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Risk prediction models for depression in community-dwelling older adults

Running title: Risk prediction models of late-life depression

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27 **Abstract (246 w)**

28 **Objectives:** to develop streamlined Risk Prediction Models (*Manto* RPMs) for late-life
29 depression.

30 **Design:** Prospective study.

31 **Setting:** the Survey of Health, Ageing and Retirement in Europe (SHARE) study.

32 **Participants:** Participants were community residing adults aged 55 years or older.

33 **Measurements:** The outcome was presence of depression at a two-year follow up evaluation.
34 Risk factors were identified after a literature review of longitudinal studies. Separate RPMs were
35 developed in the 29,116 participants who were not depressed at baseline and in the combined
36 sample of 39,439 of non-depressed and depressed subjects. Models derived from the combined
37 sample were used to develop a web-based risk calculator.

38 **Results:** We identified 129 predictors of late-life depression after reviewing 227 studies. In non-
39 depressed participants at baseline, the RPMs based on regression and LASSO penalty (34 and
40 58 predictors, respectively) and the RPM based on Artificial Neural Networks (124 predictors) had
41 a similar performance (AUC: 0.730 – 0.743). In the combined depressed and non-depressed
42 participants at baseline, the RPM based on neural networks (35 predictors; AUC: 0.807; 95% CI:
43 0.80 - 0.82) and the model based on linear regression and LASSO penalty (32 predictors; AUC:
44 0.81; 95% CI: 0.79 - 0.82) had satisfactory accuracy.

45 **Conclusions:** The *Manto* RPMs can identify community-dwelling older individuals at risk for
46 developing depression over two years. A web-based calculator based on the streamlined *Manto*
47 model is freely available for use by individuals, clinicians, and policy makers and may be used to
48 target prevention interventions at the individual and the population levels.

49

50

51 **Keywords:** late-life depression; older adults; risk prediction; risk factor; physical illness

52

53 **1. Introduction**

54 Late-life depression remains largely under-recognized and undertreated, despite its
55 negative impact on individuals and on society ^{1,2}. Knowledge of risk factors might improve
56 recognition of depression and help the development and targeting of prevention strategies.

57 Risk factors for late-life depression are many and diverse. Late-life depression is caused
58 by an interplay of heterogeneous dysfunctions affecting the individual's homeostasis across
59 biological, psychological, and social domains ³⁻⁵. One or more factors predisposing to depression
60 may lead to a depressive episode when they cross a threshold or when a precipitating event
61 occurs. Chronic medical illnesses ^{3,6,7}, accumulation of micro-cerebrovascular damage ⁸, chronic
62 subclinical inflammation impairing the brain's functional connectivity ⁹⁻¹¹ and social isolation ¹²
63 confer vulnerability to depression. In predisposed individuals, a depressive episode may erupt
64 after a major adverse event or when changes of the social milieu lead to changes in sleep or to
65 social withdrawal ¹³⁻¹⁵. Prospective studies have identified various risk factors for depression. ^{4,7,16}
66 Some risk prediction models (RPMs) have been developed that estimate the probability that an
67 individual will develop a clinical outcome in the future based on the presence of risk factors ¹⁷.
68 RPMs may help clinicians and policy makers to develop prevention strategies targeting
69 individuals at risk ^{5,18-22} and to improve both patient outcomes and the cost-effectiveness of care.

70 Only few studies have attempted to develop prediction models for late-life depression all
71 using small sets of risk factors, including demographic characteristics, health-related factors,
72 disability and individual depressive symptoms ^{18,23,24}. Previous models were based on samples
73 consisting of both depressed and non-depressed participants; this sample selection allows to
74 assess risk prediction without requiring information on the presence of depression. However, it
75 may overestimate the relevance of depressive symptoms as predictors of risk, since depressive
76 symptoms may be indices of vulnerability to depression ²⁵.

