression is well documented, there is a lack of consensus on its subtypes based on clinical symptoms (Ulbricht et al., 2018). There is a paucity of studies in older adults, particularly studies that additionally examine sleep, appetite, and weight changes(Pérez-Belmonte et al., 2020; Veltman et al., 2017). Data-driven efforts, such as latent profile analysis, are commonly used to identify subtypes of depression, but their findings vary in terms of the number and characteristics of subtypes identified, often focusing on overall severity rather than combinations of symptoms (Ulbricht et al., 2018). Further, substantial methodological differences (e.g., in depression definitions, populations, type and number of analysis indicators) contribute to the heterogeneity of findings and their lack of comparability (Beijers et al., 2019; Ulbricht et al., 2018).

The stress-vulnerability model of depression argues that an individual's predisposition (i.e. genetic susceptibility, personality) to depression is related to their exposures to various stressors (Monroe and Simons, 1991). Allostatic load (AL) has been proposed as a concept to measure the cumulative physiological toll ('wear and tear') of excessive stress and stress responses (Andreescu et al., 2019a; McEwen and Gianaros, 2011). AL is measured by an array of

biomarkers that span multiple physiological systems (cardiovascular, immune, metabolic, neuroendocrine) (Howard and Sparks, 2016). AL can culminate in allostatic overload, leading to poor health outcomes such as depression (Andreescu et al., 2019b; Kobrosly et al., 2014).

Consistent with the stress-vulnerability model, stressors associated with depression span biological and psychosocial domains, but consistent insight into how they relate to depression subtypes is elusive. There is evidence supporting potential links between biological dysregulation and specific depressive symptom profiles, for example, involving hypothalamus-pituitary-adrenal (HPA) axis activation (Beijers et al., 2019; Musil et al., 2018; Veltman et al., 2017; Veltman et al., 2018), and one study observed that the presence of depression was differentially associated with specific profiles of AL-related markers (Carbone, 2021). To our knowledge, there are no studies linking depression subtypes in older adults to specific AL profiles(Kobrosly et al., 2014; Pérez-Belmonte et al., 2020). In terms of psychosocial stress, adverse childhood experiences (ACEs) are known to contribute to depression (incidence and severity) (Alexopoulos, 2005; Blazer and Hybels, 2005; Fiske et al., 2009; Kim et al., 2022; Tan and Mao, 2023), and to allostatic load (Finlay et al., 2022). ACEs are stressful or harmful early adversity events that include neglect, emotional, physical and sexual abuse, as well as exposure to household problems such as violence, mental illness, incarceration, and substance use disorders (Anda et al., 2010). Taken together, although the links between stressors and depression are well documented, findings on stressors and depression subtypes are not very consistent; furthermore, no research has been conducted that comprehensively links ACEs and AL profiles to depression subtypes.

The present study aims to: (1) identify latent depression subtypes based on their unique combinations of depressive symptoms and symptom severity among middle-aged and older adults in the Canadian Longitudinal Study on Aging (CLSA); and (2) assess their relationships with objective stress measure (AL) and self-reported stress measure (ACE) profiles.

We hypothesized that 1) distinct symptom profiles would be identified that share some characteristics of commonly identified depression subtypes, e.g. a depressive profile with weight gain (typically referred to as “atypical”); 2) some depression subtypes would have different significant associations with stressors (e.g. ACE and/or AL profiles). More stress would be associated with a more severe depressive profile.

2. Methods

2.1. Study cohort

Data from the CLSA were analyzed. Information about the CLSA data collection and participants has been described elsewhere(Raina et al., 2019). This study included participants enrolled in the CLSA comprehensive-cohort who participated at baseline and follow-up 1, with complete responses for depression items and with a score of 10 or more on the Center for Epidemiological Studies Depression-10 item scale (CESD-10). A CESD-10 score of 10 or more is considered as having concurrent depression(Björgvinsson et al., 2013). Participation in the Follow-up 1 was required for the collection of ACE data. Participants with missing responses to any of the depression questions were excluded, as were any participants who did not participate in Follow-up 1, and any participants who were pregnant (Appendix 1). A total of 3966 participants were included in the current study.

2.2 Measurements

2.2.1 Depression subtypes

In the present study, depression at baseline was classified using latent profile analysis (LPA) of 14 depressive symptom items, including: ten CESD-10 items assessing positive affect, depressive affect, and somatic complaints over the past week (Appendix 2); appetite; weight loss and weight gain; and probable insomnia disorder. The probable insomnia disorder item variable, according to Cross et al. (Cross et al., 2019), accounts for frequency and intensity of sleep disturbances over the past month, including sleep quality, trouble falling asleep, trouble staying asleep, trouble staying awake. Depression subtypes were the dependent variable of the subsequent multinomial regression.

2.2.2. Allostatic load (AL)

The AL profiles were obtained from LPA of allostatic biomarker values, which were standardized to the sample means. AL biomarkers encompass multiple physiological systems, represented in this study through the following variables: systolic and diastolic blood pressure, average pulse (cardiovascular); total cholesterol, high density cholesterol, low density cholesterol, triglycerides, glycated hemoglobin 1 (HbA1c), estimated glomerular filtration rate (eGFR), serum albumin, alanine aminotransferase (metabolic); white blood cell count, ferritin,

hemoglobin, high-sensitivity C-reactive protein (immune); as well as, body mass index, waist circumference, waist-hip ratio (anthropometric). This study used biomarkers that are commonly used to measure allostatic load (McLoughlin et al., 2020).

2.2.3. Adverse childhood experiences (ACEs)

ACEs were measured using items derived from the Childhood Experiences of Violence Questionnaire(Tanaka et al., 2012; Walsh et al., 2008) and the National Longitudinal Study of Adolescent to Adult Health Wave III questionnaire(Harris and Udry, 2022), and these 14 items were used as indicators in the ACE LPA. Participants were asked whether (0 = "no", 1 = "yes") they experienced 1) the death or serious illness of a parent or primary caretaker; 2) the divorce or separation or parents, or 3) lived with a family member with mental or psychiatric illness, prior to the age of 18 years. Frequency and severity of events related to physical abuse, emotional abuse, sexual abuse, neglect and exposure to intimate partner violence, prior to the age of 16 years old, were assessed on an ordinal scale with five response options ("never", "1-2 times", "3-5 times", "6-10 times", "more than 10 times"), as described in Appendix 3, frequency thresholds for the abuse criteria according to Tanaka et al. (2012) are also listed.

2.2.4. Covariates

To control for multimorbidity, an index of 21 medical conditions with high prevalence and impact burden in North America was constructed according to Atkinson et al. (2021). These conditions span the skeletal, nervous, endocrine, cardiovascular, lymphatic and respiratory systems, and include: heart disease, myocardial infarction, angina, stroke, transient ischemic attack, peripheral vascular disease, hypertension, diabetes, chronic obstructive pulmonary disease, Parkinsonism/Parkinson's disease, epilepsy, multiple sclerosis, migraines, osteoarthritis, osteoporosis, kidney disease, cataracts, glaucoma, cancer, mood disorders, and anxiety disorders. These chronic conditions were reported by participants as having been diagnosed by a health professional, and the number of chronic conditions experienced by each participant was summed, to create a chronic conditions score.

Basic sociodemographic and potentially confounding variables were included, selected based on the literature, where they display associations with physical status and mood or cognition. Selected covariates include age group, sex, educational level, annual household income, marital status, retirement status (Alexopoulos, 2005; Djernes, 2006). The covariates

examined are important risk factors for depression and we sought to explore their associations with depression subtypes. In addition to exploring associations with sex and age, we also sought to investigate whether depression subtypes were associated with retirement status(Li et al., 2021) (i.e. fully retired, partially retired, not retired). Additional covariates associated with depression in some populations were examined, including immigration status, race (i.e. identified as white or not), and orientation (i.e. identified as heterosexual or not)(Vyas et al., 2020). Perceived social standing was selected as a potential covariate, prior to stepwise model selection. The 'Perceived social standing' score is used to measure social inequality, by using the MacArthur Scale of Subjective Social Status, to assess where participants rate their standing in their communities (1 = "lowest social standing" to 10 = "highest social standing"). Subjective social status has been shown to be associated with health outcomes (Demakakos et al., 2008; Kwong et al., 2020). Health behaviours included smoking status, frequency of alcohol consumption, and whether the participant met the World Health Organisation guidelines for physical activity for this age group, calculated as binary indicator if the guidelines were met, as per Raina et al. (2021).

2.3. Statistical analyses

2.3.1 Imputation

For participants with partially missing data for biomarkers, ACEs, chronic conditions, and sociodemographic characteristics (SDCs), missing values were imputed in *Stata* version 16.0, using multiple chained imputation. For each variable, 20 iterations were performed on missing responses, and imputed values were dependent on age and sex responses. For each missing observation, the 20 imputated values were pooled as their mean. For categorical variables (i.e. ACEs and SDCs) this value was then rounded to the nearest integer.

2.3.2. Latent profile analysis (LPA)

The *tidyLPA* package in *Rstudio* (2022.12.0) was used to perform the latent profile analyses for depressive symptom, allostatic load, and adverse childhood experience profiles. For each of the LPAs, the profile solution with the best model fit was determined based on decreased values for the fit indices, i.e. Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample size-adjusted BIC, log likelihood, bootstrap likelihood ratio test p-value,

as well as higher entropy values, adequate profile prevalences, and potential clinical interpretation for each profile.

2.3.3. Regression analysis

Depression subtypes were the outcome for the multinomial logistic regression analysis. The *multinom* function, part of the *nnet* package in *Rstudio*, was used to explore associations between the outcome and AL and ACE profiles, while controlling for other covariates. Stepwise selection was performed on all covariates of interest using the *stepAIC* function with its default arguments (part of the *MASS* package in *Rstudio*). The optimized model contained the lowest AIC and covariates with significant p-values ($p<0.05$). Models with and without interaction terms were compared using the likelihood ratio test, and the final model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test for multinomial regression.

3. Results

3.1. Characteristics of the study cohort

The characteristics of the study cohort are shown in Table 1. Briefly, the sample was predominantly in the 45-54 and 55-64 year age categories and was predominantly female (61.5%). More than half of the participants were married or living with a partner in a common-law relationship (56.7%), and most had attained post-secondary education (72.9%). The dominant annual household income categories were between $20,000 and $100,000 inclusive. Most participants were white, non-immigrant, heterosexual, and lived with an average of 3 chronic conditions (Table 1).

3.2. Latent Profiles

Figure 1 shows the four identified depression subtypes with different symptomologies: positive affect (63.5%), melancholic (10.5%), typical (14.4%), and atypical (11.6%). The positive affect subtype had fewer symptoms overall, with more frequent positive affects and less frequent depressive affects and somatic complaints compared to the other profiles. The melancholic depression subtype was characterized by the least frequent positive affects and the most frequent depressive affects and somatic complaints overall, including the highest mean score for probable insomnia and the poorest mean appetite. The last two profiles had similar frequencies of the depressive items and were characterized by their opposite weight changes: the

typical subtype had considerable weight loss, whereas the atypical subtype had weight gain. The 'atypical' profile had slightly fewer positive affects than its 'typical' counterpart, and more somatic complaints and poorer appetite.

Appendix 4 provides model fit indices comparing the depression LPA solutions, and profile estimates are in Appendix 5. Three allostatic load profiles were identified, shown in Figure 2, and were labeled "average" (47.6%), "low-cardiovascular" (35.2%), and "high-cardiovascular" (17.2%). The "average" AL profile was characterized by near-average values across the AL items, and this profile was used as the reference group for multinomial regression. The low-cardiovascular AL profile had items that were below the sample mean, including cardiovascular, anthropometric and HbA1c markers, and had higher lipid metabolism markers (except for lower triglycerides). This profile also had lower levels of ferritin and hemoglobin levels, as well as lower high-sensitivity C-reactive protein (CRP) and white blood cell (WBC) count. The final profile, labeled "high-cardiovascular", had an AL profile opposite to the "low-cardiovascular" with cardiovascular markers above the sample mean, as well as higher anthropometric markers and HbA1c (blood glucose), lower than average cholesterol markers, lower serum albumin and alanine aminotransferase, and tended to have higher immune-related biomarkers, i.e. CRP, WBC.

Model fit indices for the AL LPA are presented in Appendix 6, and profile estimates are in Appendix 7. Three profiles of adverse childhood experiences were identified, including low ACE (69.1%), moderate ACE (20.1%), and physical abuse ACE (10.9%) (Figure 3). Several models from the ACE LPA are shown in Appendix 7, and profile estimates are in Appendix 8. The low ACE profile was characterized by little or no ACE exposure on average, with some experience of physical abuse (i.e. slapping and spanking). The moderate ACE profile was characterized by relatively more experiences of ACEs related to witnessing IPV, emotional abuse and neglect, with some physical abuse (higher frequency of slap and spank). The physical abuse ACE profile had the highest mean item scores overall, with the highest frequency of physical abuse (kicking, pushing, slapping, spanking) and the highest prevalence of sexual abuse.

3.3. Associations between depression subtypes and stress measures (AL and ACE profiles)

Interactions between stressor profiles (ACE, AL) and age group and identified sex were examined but were not significant and were not included in the final model; additionally, models with and without interaction terms were compared. The final model fit was adequate ($p>0.05$).

Table 2 shows the unadjusted and final models from the multinomial logistic regression on factors associated with depression subtypes. After adjusting for covariates of interest and potential interactions, the melancholic depression subtype had a significantly decreased risk of the low-cardiovascular AL profile (relative risk ratio (RRR) 0.72, 95%CI: 0.53-0.99), whereas the typical depression subtype had a significantly decreased relative risk of the high-cardiovascular AL profile (RRR 0.63, 95% CI: 0.43, 0.92) compared to the positive affect group. The atypical subtype was significantly associated with both a higher relative risk of the low-cardiovascular AL profile (RRR 1.31, 95%CI: 1.02-1.68) and a lower risk of the high-cardiovascular AL profile (RRR 0.64, 95% CI: 0.49, 0.85). The physical abuse ACE profile was significantly associated with a lower relative risk of the atypical depression subtype (RRR 0.73, 95% CI: 0.57,0.93) compared with the positive affect depression subtype. Depression subtypes had different significant associations with the other covariates (age, sex, smoking status, chronic condition score, marital status, physical activity). For example, higher relative risk of the atypical depression subtype was additionally significantly associated with increasing age categories (RRRs increased with age), male sex (RRR 1.65, 95% CI: 1.30-2.10), but a lower relative risk for a given chronic condition score (RRR 0.92, 95% CI: 0.88-0.97), compared with the positive-affect depression subtype.

4. Discussion

The present study provides evidence of associations between latent profiles of ACEs and AL, and depressive symptom-based subtypes in middle-aged and older adults. As expected, specific depression subtypes were associated with unique profiles of ACEs and AL biomarkers, with the largest difference between positive affect and atypical depression subtypes.