77 Extending our previous study ¹⁸ and others, ^{23,24} the present study uses an extensive set
78 of literature-informed predictors, an information-rich, large database of community residing older

79 adults followed for 2 years, and multiple methods to develop and validate the *Manto** RPMs for
80 late-life depression. Our primary aim has been to obtain a model that estimates the risk of
81 developing depression among older adults who are not depressed at the time of risk assessment.
82 In addition, we developed streamlined models from a larger sample that included both depressed
83 and non-depressed individuals so that they can be compared with models of earlier studies and
84 used by both depressed and non-depressed individuals through an open-access web-based
85 calculator.

86

87 **2. Methods**

88 This study followed the TRIPOD tool for transparent reporting of multivariable prediction models
89 ²⁶.

90

91 **2.1 Identification and selection of predictors for model development**

92 We conducted a literature review to narrow the number of SHARE variables introduced in
93 our prediction models (Supplementary Methods, par. 1.2). The review included longitudinal
94 studies of community-dwelling participants older than 50 years, examining the association
95 between predictors and depression over a follow-up of at least six months. To include a predictor
96 in the RPM, it had to be: (i) prospectively associated with depression; (ii) assessed with simple
97 questions that respondents could answer and not requiring instrumental or laboratory measures,
98 as judged by consensus between M.B.M. and F.T.; and (iii) included in the Survey of Health,
99 Ageing and Retirement in Europe (SHARE) database.

100

101 **2.2 Study design, setting, and study population**

* The name *Manto* of our RPMs is derived from Greek mythology. Manto (Greek: Μαντώ) was a sibyl oracle, daughter of the Theban blind oracle Tiresias. After the sack of Thebes, she fled, founded the Italian city of Mantua, and created the Mantua lake with her tears. Most of her prophesies were about misfortunes.

102 In constructing the Manto RPMs, we used a large number of demographic, health, and
103 psychosocial risk variables from the SHARE Study. The selection of SHARE variables was
104 guided by a review of risk factors of depression ²⁷. SHARE collected information on a wide range
105 of factors from community-dwelling Europeans aged 50 years or older ²⁷. Our study used
106 predictor data from wave 5 (collected in 2013), consisting of baseline and retrospective
107 information, and outcome data from wave 6 (collected in 2015). Eligibility criteria for this study
108 were age older than 55 years at wave 5 and availability of data on depression at wave 6, obtained
109 2 years after wave 5. We included individuals in midlife (55+) because it is the time in which some
110 adults experience stress by the nearing transition to retirement and also the time in which health
111 problems begin to emerge.

112 The SHARE study had been approved by the Ethics Council of the Max Planck Society
113 and by each country's ethics committees. The authors assert that all procedures contributing to
114 this work comply with the ethical standards of the relevant national and institutional committees
115 on human experimentation and with the Helsinki Declaration of 1975, revised in 2008.

116

117 **2.3 Outcome definition**

118 Depression was assessed with the EURO-D, ²⁸ which rates the presence or absence of 12
119 depressive symptoms (depressed mood, pessimism, death wishes, guilt, sleep problems, loss of
120 interest, irritability, loss of appetite, fatigue, concentration difficulties, lack of enjoyment, and
121 tearfulness). The EURO-D has sound psychometric properties documented in previous studies
122 ^{28,29}. The total score ranges from 0 to 12; a score of 4 or higher indicates the presence of major
123 depression. This criterion has been validated with interview-based assessments ²⁸.

124

125 **2.4 Data analysis**

126 First, analyses were conducted in participants without a diagnosis of depression at baseline
127 (EURO-D score < 4) to identify risk factors unrelated to depressive symptoms. Then, analyses

128 were repeated on the combined sample of depressed and non-depressed subjects to build a
129 streamlined web-based depression risk calculator for use by the public. Analyses on the
130 combined sample were based on the assumption that users of the risk calculator may not know
131 their depression status. For each population, we developed one model employing the Artificial
132 Neural Network (ANN) and two models employing Logistic Regression (LR). ANN are prediction
133 algorithms that allow complex nonlinear relationships between the response variable and its
134 predictors. These ANN models were based on multilayer perceptrons with fully connected layers
135 of neurons. The ANN of the non-depressed sample aimed to maximize the accuracy of prediction
136 by using all available information on risk factors. The ANN of the combined sample was used to
137 develop the web risk calculator, which is intended for use by the public. For this reason, we
138 limited the questions to a number likely to be answered by users and achieve an optimal trade-off
139 between accuracy and number of predictor variables.

140 LR models employed the Least Absolute Shrinkage and Selection Operator (LASSO)
141 penalty³⁰, a variable selection method that removes variables with a weak association with the
142 model's outcome. In each set of analyses, we developed two LR models by varying the level of
143 required information. The first logistic models (full-LR) select predictors by choosing the penalty
144 parameter that minimizes the Mean Squared Error (MSE). The second logistic model (lean-LR)
145 imposed an additional restriction on the maximum number of predictors. This optimal trade-off
146 was established based on the examination of validation curves which display the relationship
147 between the number of predictors and model performance. In the LR models, missing data on
148 continuous variables were imputed by the median value because some variables had skewed
149 distributions, while on categorical predictors a "missing data" additional category was used.

150 All models were validated with a k-fold cross-validation (CV). The models' predictive
151 accuracy was evaluated with the Area Under the Receiver Operating Characteristic curve (AUC-
152 ROC for model discriminative accuracy) and with the Mean Squared Error (MSE, equivalent to
153 the Brier score). We report the optimal values of Sensitivity, Specificity, Positive Predictive Value

154 (PPV) Negative Predictive Value (NPV) , as well as calibration data and curves to describe the
155 agreement between the estimated and observed number of events *at each threshold of risk*³¹.
156 Calibration is particularly relevant to examining whether a model under- or overestimates risk
157 among specific ranges of risk scores.

158 Finally, the performance of models built on the total sample were compared with that of
159 previous RPMs on late-life depression,^{18,23,24} conducted on samples consisting of depressed and
160 non-depressed individuals.

161

162 **3. Results**

163 **3.1 Identification and selection of predictors**

164 Literature review was conducted on June the 1st, 2019 and identified 209 prospective
165 studies and 18 meta-analyses assessing the prospective association of sociodemographic and
166 clinical risk factors with late-life depression (Figure S1). This review enabled us to identify 71
167 distinct types of risk factors, 19 within the sociodemographic domain, 21 within the psychological
168 domain, and 31 within the physical domain (Table S2). We matched risk factors identified from
169 literature with available data on individual variables from the SHARE study (Table S3), excluding
170 risk factors that could not be translated into questions (n=2), predictors that were not measured
171 by the SHARE study (n=21), and variables with many missing data (n=3). Ten predictors with
172 missing data above the pre-defined threshold were retained because of their clinical relevance. In
173 the end, 129 variables remained available for model development, of which 107 had less than 3%
174 of missing data.

175

176 **3.2 Sample characteristics**

177 There were 66,188 eligible participants in wave 5 of the SHARE study. Of these, 57,444
178 participants were aged 55 years or older and 39,439 participants had depression data at wave 6.
179 A EURO-D score of 4 or higher was identified in 9,848 participants, indicating the presence of

180 major depression. Of the 29,116 participants without major depression (EURO-D < 4) at baseline
181 (Figure S2), 51.5% were female, with a mean age of 67 years (Table 1, Figure S3 and Table S4).

182 In the combined sample at wave 5, 24.6% (9,688/39,439) of participants had depression.
183 Those with depression symptoms at baseline were more likely to have depression during follow
184 up (Figure S4). Among those who had depression at follow-up (wave 6), 54.9% (5,433/9,904) had
185 been already depressed at baseline, 45.1% (4,471/9,904) had not been depressed.