We identified four distinct depression subtypes, including positive affect, melancholic, atypical, and typical depression. The patterns of depressive symptoms in each subtype were similar overall and differed mainly in severity. The positive affect subtype had lower overall levels of symptoms, including the most common mood reactivity, but had similar mean weight changes to the melancholic depression. Although no direct comparison can be made between the

melancholic subtype and the corresponding DSM-5 specifier MD 'with melancholic features', this subtype showed some similarities, such as low mood reactivity ('felt happy', 'felt hopeful'); distinct quality of depressed mood ('felt depressed');and marked psychomotor agitation or retardation, (felt 'everything is effort', 'couldn't get going')(American Psychiatric, 2022). Unlike the DSM-5 criteria, excessive or inappropriate guilt was not measured, and this subtype did not experience significant weight loss (American Psychiatric, 2022). We found two depression subtypes, "atypical" and "typical", with significant weight changes. The nature of the person-based procedure (as well as differences in methodology) precludes direct comparisons with other studies; however, we observed some similarities with other findings (i.e., melancholic, atypical, positive-affect), as suggested in a recent review of depression subtypes (Ulbricht et al., 2018). We did not identify a "somatic" subtype, which is consistent with the findings in previous studies (Beijers et al., 2019). Notably, the application of different methodologies to identify depression subtypes hinders the comparison of various data-driven findings (Beijers et al., 2019). The identified subtypes had different associations with psychosocial and biological stress.

There is substantial evidence of an association between childhood maltreatment and the risk of developing depression later in life (Gardner et al., 2019; Li et al., 2022a; Tan and Mao, 2023). Other research suggests that physical abuse may be associated with an increased risk of developing atypical depression, i.e. MD with reversed neurovegetative symptoms (hypersomnia and weight gain or hyperphagia), compared with those broadly categorized as non-atypical MD (Brailean et al., 2020; Matza et al., 2003). Because the aforementioned studies, as well as the current study, used different reference groups, we cannot draw conclusion about the specific association between certain childhood adversities and depression subtypes. Notable differences in the current study compared to the others are the use of the positive-affect depression subtype as the reference group and the omission of depression severity and MD diagnosis. In the literature, ACEs are associated with greater depression severity (Chen et al., 2022; Tan and Mao, 2023), and in the above studies atypical-depression was associated with greater severity (Brailean et al., 2020; Matza et al., 2003), so this may also contribute to the discrepancy in the findings. A recent study using the UK biobank found that physical abuse was strongly associated with suicidal behaviour, psychomotor changes, and low mood (Chaplin et al., 2021). This is consistent with the association we found between physical abuse-ACE and atypical depression, as this subtype of depression was characterized by slightly lower positive affect but higher

somatic complaints. We found a differential effect of physical abuse-ACE on positive affect compared to atypical depression.

Associations between ACEs and depression have been linked to findings on AL-biomarkers (Finlay et al., 2022; O'Shields and Gibbs, 2021; Scheuer et al., 2018). AL as a concept has been proposed to understand the psycho-neuroendocrinological consequences of stress (Mello et al., 2009) as well as the negative consequences of childhood adversity in the current context. Previous research has suggested that alterations in the HPA axis may mediate the response to childhood adversity and manifestations of depressive symptoms, which have been used to group depression subtypes (Vares et al., 2015). The unique associations between depression subtypes and AL profiles that we identified also support this hypothesis. Compared to the positive affect depression subtype, melancholic depression was less likely to have a low-cardiovascular AL profile, whereas atypical and typical depression were less likely to have a high-cardiovascular AL profile. There is a paucity of research on the relationships among different ACE profiles, AL profiles, and depression subtypes; however, based on separate research findings between ACEs and depression and AL and depression, the potential explanations for the identified associations are as follows. Exposures to ACEs would contribute to allostatic overload, i.e. dysregulation of biological factors involved in the stress response. Accordingly, the dysregulated HPA axis may give rise to a large number of chemical and inflammatory biomarkers, involved in mediating the stress response process(Felger and Lotrich, 2013; Heim et al., 2008). In response to such signaling, the brain would determine the behavioral and physiological responses to such stress challenges. The limbic system is known to be intimately involved in the etiopathogenesis of depression and other mood disorders. In particular, the hippocampus and amygdala are among the most plastic brain regions that are critical for stress responses, as they play crucial roles in selective attention, memory, fear, anxiety, and aggression (Felger and Lotrich, 2013; Heim et al., 2008).There were other factors that contributed to significant differences between depression subtypes, including age group, sex, smoking status, physical activity, and marital status. These factors may be helpful in further delineating depression subtypes, and warrant further investigation in future research, for example as risk factors for different subtypes in confirmatory analyses. We did not find any interactions between any of the variables studied. In other words, none of these variables had moderating effects on other studied variables when comparing positive affect with the other depression

subtypes. Notably, these findings reflect cross-sectional data, and given the dynamic nature of AL and the stress response, future research should examine how these factors interact with ACEs over time. A finer delineation of depression subtypes, including their associated stressors, may lead to different clinical treatments and various intervention and prevention strategies for better depression management.

The strengths of the study include the use of a holistic conceptual framework, by including both self-reported measures of stress (ACEs) and objective measures of stressors (AL-biomarkers) to identify specific associations between depression subtypes and stressors. Results were based on a large national sample and person-centered methods, to produce robust results. Person-centered approaches have the advantage of being hypothesis-free and providing categorization based on differences that exist in a real-world setting. There are several limitations. First, the variables studied were measured cross-sectionally, which limits the ability to infer potential causal relationships between AL profiles and depression subtypes. Second, ACEs and depressive symptoms were self-reported, which is subject to the recall bias. Third, the CESD-10 used to indicate the presence of depressive symptoms cannot provide a clinically equivalent diagnosis of depression; i.e. we observed subtypes of elevated depressive symptoms, rather than clinical subtypes of depression.

Overall, we contributed to the literature by providing a more detailed examination of specific depression subtypes, AL profiles and ACEs. The heterogeneity of depression subtypes was not only associated with different depressive symptom profiles, but also separately with different stressors-related measures, suggesting the possibility of a distinguished etiological diversity and complexity of depression. The results of the study may have direct clinical and practical implications in terms of personalized clinical managements and etiological exploration, as well as early intervention and prevention for those exposed to early life stressors. Knowledge of specific exposure experiences, i.e. ACE profiles, and their association with depressive symptom presentations may contribute to the prevention of depression through early intervention.

Table 1. Characteristics of the study cohort

Sample size	3966
Age group (%)	
45-54	1089 (27.5)
55-64	1361 (34.3)
65-74	874 (22.0)
75+	642 (16.2)
Sex = M (%)	1526 (38.5)
Marital status (%)	
Single, never married or never lived with a partner	524 (13.2)
Married/Living with a partner in a common-law relationship	2249 (56.7)
Widowed, Divorced or Separated	1220 (30.0)
Highest education (%)	
Less than secondary school graduation	315 (7.9)
Secondary school graduation, no post-secondary education	409 (10.3)
Some post-secondary education	352 (8.9)
Post-secondary degree/diploma	2890 (72.9)
Total household income (%)	
Less than $20,000	415 (10.5)
$20,000 or more, but less than $50,000	1221 (30.8)
$50,000 or more, but less than $100,000	1364 (34.4)
$100,000 or more, but less than $150,000	593 (15.0)
$150,000 or more	373 (9.4)
Perceived social standing (mean $\pm$ SD))	5.59 $\pm$ 2.03
Subjective retirement status (%)	
Completely retired	1762 (44.4)
Partly retired	390 (9.8)
Not retired	1814 (45.7)
Race = non-white identity (%)	401 (10.1)
Immigrant status= yes (%)	718 (18.1)

Orientation = does not identify as “heterosexual ”(%)	120 (3.0)
Chronic conditions score mean(SD)	2.75 ± 2.45

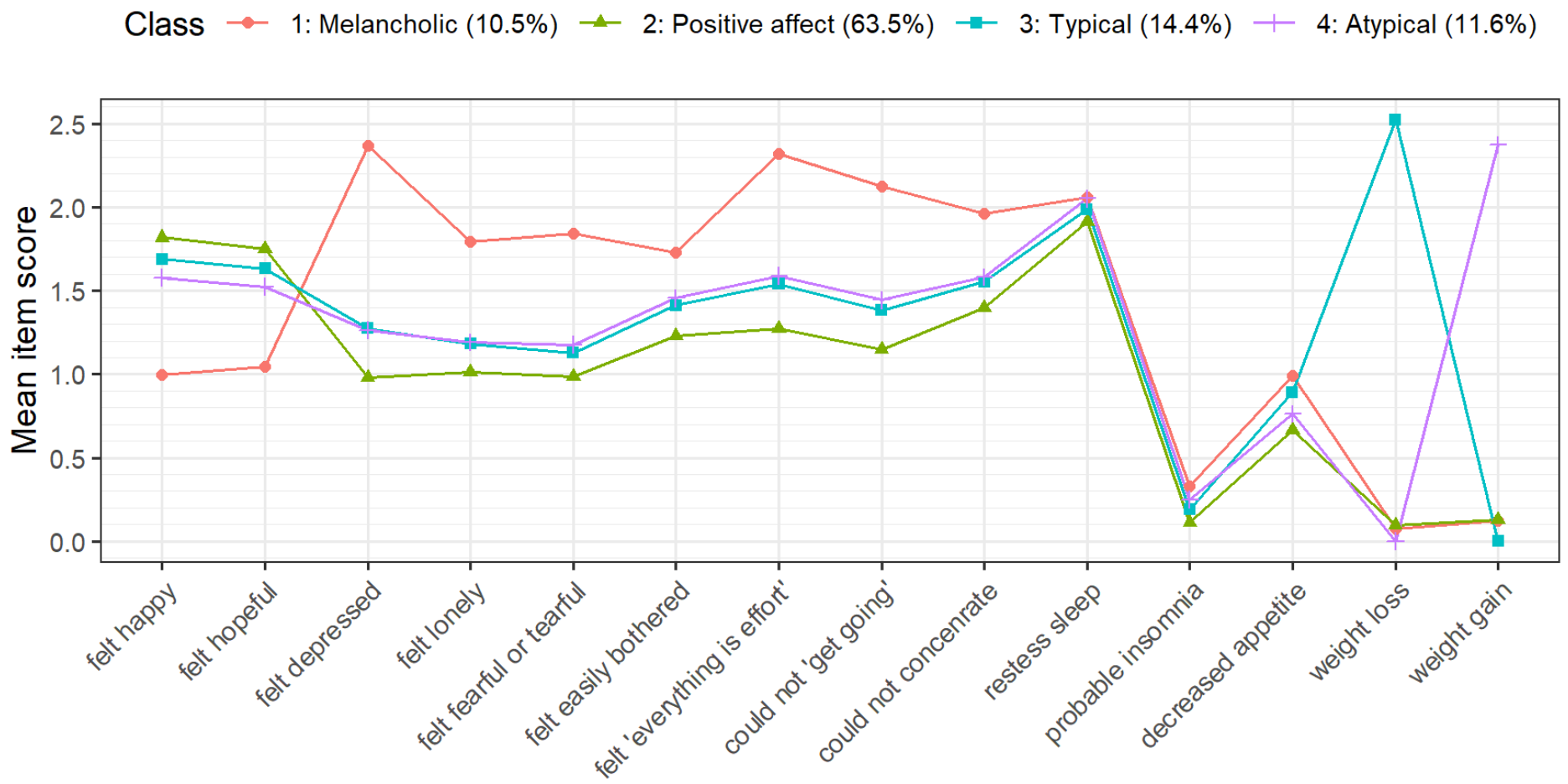

Figure 1. Depression subtypes identified by latent profile analysis (*n*=3966). Depression subtypes were determined via latent profile analysis of CESD-10 items (Appendix 2) , as well as derived probable insomnia, decreased appetite, weight loss and weight gain items. Increased mean item score corresponds to increased frequency or intensity of the symptom. Y-axis categories: for the CESD-10 items (1 = "rarely or never" to 4 = "most or all of the time"), decreased appetite (1 = "very good" to 4 = "poor"), weight loss and weight gain indicators (1 = "same weight", 2 = "non-significant (≤ 5 lbs)", 3 = "significant (6-10lb)", 4 = "very significant

(>10 lb), and probable insomnia disorder item (1 = “no insomnia”, 2= “insomnia symptoms only”, 3 = ‘probable insomnia disorder”). Protile estimates are in Appendix 5.

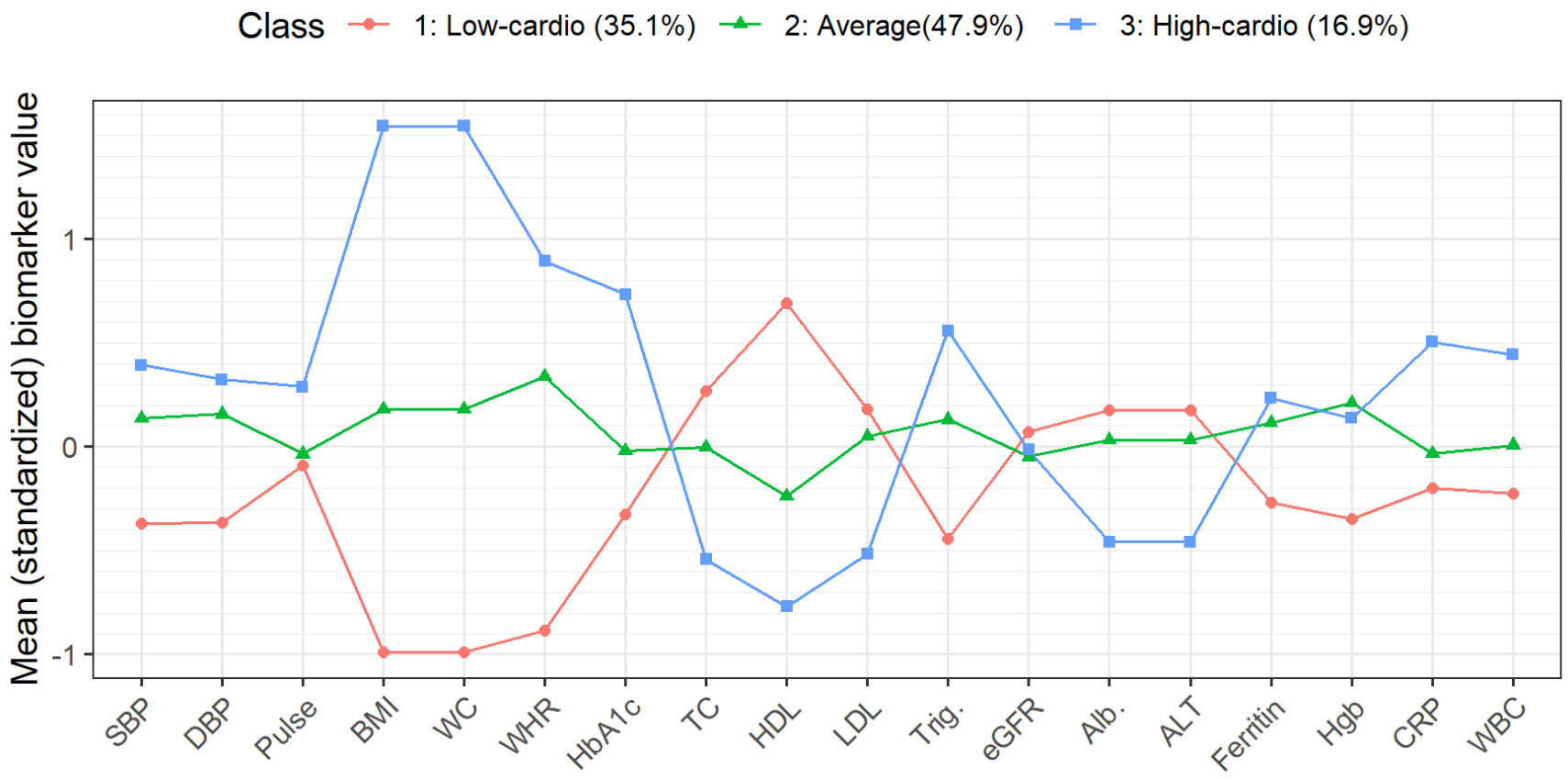

Figure 2. Allostatic load biomarker profiles identified by latent profile analysis (*n* = 3966). Determined via latent profile analysis of biomarker values, standardized to the sample mean. Three profiles were identified, with the following prevalences: a low-cardiovascular profile (low-cardio) 35.1%, average profile 47.9%, and high-cardiovascular profile (high-cardio) 16.9%. Biomarkers include: Systolic blood pressure (SBP); Diastolic blood pressure (DBP); Pulse; Body mass index (BMI): Waist circumference (WC);

glycated hemoglobin (HbA1c); Total cholesterol (TC); High-density lipoprotein (HDL); Low-density lipoprotein (LDL); Triglycerides (Trig.); estimated glomerular filtrate (eGFR); Serum albumin (Alb.); Alanine aminotransferase (ALT); Ferritin; Hemoglobin (Hgb); high-sensitivity C-reactive protein (CRP); White blood cell count (WBC). Profile estimates are in Appendix 7.