186

187 **3.3 RPMs among non-depressed participants at baseline**

188 In non-depressed participants (N=29,116), the three RPM models had similar predictive
189 accuracy (all values of AUC-ROC above 0.73, Table 2) despite large differences in the number of
190 retained predictors. Specifically, the ANN model selected 124 predictors and the full-LR model
191 selected 58. We plotted validation curves of the relationship between regression model
192 complexity and performance (Figure S5). The performance of complex models with over 100
193 predictors was only slightly worse than its peak value. Overall, retaining 20 to 40 predictors was
194 associated with steep improvement in model performance. Thus, we limited the number of
195 predictors of the lean-LR model to 35, and 34 were retained. All models yielded satisfactory
196 specificity. Despite similar discrimination profiles, however, the ANN and the full-LR model had a
197 marginally better calibration than the lean-LR model (Table 2 and Figure 1, right panel). Thus, the
198 full-LR model may be considered the best trade-off between the level of required information and
199 prediction performance (Tables S5 – S7).

200 All models included the following predictors (Table 3, Tables S8 and S9): Age, sex, low
201 participation in activities, depressive symptoms, use of medications for anxiety or depression,
202 loneliness, low quality of life, negative views on aging, lack of vitality, low optimism, poor
203 perceived physical health, many medical consultations, and use of painkillers and hypnotics. The
204 full-LR model included additional information on socioeconomic variables, a broad range of

205 depressive symptoms and views on aging, predictors related to medical health and unhealthy
206 lifestyle.

207

208 **3.4 RPMs in the combined sample of depressed and non-depressed participants at** 209 **baseline**

210 We repeated analyses in the combined sample (N=39,439) to develop RPMs for use by
211 the public. We imposed a maximum number of 35 predictors in the ANN model, while the full-LR
212 model retained 70 predictors. Based on validation curves, the number of predictors in the lean-LR
213 model was limited to 35, of which 32 were retained (Table S10). The three models yielded similar
214 levels of accuracy despite different RPM methodology and number of predictors. Performance
215 was better in the combined sample of depressed and non-depressed participants at baseline than
216 in non-depressed participants at baseline (all values of AUC-ROC above 0.80, Table 2). All
217 models had satisfactory calibration profiles; the ANN and the full-LR models had only a slight
218 advantage over the lean-LR at high values of observed risk (Figure S6; Tables S11 – S13).
219 Nonetheless, the lean-LR model was chosen because of its brevity and the ease of interpretation
220 lend it best for clinical use. Applying a risk threshold of 20%, the lean-LR model maintained a high
221 level of sensitivity (84%) and NPV (91.5%) but a lower PPV (41.3%) and is suitable for
222 depression screening by clinicians who can ascertain the presence of depression through clinical
223 examination. In contrast, a high-risk threshold of 55% would yield a more balanced trade-off
224 between positive predictive value (74%) and negative predictive value (79.4%) and may be
225 informative to individual users.

226 Predictors in the lean-LR model included sex, age, not reading books or newspapers,
227 absence of activities in the previous year, depressive symptoms, loneliness, poor quality of life,
228 negative views on aging, lack of vitality and optimism, difficulty in activities of daily living,
229 dizziness, pain, and fatigue (Table S10, S14, S15).

230

231 **3.5 Comparison with previous models**

232 The newly developed models had better discrimination and calibration profiles (AUC 0.66) than
233 the DRAT-up (AUC 0.74)¹⁸ and the Okamoto-Harasawa (AUC: 0.657) models²⁴. DRAT-up
234 significantly underestimated the risk of depression in the high-risk strata (Figure S6, Table S16 –
235 S17). The models of Xu et al. could not be reproduced due to lack of data on network parameters
236²³. Our models used information on individual depressive symptoms. Our symptom-based models
237 were superior to a model, in which prediction was based on information on categorical information
238 on depression (present/absent) at baseline, which resulted in a sensitivity of 55% and specificity
239 of 85% (AUC 0.701, Table S16).

240 **4. Discussion**

241 We developed *Manto*, a set of risk prediction models (RPMs), and showed that they have
242 satisfactory accuracy in predicting the development of major depression in non-depressed,
243 community residing older adults over a period of two years. The prediction performance of *Manto*
244 RPMs is even stronger in the combined sample of both depressed and non-depressed individuals
245 at baseline. *Manto* is available as a web-based risk calculator for clinicians and individuals.
246 The *Manto* RPMs and the online calculator we developed (<https://manto.unife.it/>) may be used by
247 individuals, clinicians, and policy makers to identify older persons at risk for depression. Our web-
248 based risk calculator is freely available and is based on information that can be obtained during
249 the time frame of a routine medical visit (about 15 minutes)³². It uses predictors from the lean-LR
250 model of the combined sample to estimate the probability of being at high risk for depression in
251 the next two years, expressed as a percentage. Depression is best managed by shared decision-
252 making³³. The risk calculator may contribute to this process by offering to users a continuous
253 estimate of risk that may aid individuals and their health care provider in clinical decision making.
254 We did not study the relationship of *Manto* prediction scores to treatment and prevention
255 interventions and, thus, cannot provide risk cut-off points for clinical decisions. The relationship of
256 risk scores to clinical action depends on the healthcare context and on the availability of cost-

257 effective preventive interventions ³³⁻³⁵. For instance, a high-risk score (e.g. above 50 - 60%) may
258 yield the best trade-off between positive and negative predictive values and aid individual users in
259 the decision to seek clinical evaluation. In contrast, a low risk score (e.g. 20%) may guide large
260 scale screening initiatives that require higher sensitivity. The role of Manto needs to be further
261 studied in specific clinical and community contexts.

262 Many of the identified predictors of late-life depression are modifiable and may inform the
263 selection and targeting of prevention interventions. Among non-depressed individuals at baseline,
264 the full-LR model identified paucity of leisure and intellectual activities, scarcity of social activities,
265 poor physical health, unhealthy lifestyle, depressive symptoms, and negative views on aging as
266 significant predictors of development of depression. A subset of variables from these domains
267 were also part of the streamlined lean-LR model, with only a small loss in accuracy, i.e. a
268 tendency to overestimate the risk of depression at higher risk values, and to underestimate the
269 risk at lower risk values ³¹. Loss of purpose, demoralization, pessimism ^{15,36}, perceived poor
270 health and life satisfaction were predictors of depression, but may also be symptoms of
271 depression or indices of vulnerability related to depression ⁵. Consistent with a dynamic symptom
272 network theory of late-life depression ^{4,14,37}, risk factors for depression or symptoms of depression
273 can initiate a cascade of interactions among them that may evolve into a self-sustained
274 depressive syndrome ¹⁵. Interventions targeting modifiable risk factors may prevent the
275 development of a full-blown depression, but empirical studies need to examine whether and to
276 what extent such interventions are successful.

277 Self-help interventions ³⁸, vigilant follow-up, treatment of subclinical depression symptoms
278 ^{14,37,39}, and streamlined psychosocial interventions aimed to increase meaningful, rewarding
279 activities ^{19,40-42} may be used to prevent development of depression in older adults at risk. Policy
280 makers may use the Manto RPMs to target older populations at risk for depression and develop
281 appropriate interventions or consider some of the available community-based interventions ⁴³,