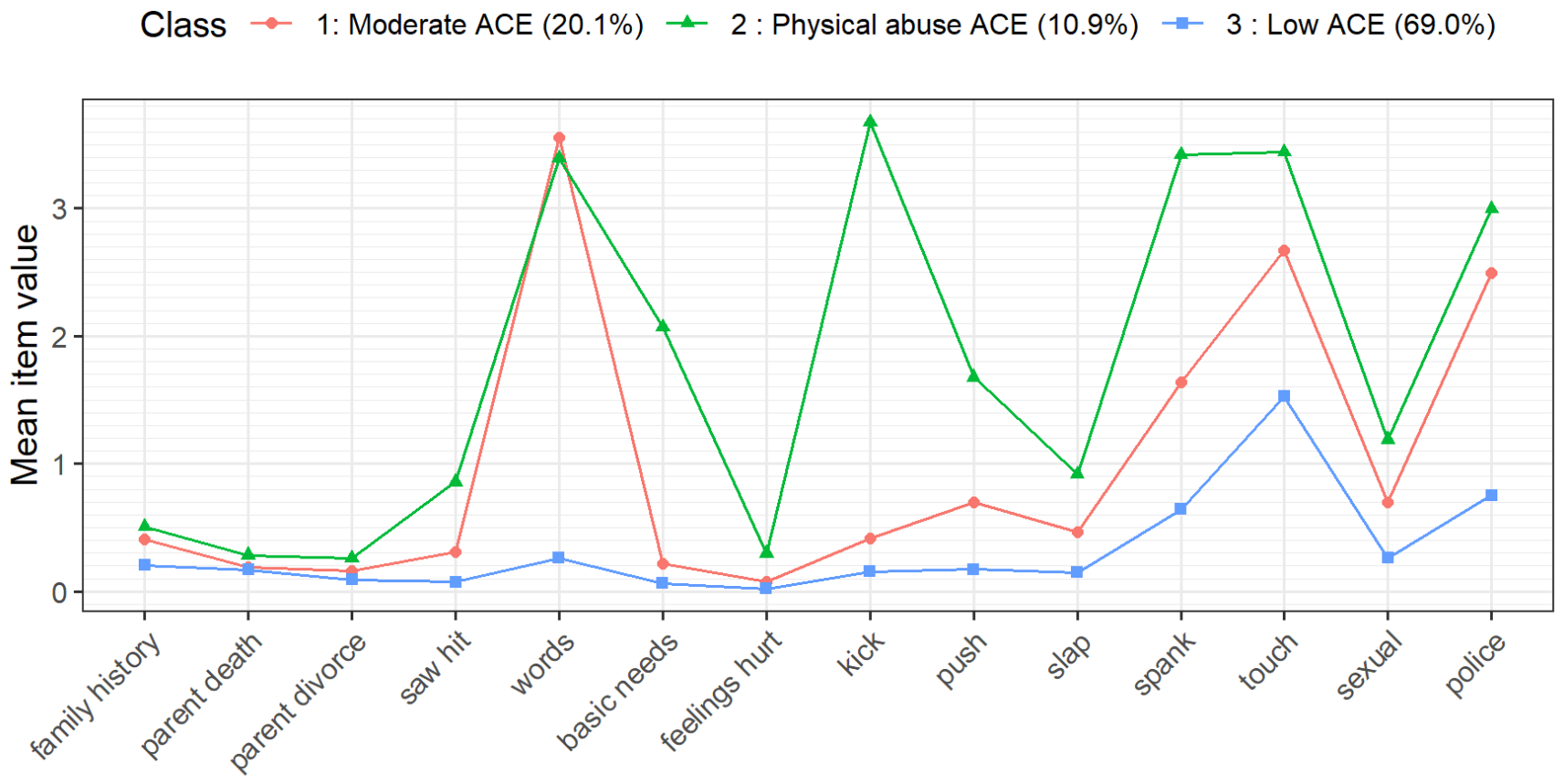

Figure 3. Adverse childhood experiences profiles identified by latent profile analysis (*n*= 3966). Mean item values reflect frequency of a given ACE, where the first three items are binary (0,1), the next eleven are rated 0 = never, 1 = 1-2 times, 2 = 3-5 times, 3 = 6-10 times, 4 = more than 10 times. Item legend details are described in Appendix 3, and profile estimates are in Appendix 9.

Table 2. Multinomial logistic regression results for depression subtypes. Model 1 (unadjusted) and final model**.**

	Melancholic subtype vs. positive affect subtype		Atypical subtype vs. positive affect subtype		Typical subtype vs. positive affect subtype	
	RRR	95% CI	RRR	95% CI	RRR	95% CI
Model 1:						
intercept	1.50	1.23, 1.83	6.84	5.79, 8.07	0.91	0.72, 1.13
Allostatic load profile						
Average	1.00	-	1.00	-	1.00	-
High-cardiovascular	1.10	0.81, 1.49	0.58	0.44, 0.75	0.64	0.44, 0.92
Low-cardiovascular	0.68	0.50, 0.91	1.09	0.870, 1.37	1.14	0.85, 1.54
Adverse childhood experiences profile						
Low	1.00	-	1.00	-	1.00	-
Moderate	0.79	0.54, 1.16	0.62	0.45, 0.84	1.20	0.81, 1.78
Physical abuse	0.72	0.54, 0.98	0.62	0.49, 0.79	1.03	0.75, 1.41
Final model:						
intercept	0.65	0.39, 1.08	1.92	1.28, 2.88	0.65	0.39, 1.10
Allostatic load profile						
Average	1.00	-	1.00	-	1.00	-
High-cardiovascular	1.18	0.86, 1.63	0.64	0.49, 0.85	0.63	0.43, 0.92
Low-cardiovascular	0.72	0.53, 0.99	1.31	1.02, 1.68	1.21	0.88, 1.67
Adverse childhood experiences profile						

Low	1.00	-	1.00	-	1.00	-
Moderate	0.86	0.58, 1.26	0.76	0.55, 1.04	1.25	0.84, 1.87
Physical abuse	0.77	0.57, 1.05	0.73	0.57, 0.93	1.06	0.77, 1.45
Age group						
45-54	1.00	-	1.00	-	1.00	-
55-64	1.15	0.84, 1.57	1.41	1.10, 1.81	1.40	1.01, 1.94
65-74	1.80	1.21, 2.66	2.40	1.73, 3.33	1.71	1.12, 2.64
75+	1.78	1.08, 2.93	3.92	2.59, 5.93	1.35	0.77, 2.38
Sex						
Female	1.00	-	1.00	-	1.00	-
Male	1.10	0.82, 1.46	1.65	1.30, 2.10	1.10	0.80, 1.51
Chronic conditions score	1.01	0.95, 1.06	0.92	0.88, 0.97	0.96	0.94, 1.06
Smoking status						
Current-smoker	1.00	-	1.00	-	1.00	-
Never a smoker	0.93	0.64, 1.36	1.41	1.04, 1.91	0.98	0.66, 1.45
Former smoker	1.19	0.82, 1.72	1.36	1.00, 1.84	0.98	0.66, 1.45
Sufficient physical activity						
no	1.00	-	1.00	-	1.00	-
yes	1.60	1.17, 2.18	1.32	1.02, 1.72	1.04	0.74, 1.47
Marital status						
Married or living with a partner in a common-law relationship	1.00	-	1.00	-	1.00	-

Single, never married or never lived with a partner	1.50	1.05, 2.15	1.62	1.22, 2.15	1.08	0.75, 1.55
Divorced, separated, or widowed	1.49	1.00, 2.22	1.32	0.96, 1.82	0.96	0.64, 1.46

Depression subtypes relative to the ‘positive affect’ depression subtype. Relative Risk Ratio (RRR). 95% Confidence Interval (2.5%, 97.5%).

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Appetite and weight items from the AB SCREEN™ were used as in indicators in the depressive symptom LPA. The AB SCREEN™ II assessment tool is owned by Dr. Heather Keller. Use of the AB SCREEN™ II assessment tool was made under license from the University of Guelph.

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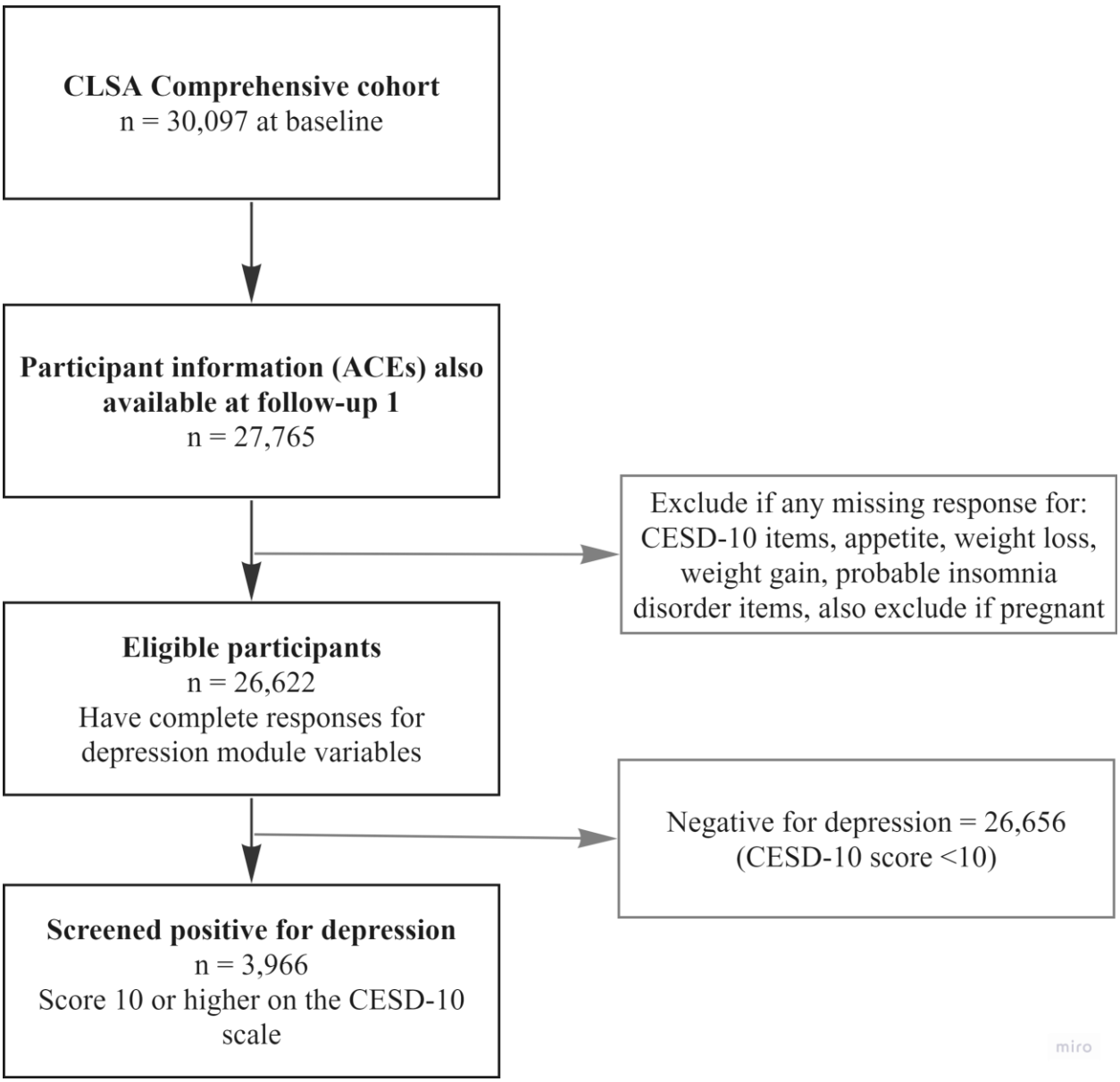
Appendices

Appendix 1. Sample selection process



Appendix 2. Center for Epidemiologic Studies Depression-10 (CESD-10) item, questions asked by CLSA, corresponding abbreviation in latent profiles analysis (Figure 1) and domain of depressive symptomology assessed.

CESD-10 item	**Question asked**	**Domain of depressive symptomology**	**Abbreviation used in Figure 1**
Frequency feel everything is an effort	How often did you feel that everything you did was an effort?	Depressive affect	Felt 'everything is effort'
Frequency feel depressed	How often did you feel depressed?	Depressive affect	Felt depressed
Frequency feel fearful or tearful	Remember, we are asking about how you have felt in the past week. How often did you feel fearful or tearful?	Depressive affect	Felt fearful or tearful
Frequency feel could not 'get going'	How often did you feel that you could not "get going"?	Somatic complaint	Could not 'get going'
Frequency feel happy	How often were you happy?	Positive affect	Felt happy
Frequency feel hopeful about the future	How often did you feel hopeful about the future?	Positive affect	Felt hopeful
Frequency feel lonely	How often did you feel lonely?	Depressive affect	Felt lonely
Frequency trouble concentrating	How often did you have trouble keeping your mind on what you were doing?	Somatic complaint	Could not concentrate
Frequency sleep is restless	How often was your sleep restless?	Somatic complaint	Restless sleep

Appendix 3. Description of adverse childhood experiences items, abuse threshold criteria according to Tanaka et al. (2012), and abbreviation for the item used in the latent profile analysis (Figure 3).

ACE item	Category of abuse	Abuse threshold	Abbreviation in Figure 3
How many times did you see or hear any one of your parents, step-parents or guardians hit each other or another adult in your home?	Childhood exposure to intimate partner violence	3 or more times	See hit
How many times did you see or hear any one of your parents, step-parents or guardians say hurtful or mean things to each other or to another adult in your home?	Childhood exposure to intimate partner violence	6 or more times	Words
How many times did your parents, step-parents or guardians not take care of your basic needs, such as keeping you clean or providing food or clothing?	Neglect	1 or more times	Care
How many times did any one of your parents, step-parents or guardians swear at you, or say hurtful, insulting things that made you feel like you were not wanted or loved?	Emotional abuse	3 or more times	Feelings hurt
How many times did an adult kick, bite, punch, choke, burn you, or physically attack you in some way?	Physical abuse	1 or more times	Kick
How many times did an adult push, grab, shove or throw something at you to hurt you?	Physical abuse	3 or more times	Push
How many times did an adult slap you on the face, head or ears or hit or spank you with something hard to hurt you?	Physical abuse	3 or more times	Slap

How many times did a parent or caregiver spank you with their hand on your bottom (bum), or slap you on your hand?	Physical abuse	3 or more times	Spank
How many times did an adult touch you against your will in any sexual way?	Sexual abuse	1 or more times	Touch
How any times did an adult force you or attempt to force you into any unwanted sexual activity, by threatening you, holding you down or hurting you in some way?	Sexual abuse	1 or more times	Sexual
Did you ever see or talk to the police or anyone from child protective services about any of the things you mentioned?	NA	NA	Police

Appendix 4. Model indices for depression subtypes latent profile analysis

Profiles	LogLik	AIC	BIC	SABIC	Entropy	BLTR p	Smallest profile (%)
2	-64282.08	128650.16	128920.44	128783.8	1.00	0.01	16.1
3	-63017.13	126150.26	126514.82	126330.5	1.00	0.01	11.8
4	**-65420.62**	**130987.24**	**131446.08**	**131214.1**	**0.94**	**0.01**	**10.5**
5	-61661.73	123499.46	124052.59	123773.0	0.95	0.01	7.2

AIC, Akaike information criterion; BIC, Bayesian information criterion; SABIC, sample size-adjusted Bayesian information criterion; BLRT p, bootstrap likelihood ratio test p-value; Smallest profile, the prevalence of the smallest profile within a given profile-solution. The selected profile-solution is in bold.

Appendix 5. Mean item estimates, their standard error (se) and p-values (p), for item in the depression latent profile analysis, by depression profile, corresponding to Figure 1.

	Melancholic			**Positive affect**			**Typical**			**Atypical**		
	estimate	se	p	estimate	se	p	estimate	se	p	estimate	se	p
Felt happy	1.00	0.04	0.00	1.82	0.02	0.00	1.69	0.03	0.00	1.58	0.04	0.00
Felt hopeful	1.05	0.05	0.00	1.75	0.02	0.00	1.63	0.04	0.00	1.52	0.05	0.00
Felt depressed	2.37	0.03	0.00	0.98	0.02	0.00	1.28	0.04	0.00	1.26	0.04	0.00
Felt lonely	1.79	0.05	0.00	1.01	0.02	0.00	1.18	0.04	0.00	1.19	0.05	0.00
Felt fearful or tearful	1.85	0.05	0.00	0.99	0.02	0.00	1.13	0.04	0.00	1.18	0.04	0.00
Felt easily bothered	1.73	0.06	0.00	1.23	0.02	0.00	1.41	0.04	0.00	1.46	0.04	0.00
Felt 'everything is effort'	2.32	0.05	0.00	1.27	0.02	0.00	1.54	0.04	0.00	1.59	0.05	0.00
Could not get going	2.13	0.06	0.00	1.15	0.02	0.00	1.38	0.04	0.00	1.44	0.05	0.00
Could not concentrate	1.96	0.06	0.00	1.40	0.02	0.00	1.55	0.04	0.00	1.58	0.04	0.00
Restless sleep	2.06	0.05	0.00	1.91	0.02	0.00	1.99	0.04	0.00	2.05	0.05	0.00

Probable insomnia	0.33	0.03	0.00	0.11	0.01	0.00	0.19	0.02	0.00	0.25	0.02	0.00
Decreased appetite	0.99	0.05	0.00	0.66	0.01	0.00	0.89	0.04	0.00	0.76	0.04	0.00
Weight loss	0.08	0.01	0.00	0.10	0.01	0.00	2.53	0.02	0.00	0.00	0.00	0.59
Weight gain	0.12	0.02	0.00	0.13	0.01	0.00	0.00	0.00	0.72	2.37	0.02	0.00

Appendix 6. Model fit indices for allostatic load latent profile analysis

Profiles	LogLik	AIC	BIC	SABIC	Entropy	BLTR p	Smallest profile (%)
2	-97068.83	194247.7	194593.4	194418.6	0.84	0.01	47.2
3	**-95191.98**	**190532.0**	**190997.1**	**190762.0**	**0.88**	**0.01**	**16.9**
4	-94207.12	188600.2	189184.8	188889.3	0.84	0.01	15.6
5	-93261.62	186747.2	187451.2	187095.3	0.85	0.01	3.1

AIC, Akaike information criterion; BIC, Bayesian information criterion; SABIC, sample size-adjusted Bayesian information criterion; BLRT p, bootstrap likelihood ratio test p-value; Smallest profile, the prevalence of the smallest profile within a given profile-solution. The selected profile-solution is in bold.

Appendix 7. Mean item estimates (standardized to the sample mean), as well as their standard error (se) and p-values (p) for each biomarker item in the allostatic load latent profile analysis, by allostatic load profile (AL) corresponding to Figure 2.

	Low-cardiovascular AL			Average AL			High-cardiovascular AL		
	estimate	**se**	**p**	**estimate**	**se**	**p**	**estimate**	**se**	**p**
Systolic blood pressure	-0.37	0.03	0.00	0.39	0.04	0.00	0.14	0.03	0.00
Diastolic blood pressure	-0.37	0.03	0.00	0.33	0.05	0.00	0.16	0.03	0.00
Pulse	-0.09	0.02	0.00	0.29	0.05	0.00	-0.04	0.03	0.19
Body mass index	-0.99	0.02	0.00	1.54	0.05	0.00	0.18	0.03	0.00
Waist circumference	-0.99	0.02	0.00	1.54	0.05	0.00	0.18	0.03	0.00
Waist-hip ratio	-0.88	0.03	0.00	0.90	0.04	0.00	0.34	0.03	0.00
Glycated hemoglobin A1c	-0.33	0.02	0.00	0.71	0.07	0.00	-0.01	0.03	0.77
Total cholesterol	0.27	0.03	0.00	-0.53	0.04	0.00	-0.01	0.03	0.74
High-density lipoprotein	0.69	0.03	0.00	-0.77	0.03	0.00	-0.24	0.03	0.00
Low-density lipoprotein	0.19	0.03	0.00	-0.50	0.05	0.00	0.04	0.03	0.15
Triglycerides	-0.44	0.02	0.00	0.56	0.06	0.00	0.13	0.03	0.00
Estimated glomerular filtrate	0.07	0.03	0.01	-0.02	0.04	0.64	-0.05	0.03	0.06
Serum albumin	0.18	0.03	0.00	-0.45	0.06	0.00	0.03	0.03	0.37
Alanine aminotransferase	0.18	0.03	0.00	-0.45	0.06	0.00	0.03	0.03	0.37
Ferritin	-0.27	0.02	0.00	0.24	0.06	0.00	0.12	0.03	0.00
Hemoglobin	-0.35	0.03	0.00	0.14	0.06	0.02	0.21	0.03	0.00
C-reactive protein	-0.20	0.03	0.00	0.48	0.07	0.00	-0.02	0.02	0.24
White blood cell count	-0.22	0.02	0.00	0.44	0.07	0.00	0.01	0.02	0.59

Appendix 8. Model fit indices for adverse childhood experiences latent profile analysis

Profiles	LogLik	AIC	BIC	SABIC	Entropy	BLTR p	Smallest profile (%)
2	-64253.79	128593.6	128863.9	128727.2	0.99	0.01	12.1
3	**-61985.82**	**124087.6**	**124452.2**	**124267.9**	**0.97**	**0.01**	**10.9**
4	-61475.44	123096.9	123555.7	123323.8	0.94	0.01	7.0
5	-59982.12	120140.2	120693.4	120413.7	0.98	0.01	2.7

AIC, Akaike information criterion; BIC, Bayesian information criterion; SABIC, sample size-adjusted Bayesian information criterion; BLRT p, bootstrap likelihood ratio test p-value; Smallest profile, the prevalence of the smallest profile within a given profile-solution. The selected profile-solution is in bold.

Appendix 9. Mean item estimates, as well as their standard error (se) and p-values (p) for each item in the adverse childhood experience (ACE) latent profile analysis, by profile corresponding to Figure 3.

	Moderate ACE			**Physical abuse ACE**			**Low ACE**		
	estimate	se	p	estimate	se	p	estimate	se	p
Family history	0.41	0.02	0.00	0.51	0.03	0.00	0.21	0.01	0.00
Parent death	0.19	0.01	0.00	0.28	0.02	0.00	0.17	0.01	0.00
Parent divorce	0.16	0.01	0.00	0.26	0.02	0.00	0.09	0.01	0.00
Saw hit	0.70	0.04	0.00	1.68	0.09	0.00	0.17	0.01	0.00
Words	2.49	0.07	0.00	3.00	0.09	0.00	0.75	0.03	0.00
Basic needs	0.31	0.03	0.00	0.86	0.08	0.00	0.07	0.01	0.00
Feelings hurt	3.56	0.03	0.00	3.39	0.08	0.00	0.26	0.01	0.00
Kick	0.22	0.02	0.00	2.07	0.10	0.00	0.06	0.01	0.00
Push	0.42	0.03	0.00	3.68	0.03	0.00	0.16	0.01	0.00
Slap	1.64	0.06	0.00	3.42	0.06	0.00	0.64	0.02	0.00
Spank	2.67	0.06	0.00	3.44	0.06	0.00	1.53	0.03	0.00
Sexual	0.46	0.04	0.00	0.92	0.08	0.00	0.15	0.01	0.00
Touch	0.70	0.04	0.00	1.19	0.08	0.00	0.26	0.01	0.00
Police	0.07	0.01	0.00	0.30	0.04	0.00	0.02	0.00	0.00

CHAPTER 3: BRIDGING SECTION

In our previous study, we characterized depression subtypes among middle-aged and older adults in the Canadian Longitudinal Study on Aging cohort and their associations with different stress profiles, including adverse childhood experiences (ACEs) and biological measures of stress, i.e. allostatic load (AL) biomarkers. We discovered four depression subtypes (melancholic, atypical, typical and positive-affects subtypes) and their specific associations with different stress measures (i.e. ACE profile, AL profile). These cross-sectional findings provide some insight into differences between depression subtypes, but the cross-sectional nature of the study design precludes causal inferences between depression subtypes and AL profiles. Meanwhile, ACEs had variable effects on depression subtypes. As one of the aims of this thesis is to elucidate how stress is related to heterogenous depression presentations, we further extend the cross-sectional findings to assess whether stress measures could serve as prognostic risk factors for depression chronicity with a longitudinal study design while remaining within the framework of stress vulnerability.

Given the dynamic and chronic nature of depression and depression symptoms, we wanted to assess how depression may change over time, taking into account the identified subtypes and other baseline variables of interest. The following manuscript is linked to the first manuscript through the stress-vulnerability framework of depression: similar to Chapter 2, depression subtypes, ACE profiles, and AL profiles were included in the investigation, but focused on chronicity as an outcome in a longitudinal sample from the CLSA.

Findings on depression chronicity and its association with depression subtypes and stress measures could help inform clinical treatment strategies, particularly if certain baseline symptom profiles are associated with an increased risk of adverse outcomes. Additionally, knowledge of the longitudinal associations of stressor profiles with depressive symptoms could provide further insight for earlier screening, intervention and potential prevention, while identified prognostic risk factors could support this and provide potential secondary intervention targets.

CHAPTER 4: MANUSCRIPT II

In this chapter, I present the second manuscript in which prognostic risk factors were tested for their associations with depression chronicity, i.e. maintenance of elevated depressive symptoms at three-year follow-up. Latent depression subtypes and stressor profiles were identified for those individuals who completed both baseline and follow-up data collection. In the discussion, I compare the rate of depression chronicity observed in the present study with the literature and discuss possible reasons for the increased odds of chronicity among atypical and melancholic depression and certain ACE profiles. This manuscript is formatted for submission to the journal *Psychiatry Research*.

Identification of factors associated with depression chronicity: An analysis of the Canadian Study on Aging (CLSA)

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Abstract

Depressive symptoms may be chronic, fluctuate over time, and overlap with the (patho)physiology of aging. In older adults, depression is associated with a more chronic course. Insight into risk factors for depressive chronicity is needed to reduce life spent with disability (mental and physical) by informing prevention and treatment strategies. This aim of this study was to assess the prevalence of chronic depression at three-year follow-up and its baseline prognostic factors. Participants from the Canadian Longitudinal Study on Aging Comprehensive cohort with a score of 10 or more on the Center for Epidemiologic Studies Depression-10 item scale (CESD-10) were included (n= 3473). Chronic depression was defined as a CESD-10 score of 10 or more at both time points. Latent profile analyses were used to determine depression subtypes and allostatic load biomarker (AL) profiles at baseline, as well as adverse childhood experience (ACE) profiles. Logistic regression was used to determine important baseline factors for depression chronicity at 3-year follow-up. The chronicity of depression in the study cohort was 46.6%. Significant baseline predictors of depressive chronicity included depression subtype, with atypical and melancholic subtypes having 1.35 (95%CI: 1.05-1.73) and 1.87 (95%CI: 1.53-2.3) times greater odds, respectively, compared with the positive affect subtype. With respect to stressors, greater odds of chronic depression were associated with moderate (OR 1.44, 95%CI: 1.21-1.72) and physical ACE profile exposure (OR 1.47, 95%CI: 1.16, 1.84), and with high-cardiovascular AL profile exposure (OR 1.07, 95%CI: 1.07-1.69), respectively compared with low ACE and average AL profiles. Other significant baseline risk factors for persistently elevated depressive symptoms included lower total annual household income category, higher chronic conditions score, lower perceived social status score, and smoking. Depression chronicity is differentially associated with baseline depressive symptom profiles, as well as biological and psychosocial stressor profiles. Such insight into longitudinal patterns for depression is relevant for prevention, through earlier identification, and treatment strategies, by providing insight into potential secondary intervention targets.

Keywords: CLSA; latent profile analysis; depression subtypes; late life depression; prognostic factors; adverse childhood experience; allostatic load

1. Introduction

Major depression is one of the largest contributors to years lived with disability (Reynolds et al., 2022). In addition to having heterogeneous clinical presentations, depression tends to be chronic and dynamic; symptoms may remit, emerge, lessen or intensify over time (Musliner et al., 2016). Compared to middle-aged adults, depression in older adults is associated with a more chronic course (i.e. higher relapse rate), which is likely moderated by comorbidities (Haigh et al., 2018).

Notably, there is a lack of research assessing the chronicity of late-life depression, with few studies assessing unfavourable course or maintenance of a positive depression screen or diagnosis (Deng et al., 2018; Jeuring et al., 2018). Due to the nature of depression measures and the time between assessments, there is often no distinction between the duration of depressive symptom episodes. As such, specific terminology such as chronic depression, recurrent depression, relapse and lack of remission (in other words, unfavourable depressive symptom course) are subsumed under the term depression chronicity in the current study. One study found that among the participants who were diagnosed with depression at baseline, 15.9% had an unfavorable course, i.e. chronic or recurrent depression, 24.6% had partial remission, and 12.7% had complete remission at 6-year follow-up (Jeuring et al., 2018). Despite the heterogeneity of studies on chronicity of depressive symptoms, the identified prognostic factors for chronicity of depression are generally consistent with the risk factors for onset of depression, spanning clinical, lifestyle and psychosocial domains (Jeuring et al., 2018); factors associated with an unfavourable course of depression include, for example, comorbid anxiety(Andreescu et al., 2007), sleep problems (Kennedy et al., 1991), chronic diseases(Katon et al., 2006; Mitchell and Subramaniam, 2005), functional limitations (Bruce, 2001), pain (Karp et al., 2005), loneliness(Holvast et al., 2015), lack of social support (Hybels et al., 2016), childhood trauma (Wielaard et al., 2017), and neuroticism (Manning et al., 2017). One of the most commonly identified risk factors for depression is stress, or life stressors (Hammen, 2005). The vulnerability stress theory argues that individuals are at increased risk for depression when they are exposed excessive or toxic stress (Monroe and Simons, 1991). Studies have found that victims of childhood maltreatment or other major life stressors are at increased risk for depression (Su et al., 2022; Tan and Mao, 2023). It is reasonable to argue that exposure to these major life stressors would also predispose individuals to adverse disease outcomes.