282 e.g. promotion of illness awareness, help-seeking, and self-management ¹, or comprehensive
283 interventions including the Program to Encourage Active, Rewarding Lives for Seniors (PEARLS)
284 ⁴⁴, Healthy IDEAS (Identifying Depression, Empowering Activities for Seniors) ⁴⁵, SAMHSA’s
285 Promoting Emotional Health and Preventing Suicide, Tool Kit ⁴⁶, and others. Providing information
286 on depression risk in an accessible way may raise awareness among clinicians and individuals ⁴⁷.
287 Depressed older adults often hold stigmatizing beliefs and do not recognize the need for help, or
288 have negative views about treatment and avoid mental health care ⁴⁸. The performance of *Manto*
289 RPMs is superior to that of DRAT-up, our earlier model for prediction of late-life depression. By
290 relying on five selected predictors, DRAT-up had reached a fair level of accuracy (AUC: 0.74 to
291 0.77) but its positive and negative predictive values were low ¹⁸. The superior performance of
292 *Manto* RPMs is likely due to the inclusion of a larger number of prediction variables and the use of
293 advanced methodology. Our findings are not directly comparable to the Xu et al RPM study on
294 late-life depression, which used machine-learning but lacked cross-validation ²³. The model of Xu
295 et al was based on twelve risk factors collected from a prospective study spanning 22 years.
296 When it included “look-back” data that had been *collected* 12 years prior to baseline, its accuracy
297 was somewhat higher than that of *Manto* RPM (AUC: 0.87, compared to *Manto*’s 0.80). Our study
298 did not use information that extends back to such a long period because recall bias might limit the
299 reliability of such information.

300 Our study has limitations. We were unable to find a dataset with a large number large
301 number of predictors similar to that of SHARE that could be used for an external validation of our
302 findings. Our model is relevant to populations of the countries participating in the SHARE Study
303 and needs to be further tested in samples with greater social and ethnic heterogeneity. In
304 addition, cognitive dysfunction, anxiety and neuroticism are risk factors for late-life depression ^{5,49}.
305 Introducing streamlined assessments in RPMs might improve their performance. Further studies
306 need to explore the model’s clinical utility and its potential for widespread implementation.
307 Considering the low rate of missing data, we used a simple imputation technique. It is doubtful

308 that the results would have changed substantially had we used multiple imputation. The RPM
309 focused on the prediction of depression over a 2-year period. Therefore, it is unclear whether the
310 same variables can predict the occurrence of depression over a shorter or a longer period.
311 Finally, the data were collected prior to the COVID pandemic, which might have shifted the
312 importance of some risk factors for late-life depression.

313 The study has several strengths. The selection of predictors for its RPMs was based on a
314 review of 227 studies on the association of sociodemographic and clinical variables with late-life
315 depression. The RPMs were tested on a database of 39,439 community residing older adults with
316 information on 129 potential predictors of depression and a 2 year follow-up. Unlike previous
317 investigations,^{18,50} the current study employed multiple advanced methods of analyses, including
318 Artificial Neural Networks and Regularized Regression algorithms to reach an optimal trade-off
319 between the number of predictors and the performance of risk prediction models.

320 In conclusion, the *Manto* RPMs can be used to identify community-dwelling older adults at risk for
321 developing depression over a period of two years. The risk calculator based on the *Manto* RPM
322 may be used by older adults and by clinicians during routine medical visits to assess the risk of
323 depression development. The *Manto* RPMs and the risk calculator may aid policy makers in
324 developing and targeting prevention strategies.

325

326 **Author contributions**

327 MBM conceived the study, contributed to data analysis and wrote the manuscript. LC, FC, PP
328 conceived the study, conducted data analysis and wrote the manuscript. FT and GA contributed
329 to the study design and wrote the manuscript.

330

331

332 **Conflict of interest**

333 Prof. Alexopoulos has served on advisory boards of Janssen and Eisai and has been on the
334 speakers' bureaus of Lundbeck, Otsuka, and Allergan. No other authors report conflicts of
335 interest.

336

337 **Data statement**

338 The data has not been previously presented orally or by poster at scientific meetings. The data
339 that support the findings of this study are openly available at the SHARE study website
340 (<http://www.share-project.org/>), specifically at <http://doi.org/10.6103/SHARE.w5.710> and
341 <http://doi.org/10.6103/SHARE.w6.710>.