As depression in older adults tends to be chronic (Jeuring et al., 2018), its associated prognostic risk factors require further investigation. Specifically, research is needed on how different depression subtypes affect the course of the disease, as well as how a history of stressors (and the perception of these stressors) affects an individuals' ability to maintain remission of depressive symptoms. Perception of stress has been linked to allostatic load (Knight et al., 2021; Mauss and Jarczok, 2021), an objective measure of the cumulative physiological burden of stress calculated from biomarker levels of a number of stress response systems (Guidi et al., 2021). Given that the course of depressive symptoms in older adults is contextualized by other key factors (Agustini et al., 2022), it is important to understand how baseline symptom profiles and stress measures might provide further insight into the course of depressive symptom.

The current study aimed to: 1) determine the percentage of depression chronicity among participants of the Canadian Longitudinal Study on Aging Comprehensive cohort who scored 10 or higher on the Center for Epidemiologic Studies Depression-10 item scale and 2) explore factors associated with maintained elevated depressive symptoms at 3-year follow-up. We hypothesized that maintenance of elevated depressive symptoms was related to specific depression subtypes at baseline, and was differentially influenced by adverse childhood experience (ACE) exposures and biomarkers of biological stress (allostatic load) at baseline. Specifically, we hypothesized that 1) atypical and/or melancholic depression would have a greater risk of maintaining chronicity; and 2) certain stress exposures, such as moderate or physical abuse ACE profiles, and/or high cardiovascular allostatic load profiles, would be associated with greater odds of maintaining elevated depressive symptoms.

2. Methods

2.1. Study cohort

Data from the Canadian Longitudinal Study on Aging (CLSA) were analyzed. Information about the CLSA data collection and participants has been described elsewhere(Raina et al., 2019). This study included participants who were in the CLSA comprehensive-cohort at baseline and follow-up, had complete responses on depression items at both timepoints, and had a score of 10 or greater on the Center for Epidemiological Studies Depression-10 item scale (CESD-10) at baseline. A CESD-10 score of 10 or more indicates the presence of depressive symptoms that are elevated enough to be considered depression (Björgvinsson et al., 2013).

Participants were excluded if they did not maintain participation at follow-up, if they had any missing response on depression item, or if they were pregnant (Appendix 1). A total of 3473 participants were included in the current study.

2.2. Measurements

2.2.1. Chronicity of depression

Chronicity of depression was determined by whether participants had a CESD-10 score of 10 or more, at both baseline and at 3-year follow-up. This was the result of the logistic regression.

2.2.2. Depression subtypes at baseline

Depression at baseline was classified using latent profile analysis (LPA) of 14 depressive symptom items, including: ten CESD-10 items on positive affect, depressive affect, and somatic complaints over the past week (Appendix 2); appetite; weight loss and weight gain compared to 6 months ago; and probable insomnia, according to Cross et al. (2019). The probable insomnia item assessed the frequency and intensity of sleep disturbances over the past month, including sleep quality, trouble falling asleep, trouble staying asleep, and trouble staying awake.

2.2.3. Allostatic load

Latent profiles of AL biomarkers were determined using 18 biomarkers commonly used to calculate allostatic load scores (McLoughlin et al., 2020). Biomarker data were obtained from participant visits to CLSA data collection sites. Biomarker values in the LPA were standardized to the sample mean values at baseline, and items included: systolic and diastolic blood pressure, mean pulse (cardiovascular); total cholesterol, high-density cholesterol, low-density cholesterol, triglycerides, glycated hemoglobin 1 (HbA1c), estimated glomerular filtration rate (eGFR), serum albumin, alanine aminotransferase (metabolic); white blood cell count, ferritin, hemoglobin, high-sensitivity C-reactive protein (immune); as well as, body mass index, waist circumference, waist-to-hip ratio (anthropometric).

2.2.4. Adverse childhood experiences

Measures of adverse childhood experiences were derived from the Childhood Experiences of Violence Questionnaire (Tanaka et al., 2012; Walsh et al., 2008) and the National Longitudinal Study of Adolescent to Adult Health Wave III questionnaire (Harris and Udry, 2022) . Items included three binary indicators of whether the participant had ever experienced parental divorce or separation, parental death or illness, or lived with a family member with poor

mental health before the age of 18 years. Additionally, the frequency and severity of exposure to physical abuse, emotional abuse, sexual abuse, neglect and intimate partner violence prior to the age of 16 years old, were assessed on an ordinal scale with five response options ("never", "1-2 times", "3-5 times", "6-10 times", "10 or times"). The items are listed in detail in Appendix 3, which describes the frequency thresholds for the abuse criteria according to Tanaka et al. (2012)

2.2.5. Covariates

To account for the presence of comorbidities, a chronic conditions score was calculated, which accounts for health conditions of high prevalence and burden in North America (Atkinson et al., 2021). The chronic condition score was calculated as the sum of indicators for the following conditions that participants reported having been diagnosed with by a health professional: heart disease, myocardial infarction, angina, stroke, transient ischemic attack, peripheral vascular disease, hypertension, diabetes, chronic obstructive pulmonary disease, Parkinsonism/Parkinson's disease, epilepsy, multiple sclerosis, migraines, osteoarthritis, osteoporosis, kidney disease, cataracts, glaucoma, cancer, mood disorders, and anxiety disorders.

In our investigation with depression subtypes, we also examined the importance of factors common in depression research, including age group, and sex assigned at birth, retirement status, race, orientation, immigration status and perceived social standing score(Li et al., 2021; Maier et al., 2021; Vyas et al., 2020). Perceived social standing score was included as a measure of social inequality, using the MacArthur Scale of Subjective Social Status, to assess where participants rate their standing in their communities (1 = "lowest social standing" to 10 = "highest social standing"). Subjective social status has been shown to be associated with health outcomes (Demakakos et al., 2008; Kwong et al., 2020). Finally, the following health behaviours were included: smoking status, frequency of alcohol consumption, and sufficient physical activity. The latter was calculated as a binary indicator on whether the participant met the World Health Organisation guidelines for physical activity for this age group, according to Raina et al. (2021).

2.3. Statistical Analyses

2.3.1 Imputation

Participants with partially missing values for biomarkers, ACEs, chronic conditions, and sociodemographic variables of interest at baseline were retained in the sample, and their missing

responses were imputed, using *Stata* version 16.0. Multiple chained imputation was used, with 20 iterations of missing responses performed for each variable. Imputed values were dependent on age at baseline and baseline sex responses, except for current sex identity, which is only part of the follow-up questionnaire, and was therefore imputed based on age at the follow-up and identified sex at birth (collected at the follow-up). For each missing observation, the 20 imputation values were pooled as their mean, then for categorical variables (i.e. ACEs and SDCs) the mean imputed values were rounded to the nearest integer.

2.3.2. Latent profile analysis

Latent profile analyses were performed in R (2022.12.0), using the *tidyLPA* package, to determine depression subtypes at baseline, allostatic load profiles at baseline, and adverse childhood experience profiles. Model selection was based on an optimized combination of: model fit index values, i.e. Akaike information criterion (AIC), Bayesian information criterion (BIC), sample size adjusted BIC (SABIC), log likelihood, bootstrap likelihood ratio test p-value; entropy; smallest profile prevalence; and profile interpretability. Specifically, decreasing model fit values indicated better fit, higher entropy was preferred and profiles with 10% prevalence or greater were preferred.

2.3.3 Stepwise model selection and logistic regression

Multivariable logistic regression was used to examine risk factors associated with depression chronicity, using the *nnet* package's *multinom* function in Rstudio. To determine which variables were important in maintaining a positive depression screen at baseline and the follow-up, a stepwise model selection was performed, starting with all variables of interest as the input. The *stepAIC* function (MASS package) in Rstudio was used with the default arguments. The resulting output model had decreased AIC and a minimum number of variables, all of which were significant ($p<0.05$), and the final model fit was assessed with the Hosmer-Lemeshow goodness-of-fit test.

3. Results

3.1. Characteristics of the study cohort

Table 1 summarizes the characteristics of the study cohort. Overall, the cohort was 61.3% female, with the most common age group being 55-64 years at baseline (34.9%), predominantly identified as white, heterosexual, and without an immigrant status. The most

common educational level was a post-secondary degree/diploma, and the most common total annual household income categories were between $20,000 or more but less than $100,000. More than half of the participants were married or living with a partner in a common-law relationship at baseline. On average, participants were living with 3 chronic conditions at baseline. Less than half (46.6%) of the participants maintained their elevated depressive symptoms at the follow-up, about 3 years later.

3.2. Identification of latent profiles of depression, allostatic load, and ACEs exposures at baseline

Depression at baseline was further classified into four subtypes. The model fit indices used to select the LPA profile are presented in Appendix 4. Figure 1 illustrates the symptomology of the four depression subtypes, and Appendix 5 contains corresponding profile estimates. The most common depression subtype (64%), positive affects, was characterized by the highest frequency of positive affects (happiness and hopefulness) and generally the lowest frequency of the other depressive symptoms. On average this profile did not experience important weight changes. The melancholic subtype was the second most common (15.5%), and was characterized by the lowest frequency of positive affect, the highest frequency of feeling depressed, and the highest frequency of somatic symptoms. This profile experienced some weight changes, but wasn't characterized by weight gain or loss, and had the worst appetite among the subtypes. The typical (11.8%) and the atypical (8.6%) depression subtypes were mainly characterized by marked weight loss and weight gain, respectively. Additionally, the atypical profile had some of the highest frequencies of feeling lonely, fearful or tearful, easily bothered (depressive affects).

AL biomarkers at baseline were grouped into four groups using the LPA models. Figure 2 shows the three AL profiles. Model fit indices for the AL biomarkers are presented in Appendix 6, and profile estimates are in Appendix 7. The most common profile (46.6%) was labelled as 'average' as this group tended to have values which were closest to the sample mean (with the exception of hemoglobin which was slightly higher than the other two groups). The least common, 'high-cardiovascular profile' (12.5%) had distinctly higher than average cardiovascular biomarker values. This profile also had notably higher blood-glucose (HbA1c), triglycerides, some immune/inflammatory markers (CRP, WBC), and the lowest mean values for total cholesterol, high-density cholesterol, and serum album. Finally, the 'low-cardiovascular' profile

(40.9%) had a phenotype opposite to the low-cardiovascular profile, where it was characterized by the lowest cardiovascular, immune markers, and lipid metabolism markers.

ACE exposures were characterized by LPA, with model fit indices for the different models presented in Appendix 8. Combinations of ACEs by profile are shown in Figure 3, and profile estimates are shown in Appendix 9. The three profiles are low ACE (69.2%), moderate ACE (20.2%) and ACE with physical abuse (10.6%), and differ primarily in the severity of the experiences. Low ACE was characterized by little or no ACE exposure on average, with some adverse experiences related to neglect and spanking. The moderate ACE profile included frequent experiences of witnessing 'word', as well as neglect, spanking, and 'feelings hurt'. On average, the physical ACE profile had the highest frequency for each ACE item, and was characterized by the prevalence of physical abuse, particularly the high mean item scores for 'kick, push, slap', when compared to the other profiles.

3.3. Relationships between depression chronicity and stress-related factors

After adjusting for the selected covariates, multivariate logistic regression was used to examine the relationships between depression chronicity and stress-related factors, including depression subtypes, ACE, and AL at baseline. The goodness of fit of the final model was tested ($p>0.05$). Table 2 shows the unadjusted model and final model for the relationship between depression chronicity and stress-related measures, which controlled for other baseline covariates. Chronic depression was significantly more likely for those with atypical (odds ratio (OR) 1.35, 95%CI: 1.05-1.73) or melancholic (OR 1.87, 95%CI: 1.53-2.30) depression subtypes at baseline (relative to the positive affect subtype); those with moderate (OR 1.44, 95%CI: 1.21-1.72) or physical abuse (OR 1.47, 95%CI: 1.16, 1.84) ACE profile exposures (relative to low ACE profile); and those classified into the high cardiovascular AL profile at baseline (OR 1.07, 95%CI: 1.07-1.69). Additionally, greater odds of chronic depression at the follow-up were significantly associated with higher chronic conditions scores (OR 1.09, 95%CI: 1.05-1.12), and inversely associated with increased perceived social standing scores (OR 0.90, 95%CI: 0.87-0.93) and higher total annual household income (ORs decreased with increasing income), at baseline. Baseline smokers were more likely (OR 1.34, 95%CI:1.06-1.68) to have this outcome than never smokers.

4. Discussion

This study provides evidence of longitudinal associations between depression chronicity depression, stress-related measures (ACEs and AL-biomarker profiles), and depressive symptom-based subtypes in middle-aged and older adults. We observed that nearly half of the participants maintained elevated depressive symptoms at 3-year follow-up and that this chronic course was associated with specific depression and stressor exposures.

4.1. Depressive chronicity rates in the literature

We found that a total of 46.6% of participants maintained their elevated depressive symptoms at the follow-up. Notably, the direct comparison of depression chronicity rates across studies is hampered by heterogeneity in the operationalization of depression chronicity, study populations and methods(Steinert et al., 2014). For example, a systematic review of prospective studies of adult depression in general practice and community settings found that a consistent percentage of 10–17% participants experienced a chronic course of depression, while recurrence rates varied considerably, ranging from 7% to 65% (Steinert et al., 2014). In a study evaluating depression in older adults, 48.4% of the participants who were clinically depressed (including minor depression) at baseline still had a diagnosis of depression by the end of the two-year follow-up (Comijs et al., 2015). In addition, 56% of the participants without a diagnosis of depression at follow-up still had residual depressive symptoms (Comijs et al., 2015). Another study on late-life depression (LLD) observed that 56.8% of participants experienced recurrence over four years (Deng et al., 2018). These findings suggest the persistence and chronicity of depressive symptoms, despite the fact that most of their participants received mental health treatment (Comijs et al., 2015). Although our study does not include diagnosis of depression or information on treatment, their observations regarding the rates of chronicity (observed over a similar time period and in an older population) are consistent with the range of chronicity rates reported elsewhere. It is not uncommon for some older populations to have chronic depression or depressive symptoms.

4.2. Factors contributing to depression chronicity

Although late-life depression often has a chronic course, there is no consensus on the main risk factors that explain its chronicity (Wielaard et al., 2017). We found that depression chronicity was associated with specific depression subtypes (atypical or melancholic depression

subtypes), moderate and physical ACE profiles, and the high-cardiovascular AL profile. To date, there is a paucity of research on the relationship between depression chronicity and depression subtypes, but some work has been done to illustrate trajectories of depression subtypes (Mallett et al., 2022). Nevertheless, our observation of greater odds of chronicity for the atypical and melancholic depression is consistent with the findings of Veltman et al. (2020). They examined the latent transition of depression subgroup profiles among older adults and found the greatest stability of symptoms among the profiles they labeled as melancholic and atypical (Veltman et al., 2020).

The literature has shown that increased ACE exposure and AL score are associated with depressive symptom severity, but there is a lack of research on whether their profiles are associated with depression chronicity, especially within this age group. In a study of the effects of childhood abuse on 2-year depression chronicity, higher baseline depressive symptoms, younger age at depression onset, higher levels of neuroticism and loneliness, and more chronic illness were associated with a poorer course of depression in older adults who reported childhood abuse (Wielaard et al., 2017). We found that participants with physical abuse- or moderate- ACE profiles were more likely to maintain elevated depressive symptoms compared to the low-ACE profile. This is in line with findings that a history of childhood abuse was associated with an increased risk of chronic MD (i.e. major depressive episodes lasting longer than 24 months) (Garcia-Toro et al., 2013).

Lower income and adverse life events are a commonly identified psychosocial risk factors for LLD incidence (Husain-Krautter and Ellison, 2021). We further demonstrated a higher risk of depression chronicity among individuals with lower perceived social status and lower income. These findings are consistent with the literature on late-life depression incidence (Vyas and Okereke, 2020). Although findings on their relevance to chronicity are lacking, our observations are consistent with expectations for chronicity risk factors based on some of their literature; for example, subjective social status was significant in predicting longitudinal depressive symptoms in older adults in terms of their depression status at 4-year follow up (Kwong et al., 2020), while another study found that lower household income was associated with a lower risk of depression at 7-year follow-up, compared to higher income (Zhou et al., 2021). Studies often identify medical comorbidity as a reason for the tendency of depression to

have a chronic course (i.e. higher relapse rate) in older adults compared to middle-aged adults (Haigh et al., 2018). Similarly, we observed that the chronicity of depression was associated with higher scores for chronic conditions. This has also been observed in other studies of depressive symptom chronicity(Liu et al., 2023).

4.3. Strengths and limitations

This longitudinal examined the relationship between depression chronicity, depression subtypes and stress-related measures over time. The data-driven, person-centered approach used for this large sample provided robust findings and novel insights into how stress and latent depression subtypes influence depression chronicity.

Several limitations should be noted. First, depressive symptoms and ACEs were based on self-reported responses to validated questionnaires, which may be subject to recall bias. There may be some selection bias, as some participants did not have information available at both time points, and thus healthier participants (relative to those who dropped out before follow-up) may have remained in the study. Second, the CESD-10 score used to assess depression subtypes and depression chronicity may not provide a clinically equivalent diagnosis of depression. Third, the cross-sectional measure of AL at baseline may not capture the dynamic process of allostasis and AL, and may not be able to estimate its dynamics with respect to depression chronicity. Finally, depression chronicity was measured within a 3-year follow-up, so additional details on the course are not available (i.e. frequency and duration of episodes of depressive symptoms). Future research on depression chronicity is warranted, especially with longer and more frequent time points to provide more insight into chronicity.

Overall, depression chronicity was associated with certain depression subtypes and stress-related measures, especially among those with lower income and poorer health (more chronic conditions). Further expansion of the current research findings is critical to understanding depressive symptoms and the course of depression. Additionally, such research could shed light on the underlying mechanisms that make certain depressive symptom subtypes more likely to become chronic. Such identified prognostic factors for depression chronicity should be targeted for intervention and prevention.

Table 1. Characteristics of the CLSA study cohort who completed both baseline and the follow-up *

n	3473
Age group at baseline (%)	967 (27.8%)
45-54	1213 (34.9%)
55-64	774 (22.3%)
65-74	519 (14.9%)
75+	
Age group at follow-up 1 (%)	577 (16.6)
45-54	1224 (35.2)
55-64	970 (27.9)
65-74	702 (20.2)
75+	
Sex at birth = Female (%) (asked at follow-up 1 only)	2130 (61.3%)
Current sex identity (at follow-up 1)	
Female	2121 (61.1%)
Male	1344 (38.7%)
Other	8 (0.2%)
Racial/ethnic identity = non-white identity (%)	342 (9.8%)
Orientation = non-heterosexual (%)	110 (3.2)
Immigrant status = Immigrant (%)	620 (17.9%)
Educational attainment (%)	
Less than secondary school graduation	262 (7.5%)
Secondary school graduation, no post-secondary education	358 (10.3%)
Some post-secondary education	309 (8.9%)
Post-secondary degree/diploma	2544 (73.3%)
Total household annual income (%)	
Less than $20,000	340 (9.8%)
$20,000 or more, but less than $50,000	1021 (29.4%)
$50,000 or more, but less than $100,000	1252 (36.0%)
$100,000 or more, but less than $150	524 (15.1%)

$150,000 or more	336 (9.7%)
Marital status	
Single, never married or never lived with a partner	458 (13.2%)
Married/Living with a partner in a common-law relationship	1998 (57.5%)
Divorced, separated, or widowed	1017 (29.3%)
Smoking status	
Current smoker (at baseline)	426 (12.3%)
Never been a smoker	1497 (43.1%)
Former smoker	1550 (44.6%)
Perceived social standing score, mean (sd)	5.60 (2.02)
Alcohol consumption frequency, past 12 months **(%)**	
Never	493 (14.2%)
Less than once a month	283 (8.1%)
About once a month	572 (16.5%)
2-3 times a month	408 (11.7%)
Once a week	387 (11.1%)
2-3 times a week	259 (7.5%)
4-5 times a week	564 (16.2%)
Almost every day (incl. 6 times a week)	507 (14.6%)
Subjective retirement status	
Completely retired	1507 (43.4%)
Partly retired	360 (10.4%)
Not retired	1606 (46.2%)
Chronic conditions score, mean (sd)	2.68 (2.41)
Sufficient weekly physical activity = yes (%)	820 (23.6%)
Number of additional people per household, excluding participant (%)	
0	1077 (31.0)
1	1458 (42.0)
2	470 (13.5)
3	333 (9.6)

4 or more	135 (3.9)
Elevated depressive symptoms at follow-up, i.e. depression chronicity (%)	1613 (46.4%)

*Data is for baseline unless otherwise indicated.

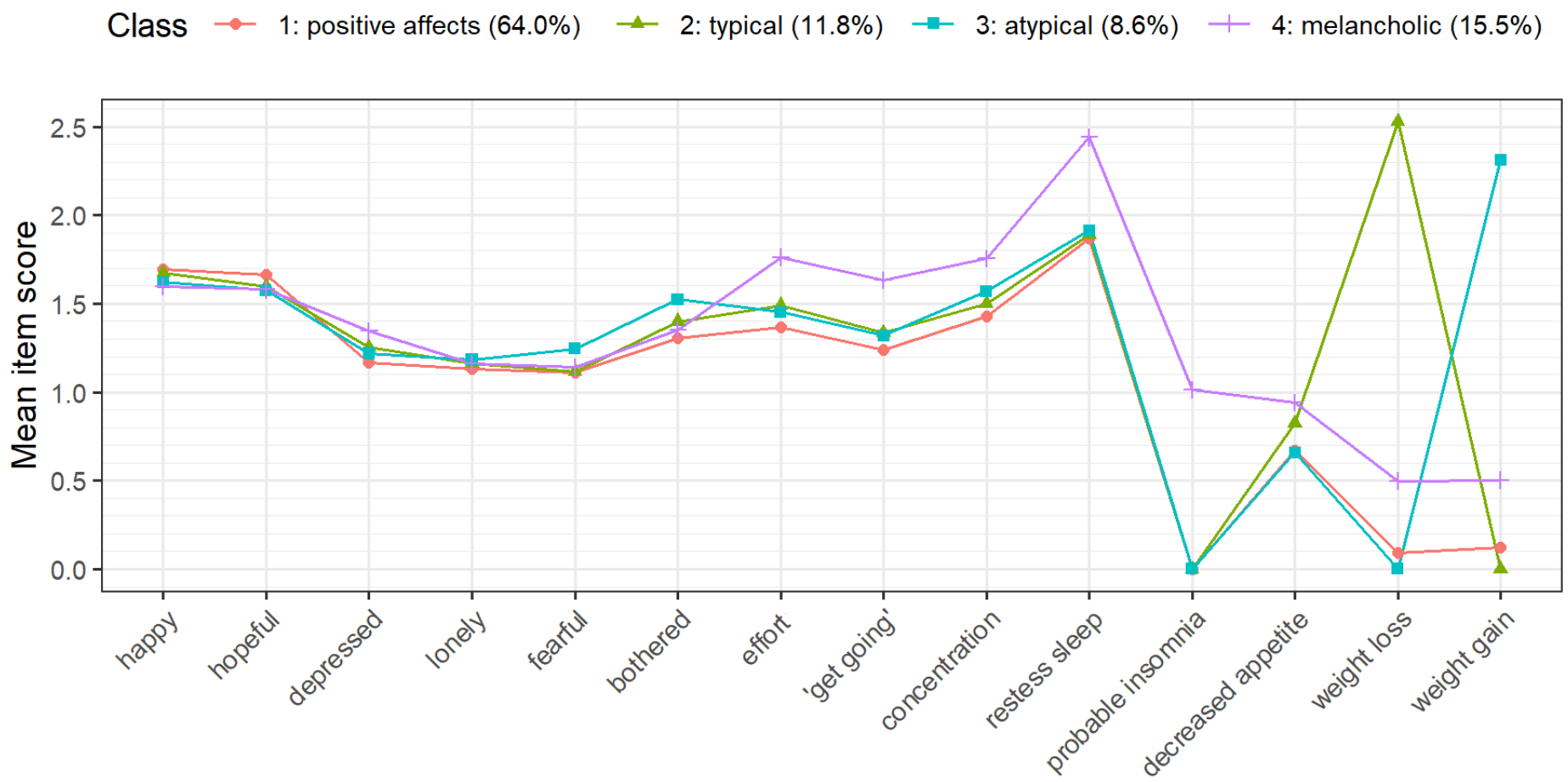

Figure 1. Depression subtypes at baseline identified by latent profile analysis (*n* = 3473). CESD-10 items, described further in Appendix 2: over the past 2 weeks, frequency that the participant felt happy, hopeful, depressed, lonely, fearful or tearful, easily bothered, that 'every thing is effort', that they could not 'get going', difficulty concentrating, restless sleep, where 0 = Rarely or never (less than 1 day), 1= Some of the time (1-2 days), 2 = Occasionally (3-4 days), 3= All of the time (5-7days); Probable insomnia disorder, over the past month (where 0 = no insomnia, 1 = insomnia symptoms only, 2 = probable insomnia disorder); Poor appetite (0 = very good, 1 = good , 2 = fair, 3= poor) and Weight loss or gain, compared to 6 months ago (0 = same weight, 1 = non-significant (=< 5 lbs), 2 = significant 6-10lb, 3 = very significant >10 lb). See Appendix 5 for profile estimates.

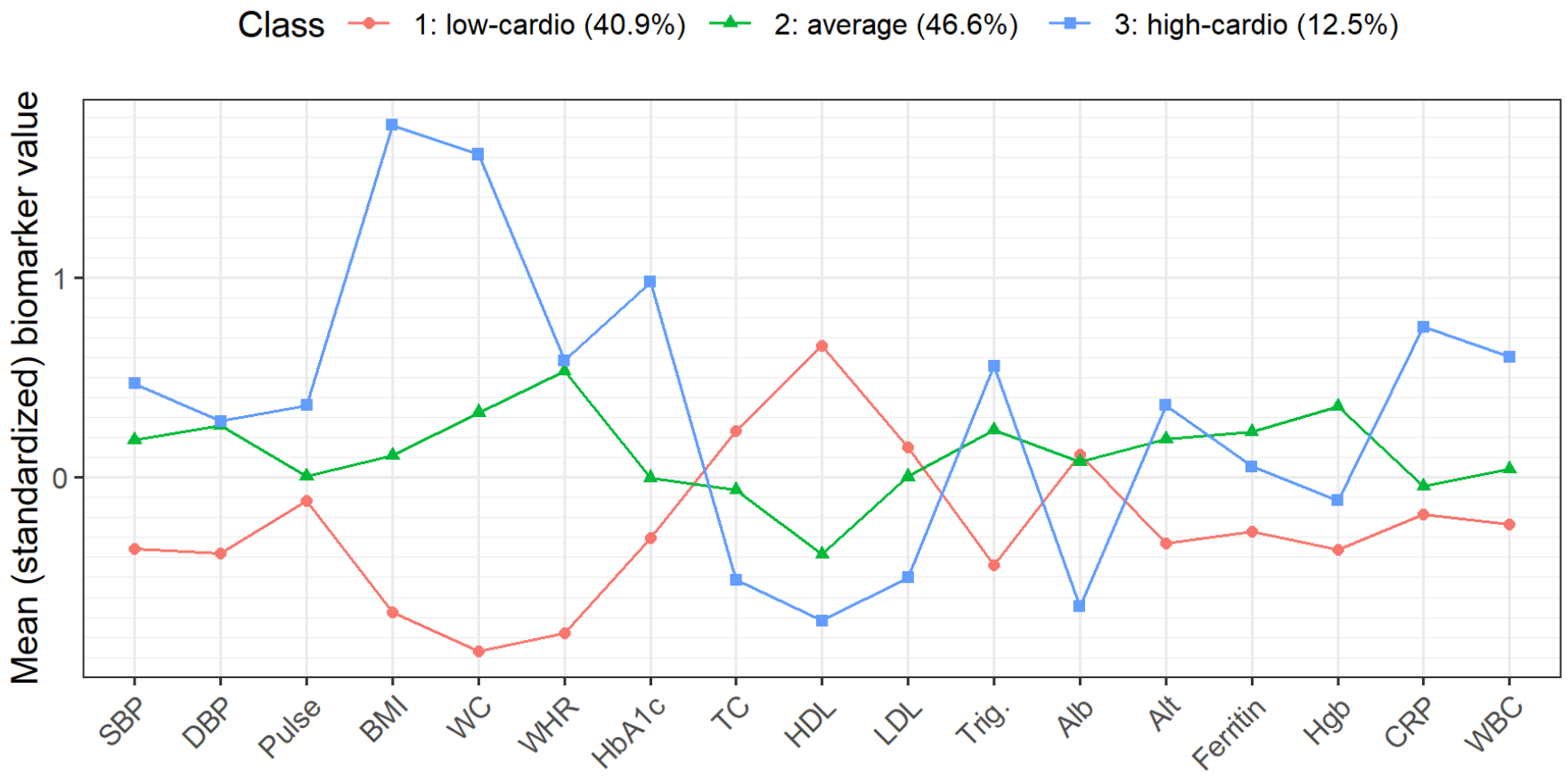

Figure 2. Allostatic load biomarker profiles at baseline identified by latent profile analysis (n = 3473). Low-cardiovascular (Low-cardio); high-cardiovascular (High-cardio); Systolic blood pressure (SBP); diastolic blood pressure (DBP); pulse; body mass index (BMI); waist circumference (WC); waist-hip ratio (WHR); glycated hemoglobin (HbA1c); total cholesterol (TC); high-density lipoprotein (HDL); low-density lipoprotein(LDL); triglycerides (Trig); serum albumin (Alb) ; alanine aminotransferase (Alt); ferritin; hemoglobin (Hgb); high-sensitivity C-reactive protein(CRP); white blood cell count (WBC). See appendix 7 for profile estimates.

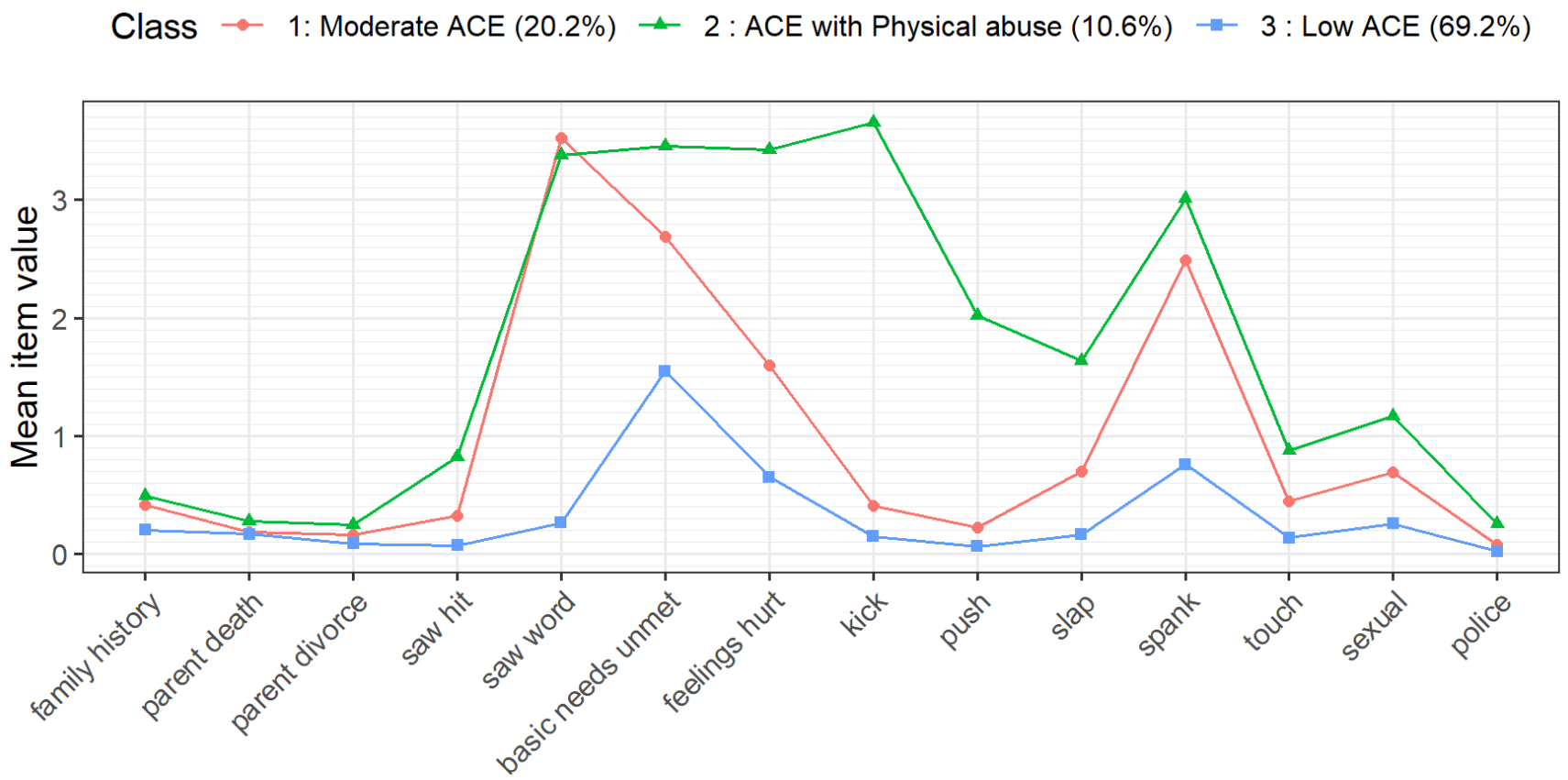

Figure 3. Adverse childhood experiences profiles at baseline identified by latent profile analysis (*n*= 3473). Identified profiles include low ACE, moderate ACE, ACE with physical abuse (Physical abuse ACE). Where 'family history', 'parent death', and 'parent divorce' are rated 0 (never) or 1 (yes) , and for the rest of the items where 0 = never, 1 = 1-2 times, 2 = 3-5 times, 3 =6-10, 4 = more than 10 times. See Appendix 3 for details on the other ACE items, and Appendix 9 for profile estimates.

Table 2. Logistic Regression results for chronicity of depression. Factors associated with chronicity depression at 3-year follow-up (n= 3743). Model 1 (unadjusted) vs. final model.

	Odds Ratio	95% Confidence interval (2.5%, 97.5%)	p-value
Model 1:			
Intercept	0.66	0.58, 0.74	0.000
Depression subtype at baseline			
Positive affects	1.00	-	-
Atypical	1.32	1.03, 1.68	0.027
Melancholic	2.00	1.65, 2.44	0.000
Typical	0.85	0.69, 1.06	0.158
Adverse childhood experience profile			
Low	1.00	-	-
Moderate	1.43	1.20, 1.70	0.000
Physical	1.52	1.22, 1.91	0.000
Allostatic load profile at baseline			
Average	1.00	-	-
High-cardiovascular	1.51	1.21, 1.88	0.000
Low-cardiovascular	1.00	0.86, 1.15	0.000
Final model:			
Intercept	1.30	0.89, 1.90	0.174
Depression subtype at baseline			
Positive affects	1.00	-	-
Atypical	1.35	1.05, 1.73	0.020
Melancholic	1.87	1.53, 2.30	0.000
Typical	0.83	0.66, 1.04	0.100
Adverse childhood experience profile			
Low	1.00	-	-
Moderate	1.44	1.21, 1.72	0.000
Physical	1.46	1.16, 1.84	0.002
Allostatic load profile at baseline			

Average	1.00	-	-
High-cardiovascular	1.34	1.07, 1.69	0.011
Low-cardiovascular	1.07	0.90, 1.27	0.429
Age group at follow-up			
45-54	-	-	-
55-64	0.87	0.70, 1.07	0.187
64-74	0.88	0.70, 1.10	0.264
75+	0.96	0.74, 1.25	0.761
Sex at birth			
Male	1.00	-	-
Female	0.92	0.78, 1.08	0.316
Total annual household income at baseline			
Less than $20,000	1.00	-	-
$20,000 or more but less than $50,000	0.88	0.68, 1.14	0.329
$50,000 or more, but less than $100,000	0.78	0.61, 1.01	0.058
$100,000 or more, but less than $150,000	0.67	0.50, 0.90	0.008
$150, 000 or more	0.54	0.39, 0.75	0.000
Perceived Social Standing Score	0.90	0.87, 0.93	0.000
Chronic conditions score	1.09	1.05, 1.12	0.000
Smoking status			
Never a smoker	1.00	-	-
Current smoker	1.34	1.06, 1.68	0.013
Former smoker	1.12	0.96, 1.30	0.144

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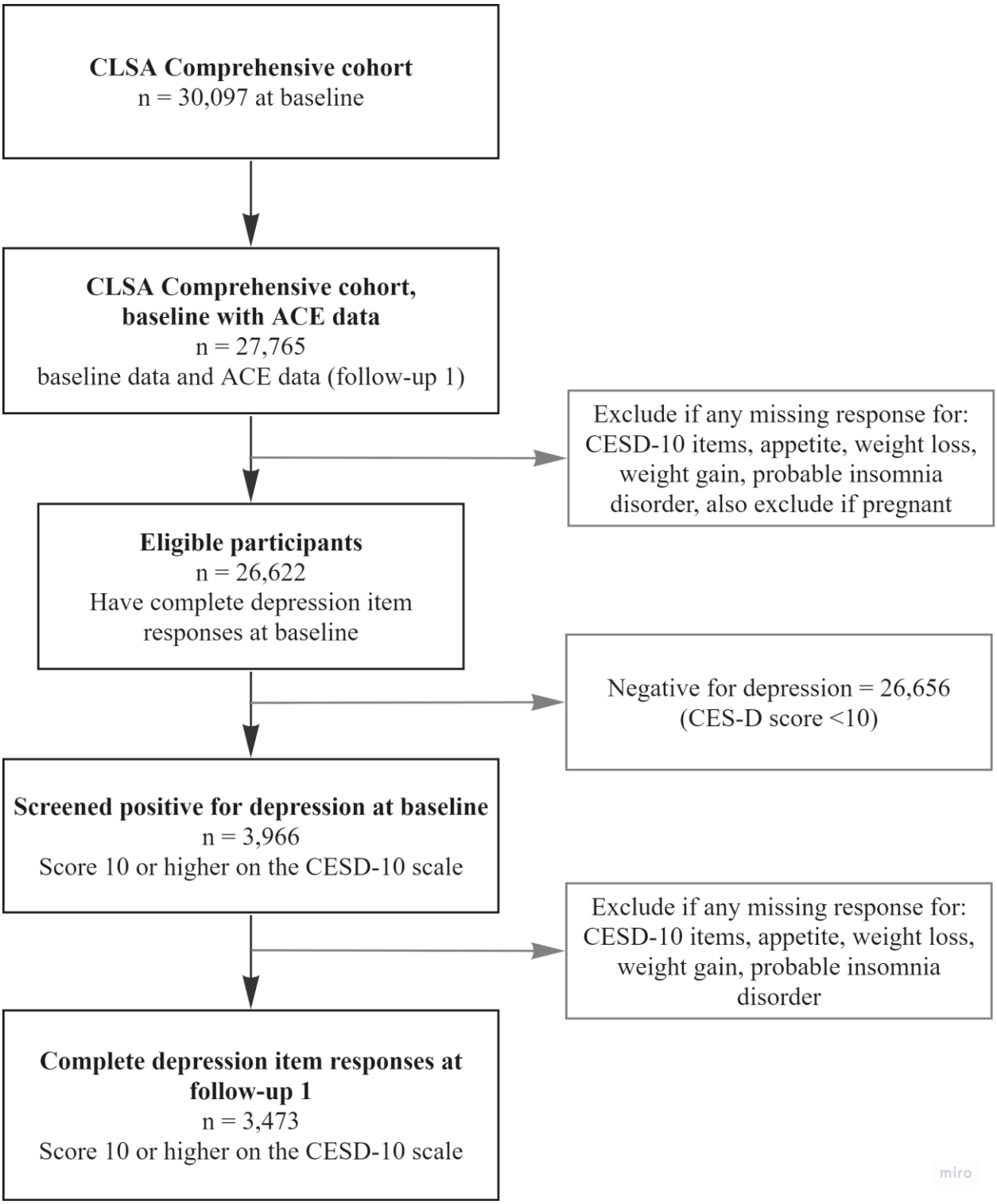
Appendices

Appendix 1. Sample selection process



Appendix 2. Center for Epidemiologic Studies Depression-10 (CESD-10) item, questions asked by CLSA, corresponding abbreviation in latent profiles analysis (Figure 1) and domain of depressive symptomology assessed.

CESD-10 item	**Question asked**	**Domain of depressive symptomology**	**Abbreviation used in Figure 1**
Frequency feel everything is an effort	How often did you feel that everything you did was an effort?	Depressive affect	effort
Frequency feel depressed	How often did you feel depressed?	Depressive affect	depressed
Frequency feel fearful or tearful	Remember, we are asking about how you have felt in the past week. How often did you feel fearful or tearful?	Depressive affect	fearful
Frequency feel could not 'get going'	How often did you feel that you could not “get going”?	Somatic complaint	‘get going’
Frequency feel happy	How often were you happy?	Positive affect	Happy
Frequency feel hopeful about the future	How often did you feel hopeful about the future?	Positive affect	Hopeful
Frequency feel lonely	How often did you feel lonely?	Depressive affect	Lonely
Frequency trouble concentrating	How often did you have trouble keeping your mind on what you were doing?	Somatic complaint	Concentration
Frequency sleep is restless	How often was your sleep restless?	Somatic complaint	Restless sleep

Appendix 3. Description of adverse childhood experiences items, abuse threshold criteria according to Tanaka et al. (2012), and abbreviation for the item used in the latent profile analysis (Figure 3).

ACE item	Category of abuse	Abuse threshold	Abbreviation in Figure 3
How many times did you see or hear any one of your parents, step-parents or guardians hit each other or another adult in your home?	Childhood exposure to intimate partner violence	3 or more times	Saw hit
How many times did you see or hear any one of your parents, step-parents or guardians say hurtful or mean things to each other or to another adult in your home?	Childhood exposure to intimate partner violence	6 or more times	Saw word
How many times did your parents, step-parents or guardians not take care of your basic needs, such as keeping you clean or providing food or clothing?	Neglect	1 or more times	Basic needs unmet
How many times did any one of your parents, step-parents or guardians swear at you, or say hurtful, insulting things that made you feel like you were not wanted or loved?	Emotional abuse	3 or more times	Feelings hurt

How many times did an adult kick, bite, punch, choke, burn you, or physically attack you in some way?	Physical abuse	1 or more times	Kick
How many times did an adult push, grab, shove or throw something at you to hurt you?	Physical abuse	3 or more times	Push
How many times did an adult slap you on the face, head or ears or hit or spank you with something hard to hurt you?	Physical abuse	3 or more times	Slap
How many times did a parent or caregiver spank you with their hand on your bottom (bum), or slap you on your hand?	Physical abuse	3 or more times	Spank
How many times did an adult touch you against your will in any sexual way?	Sexual abuse	1 or more times	Touch
How any times did an adult force you or attempt to force you into any unwanted sexual activity, by threatening you, holding you down or hurting you in some way?	Sexual abuse	1 or more times	Sexual

Did you ever see or talk to the police or anyone from child protective services about any of the things you mentioned?	na	na	Police

Appendix 4. Model fit indices of baseline depressive symptoms latent profile analysis

Profiles	**Loglik**	**AIC**	**BIC**	**SABIC**	**Entropy**	**BLRT p**	**Smallest profile %**
2	-60842.78	121771.55	122036.12	121899.5	0.84	0.01	16.5%
3	-54701.90	109519.81	109876.67	109692.4	1.00	0.01	11.8%
4	**-53918.94**	**107983.88**	**108433.03**	**108201.1**	**0.99**	**0.01**	**8.6%**
5	-53484.62	107145.23	107686.68	107407.1	0.96	0.01	6.8%

AIC, Akaike information criterion; BIC, Bayesian information criterion; SABIC, sample-adjusted Bayesian information criterion; BLRT p, bootstrap likelihood ratio test p-value; Smallest profile, the prevalence of the smallest profile within a given profile-solution. The selected profile-solution is in bold.

Appendix 5. Mean item estimates, their standard error (se) and p-values (p), for item in the depression latent profile analysis, by depression profile, corresponding to Figure 1.

	Positive affects			**Typical**			**Atypical**			**Melancholic**		
	estimate	se	p	estimate	se	p	estimate	se	p	estimate	se	p
Happy	1.69	0.02	0.00	1.67	0.04	0.00	1.62	0.05	0.00	1.60	0.03	0.00
Hopeful	1.66	0.02	0.00	1.60	0.05	0.00	1.57	0.05	0.00	1.58	0.04	0.00
Depressed	1.17	0.02	0.00	1.25	0.04	0.00	1.22	0.06	0.00	1.35	0.04	0.00
Lonely	1.13	0.02	0.00	1.16	0.05	0.00	1.18	0.06	0.00	1.16	0.04	0.00
Fearful	1.11	0.02	0.00	1.11	0.05	0.00	1.24	0.06	0.00	1.14	0.04	0.00
Bothered	1.30	0.02	0.00	1.40	0.05	0.00	1.52	0.06	0.00	1.35	0.04	0.00
Effort	1.37	0.02	0.00	1.49	0.05	0.00	1.45	0.05	0.00	1.76	0.05	0.00
Get going	1.24	0.02	0.00	1.33	0.05	0.00	1.32	0.06	0.00	1.63	0.04	0.00
Concentration	1.43	0.02	0.00	1.50	0.04	0.00	1.57	0.06	0.00	1.76	0.04	0.00
Restless sleep	1.87	0.02	0.00	1.89	0.05	0.00	1.91	0.05	0.00	2.44	0.04	0.00
Probable insomnia	0.00	0.00	1.00	0.00	0.00	1.00	0.00	0.00	1.00	1.01	0.00	0.00
Decreased appetite	0.67	0.01	0.00	0.82	0.05	0.00	0.66	0.05	0.00	0.94	0.04	0.00
Weight loss	0.09	0.01	0.00	2.53	0.02	0.00	0.00	0.00	0.18	0.50	0.04	0.00
Weight gain	0.12	0.01	0.00	0.00	0.00	0.32	2.31	0.03	0.00	0.50	0.04	0.00

Appendix 6. Model fit indices of baseline allostatic load biomarkers latent profile analysis

Profiles	Loglik	AIC	BIC	SABIC	Entropy	BLTR p	Smallest profile %
2	-80647.46	161398.92	161718.86	161553.6	0.81	0.01	44.5%
3	**-79399.11**	**158938.22**	**159368.91**	**159146.5**	**0.84**	**0.01**	**12.5%**
4	-78416.63	157009.26	157550.70	157271.1	0.87	0.01	3.3%
5	-77700.41	155612.82	156265.01	155928.2	0.83	0.01	3.2%

AIC, Akaike information criterion; BIC, Bayesian information criterion; SABIC, sample-adjusted Bayesian information criterion; BLRT p, bootstrap likelihood ratio test p-value; Smallest profile, the prevalence of the smallest profile within a given profile-solution. The selected profile-solution is in bold.

Appendix 7. Mean item estimates (standardized to the sample mean), as well as their standard error (se) and p-values (p) for each biomarker item in the allostatic load latent profile analysis, by allostatic load profile corresponding to Figure 2.

	Low-cardiovascular			**Average**			**High-cardiovascular**		
	estimate	se	p	estimate	se	p	estimate	se	p
Systolic blood pressure	-0.36	0.03	0.00	0.19	0.03	0.00	0.47	0.06	0.00
Diastolic blood pressure	-0.38	0.03	0.00	0.26	0.04	0.00	0.28	0.08	0.00
Pulse	-0.12	0.02	0.00	0.00	0.03	0.91	0.36	0.06	0.00
Total cholesterol	0.23	0.03	0.00	-0.06	0.04	0.08	-0.51	0.07	0.00
High density lipoprotein	0.66	0.03	0.00	-0.39	0.05	0.00	-0.72	0.05	0.00
Low density lipoprotein	0.15	0.03	0.00	0.00	0.03	0.92	-0.50	0.06	0.00
Triglycerides	-0.44	0.02	0.00	0.24	0.05	0.00	0.56	0.10	0.00
Glycated hemoglobin A1c	-0.30	0.01	0.00	0.00	0.04	0.97	0.98	0.12	0.00
Serum albumin	0.11	0.03	0.00	0.08	0.03	0.02	-0.65	0.10	0.00
Alanine aminotransferase	-0.33	0.02	0.00	0.19	0.06	0.00	0.36	0.11	0.00
Ferritin	-0.27	0.02	0.00	0.23	0.05	0.00	0.05	0.12	0.65
Hemoglobin	-0.36	0.03	0.00	0.36	0.05	0.00	-0.11	0.11	0.29

White blood cell count	-0.24	0.02	0.00	0.04	0.03	0.14	0.60	0.08	0.00
High-sensitivity C-reactive protein	-0.19	0.03	0.00	-0.04	0.02	0.06	0.75	0.13	0.00
Waist-hip ratio	-0.78	0.03	0.00	0.53	0.05	0.00	0.58	0.10	0.00
Waist circumference	-0.87	0.03	0.00	0.32	0.05	0.00	1.61	0.06	0.00
Body mass index	-0.67	0.03	0.00	0.11	0.03	0.00	1.76	0.12	0.00

Appendix 8. Model fit indices of adverse childhood experiences latent profile analysis

Profiles	Loglik	AIC	BIC	SABIC	Entropy	BLTR p	Smallest profile %
2	-55707.80	111501.61	111766.18	111629.5	0.99	0.01	11.8%
3	**-53764.45**	**107644.90**	**108001.76**	**107817.5**	**0.97**	**0.01**	**10.6%**
4	-53300.07	106746.13	107195.28	106963.3	0.94	0.01	9.5%
5	-52473.13	105122.27	105663.71	105384.1	0.95	0.01	3.8%

AIC, Akaike information criterion; BIC, Bayesian information criterion; SABIC, sample-adjusted Bayesian information criterion; BLRT p, bootstrap likelihood ratio test p-value; Smallest profile, the prevalence of the smallest profile within a given profile-solution. The selected profile-solution is in bold.

Appendix 9. Mean item estimates, as well as their standard error (se) and p-values (p) for each item in the adverse childhood experience (ACE) latent profile analysis by profile, corresponding to Figure 3.

	Moderate ACE			**Physical abuse ACE**			**Low ACE**		
	estimate	se	p	estimate	se	p	estimate	se	p
Family history	0.42	0.02	0.00	0.49	0.03	0.00	0.20	0.01	0.00
Parent death	0.19	0.02	0.00	0.28	0.03	0.00	0.17	0.01	0.00
Parent divorce	0.17	0.02	0.00	0.25	0.02	0.00	0.09	0.01	0.00
Saw hit	1.70	0.05	0.00	2.64	0.10	0.00	1.17	0.01	0.00
Saw word	3.49	0.06	0.00	4.01	0.10	0.00	1.76	0.03	0.00
Basic needs unmet	1.32	0.04	0.00	1.83	0.09	0.00	1.07	0.01	0.00
Feelings hurt	4.52	0.03	0.00	4.38	0.09	0.00	1.26	0.01	0.00
Kick	1.23	0.03	0.00	3.02	0.18	0.00	1.07	0.01	0.00
Push	1.41	0.06	0.00	4.66	0.04	0.00	1.15	0.01	0.00
Slap	2.60	0.07	0.00	4.42	0.06	0.00	1.65	0.02	0.00
Spank	3.69	0.06	0.00	4.45	0.06	0.00	2.55	0.03	0.00
Touch	1.69	0.05	0.00	2.17	0.08	0.00	1.26	0.02	0.00
Sexual	1.45	0.05	0.00	1.87	0.07	0.00	1.14	0.01	0.00
Police	1.08	0.01	0.00	1.25	0.05	0.00	1.02	0.00	0.00

CHAPTER 5: DISCUSSION AND CONCLUSIONS

This M.Sc. thesis includes two manuscripts comprehensively examining the associations of stress and depression; specifically, investigating depression subtypes, as well as depression chronicity. The two manuscripts contribute to the literature by finer characterization of depression subtypes and their associations with profiles of stress measures (ACEs and AL-biomarkers), and by further expanding the knowledge of how stress profiles and depression subtypes are linked to depression chronicity. The first manuscript of this M.Sc. thesis, presented in Chapter 2, reports distinct, data-driven, symptom-based depression subtypes in a population-based cohort. We uncovered specific stress profiles associated with distinct depression subtypes. In Chapter 3, depression chronicity at 3-year follow-up was identified as 46.6% of the study cohort, and prognostic factors for depression chronicity included baseline depression subtypes, stress profiles (baseline AL profile and ACE exposure profiles), and other factors, as described in the second manuscript.

As the importance of identifying depression subtypes has been increasingly recognized, the relevance of these findings lies in the potential for finer characterization of depression, which is heterogeneous in both clinical presentations and course. The identified subtypes are, to some extent, in line with previous findings. Specifically, the melancholic and atypical subtypes with particular clinical symptomology tend to be the observed depression subtypes in other studies and populations. The thesis contextualizes the heterogeneity of depression in the framework of stress-vulnerability theory, examining the role of stress profiles acting as both risk and prognostic factors for depression subtypes and chronicity, and observed that specific associations exist between various stress profiles (either objectively measured and self-reported measures) and depression outcomes. The application of person-centered approaches for stressors may provide insightful aggregation of well-established stressor associations with depression outcomes. For example, ACEs are known to cluster (Lacey et al., 2020; Li et al., 2022b), so the calculation of ACE scores lacks specificity for the patterning of adversity that is informative for interventions (Lacey et al., 2022). Similarly, the typical assessment of AL as a score may mask meaningful concurrent dysregulation of the relevant systems; however there is a lack of evidence regarding which biological systems are concurrently dysregulated in producing these outcomes. Thus, the association of depression subtypes and chronicity with these stressor profiles may

contribute to a more comprehensive understanding of the associated risks, thereby providing an opportunity to better predict, prevent and treat these outcomes.

This thesis has the following strengths: 1) the application of a person-centered approach allowed the exploration of latent profiles of depression and stressors; 2) the relationships between stressor profiles and depression outcomes were tested in a large sample with repeated measures on depression, thus the thesis provided robust findings in a population-based study; and 3) the holistic biopsychosocial approach contributes to the literature with findings on unique associations between stress and depression. The investigation of latent profiles of stressors and depression contributes finer insight into previously elucidated associations with depression. There are several limitations to consider. Firstly, operationalizations of depression subtypes and depression chronicity vary in the literature. The present studies rely on a score of 10 or more on the CESD-10 scale to define the presence of depression. Although the CESD-10 is a validated scale used for depression in population studies (Björgvinsson et al., 2013), it is not equivalent to a diagnosis. Similarly, we assessed depressive symptoms profiles, which are not equivalent to clinical definitions of depression presentation. Second, AL is tied to conceptualizations of the stress response system (McEwen, 2000), and thus measures of AL must accurately represent these systems. As such, the unavailability of neuroendocrine data within our measure of AL profiles may hinder proper investigation of this concept, by not fully capturing the whole picture of AL; i.e. perhaps the factors investigated were too down-stream of the stress-response process. Future investigations of AL profiles should include neuroendocrine measures, which are more upstream components of the allostatic process, and whose dysregulation leading to the dysregulation of other body systems is a central component of this framework (Arnaldo et al., 2022). AL may be better represented by multiple time point assessments, preferably including more upstream allostatic correlates, such as cortisol. For example, some studies have used hair cortisol (Berger et al., 2019; Lanfear et al., 2020; Staufenbiel et al., 2013). Moreover, future studies should include additional time-point measures of AL to better describe this dynamic process. As discussed, ACEs experienced tend to cluster and likely predispose to life-long sensitivity and resilience to stress (stress responses), for example, through epigenetic changes in response to early life stress (Jiang et al., 2019; Wilson-Genderson et al., 2022). In terms of the observed ACE clusters, we mostly observed profiles which differed in severity. The profile with the most frequent ACEs included physical abuse as a distinguishing factor, from the relatively

moderate and low ACE profiles. Research on further categorization into ACEs may provide more detail on the clusters of abuse experienced simultaneously (e.g. threat and deprivation, or emotional, neglect, physical, sexual abuse).

Having identified prognostic risk factors for chronic depression and observed a tendency towards chronicity and its associated subtypes, latent transition analysis should be applied to further delineate depressive symptom trajectories. Beyond the maintenance of depressive symptoms, it would be helpful to know how symptoms profiles may change (in characteristics, and intensity) over time. Further, the third component of the stress-vulnerability framework, i.e. protective factors, needs to be investigated. The observed associations between ACE, AL, depression subtypes and chronicity may be mediated by protective factors, such as social support (Atkinson et al., 2021; Cheong et al., 2017; Fiske et al., 2009; Gao et al., 2023). Such factors may influence perceived stress and thus the stress response, i.e. allostatic pathways (Brooks et al., 2014; Mauss and Jarczok, 2021), and associated depression-related outcomes (Gabarrell-Pascuet et al., 2022; Giovanelli et al., 2020; Holvast et al., 2015).

Additional future directions include the replication and validation of these findings in other populations. Replication in other populations, such as specifically younger or older adults, could shed light on whether depressive symptom profiles, and their associations, are age-specific. Replication in the UK biobank for example, could be used to verify if similar patterns are observed. Investigations into both age and sex (which the current studies did not have the power for) could also shed light on relevant differences. Further investigations into the effects of gender are required, as gender-specific information is limited in the CLSA and so this aspect of psychosocial stress was unable to be thoroughly investigated. In terms of potential public health relevance, the identified subtypes should be replicated and validated further. The hypothesis-free nature of latent profile analyses lends to different results when different instruments (i.e. depression questionnaire) and items are used in the analysis. While the present studies investigate self-reported depressive symptoms, this study should be replicated with items from other validated scales, such as the clinical Patient Health Questionnaire-9. Moreover, the present study investigated a well-established cut-off for the CESD-10 score. Future direction should incorporate further investigations on whether different profiles are observed using different

CESD-10 cut-offs, for example, to compare between identified profiles for different severities of depressive symptoms.

Depression is an artificially delineated and heterogenous condition, with opposite symptoms (e.g. overeating versus low appetite, fatigue versus agitation). As such, it is important that its subtypes are finely characterized, with regards to these potentially opposite clinical presentations, as they might provide useful insight at clinical and population levels. Ultimately, for clinical and public-health relevance, the identified depression subtypes must also be validated and reliable when it comes to determining associated health outcomes; they must be equally or more reliable than current methods of studying risk, for example, compared to the CESD-10 score. Therefore, the usefulness of depression subtypes in predicting other health outcomes must be ascertained in future population-based studies. For example, increased CESD score is associated with increased risk of cardiovascular disease (Harshfield et al., 2020). Specific presentations of depression, for example the atypical subtype, may be associated with increased risk of diabetes compared to other subtypes. Finer categorizations of depression and its chronicity may contribute more precise predictions to adverse health outcomes associated with depression, thereby enabling their prevention, for example, cardiovascular outcomes. Importantly, those who seek depression treatments must typically undergo an iterative process of sequential trial and failure, to determine which pharmaco-therapy is the most compatible in treating their depressive presentations. By effectively honing depression subtypes, i.e. in relation to stress, specific therapeutic processes may linked to the appropriate depression subtype, thereby enabling smoother pharmaco-treatment and clinical management, and improved prognosis.

Conclusion and summary

The present M.Sc. thesis investigation of stress profiles of ACE and AL allowed us to distinguish between diverse presentations of depressive symptoms, and to elucidate prognostic risk factors for chronic course of depression. We characterized four depressive symptom-based subtypes (melancholic, atypical, typical and positive affect) within CLSA baseline data in cross-sectional and longitudinal samples. We observed differential associations between baseline depression subtypes, ACE exposure and concurrent AL profiles, as well as other factors. We also identified prognostic risk factors for the 3-year course of depression that are lacking in the

literature, despite the propensity for chronic depression in this age group. These included ACEs, baseline depressive subtype and AL profile, and other factors which have been associated with depression incidence. Importantly, stress (biological and psychological) plays a significant role in depressive symptom subtypes and course of depressive symptoms. Overall, these findings contribute to research on finer characterizations of depression (including its course). Such a refined categorization is essential to identify and link effective clinical management strategies to the specific presentation of depression. Moreover, a deeper understanding of associated stressors may contribute to earlier identification and intervention for these depression subtypes. Finally, identification of such associated stressors and prognostic factors may provide insight into secondary targets for intervention.

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