342

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REFERENCES

- 362 1. Horackova K, Kopecek M, Machů V, et al. Prevalence of late-life depression and gap in
363 mental health service use across European regions. *Eur Psychiatry*. 2019;57:19-25.
364 doi:10.1016/j.eurpsy.2018.12.002
- 365 2. Andreas S, Schulz H, Volkert J, et al. Prevalence of mental disorders in elderly people: The
366 European MentDis-ICF65+ study. *Br J Psychiatry*. 2017;210(2):125-131.
367 doi:10.1192/bjp.bp.115.180463
- 368 3. Alexopoulos GS. Mechanisms and treatment of late-life depression. *Transl Psychiatry*.
369 2019;9(1). doi:10.1038/s41398-019-0514-6
- 370 4. Andreescu C, Ajilore O, Aizenstein HJ, et al. Disruption of Neural Homeostasis as a Model
371 of Relapse and Recurrence in Late-Life Depression. *Am J Geriatr Psychiatry*. 2019.
372 doi:10.1016/j.jagp.2019.07.016
- 373 5. Laird KT, Krause B, Funes C, Lavretsky H. Psychobiological factors of resilience and
374 depression in late life. *Transl Psychiatry*. 2019;9(1). doi:10.1038/s41398-019-0424-7
- 375 6. Alexopoulos GS. Depression in the elderly. *Lancet*. 2005;365(9475):1961-1970.
376 doi:10.1016/S0140-6736(05)66665-2
- 377 7. Köhler CA, Evangelou E, Stubbs B, et al. Mapping risk factors for depression across the
378 lifespan: An umbrella review of evidence from meta-analyses and Mendelian randomization
379 studies. *J Psychiatr Res*. 2018;103(October 2017):189-207.
380 doi:10.1016/j.jpsychires.2018.05.020
- 381 8. Van Agtmaal MJM, Houben AJHM, Pouwer F, Stehouwer CDA, Schram MT. Association of
382 microvascular dysfunction with late-life depression: A systematic review and meta-analysis.

- 383 *JAMA Psychiatry*. 2017;74(7):729-739. doi:10.1001/jamapsychiatry.2017.0984
- 384 9. Sonsin-Diaz N, Gottesman RF, Fracica E, et al. Chronic Systemic Inflammation Is
385 Associated With Symptoms of Late-Life Depression: The ARIC Study. *Am J Geriatr*
386 *Psychiatry*. 2020;28(1):87-98. doi:10.1016/j.jagp.2019.05.011
- 387 10. Milaneschi Y, Lamers F, Berk M, Penninx BWJH. Depression Heterogeneity and Its
388 Biological Underpinnings: Toward Immunometabolic Depression. *Biol Psychiatry*.
389 2020;88(5):369-380. doi:10.1016/j.biopsych.2020.01.014
- 390 11. Alexopoulos GS, Morimoto SS. The inflammation hypothesis in geriatric depression. *Int J*
391 *Geriatr Psychiatry*. 2011;26(11):1109-1118. doi:10.1002/gps.2672
- 392 12. Lutz J, Van Orden KA, Bruce ML, Conwell Y. Social Disconnection in Late Life Suicide: An
393 NIMH Workshop on State of the Research in Identifying Mechanisms, Treatment Targets,
394 and Interventions. *Am J Geriatr Psychiatry*. 2021. doi:10.1016/j.jagp.2021.01.137
- 395 13. Belvederi Murri M, Grassi L, Caruso R, et al. Depressive symptom complexes of
396 community-dwelling older adults: a latent network model. *Mol Psychiatry*. 2021.
397 doi:10.1038/S41380-021-01310-Y
- 398 14. Meeks TW, Vahia I V., Lavretsky H, Kulkarni G, Jeste D V. A tune in “a minor” can “b
399 major”: A review of epidemiology, illness course, and public health implications of
400 subthreshold depression in older adults. *J Affect Disord*. 2011;129(1-3):126-142.
401 doi:10.1016/j.jad.2010.09.015
- 402 15. Belvederi Murri M, Amore M, Respino M, Alexopoulos GS. The symptom network structure
403 of depressive symptoms in late-life: Results from a European population study. *Mol*
404 *Psychiatry*. 2018;1. doi:10.1038/s41380-018-0232-0
- 405 16. Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: A
406 systematic review and meta-analysis. *Am J Psychiatry*. 2003;160(6):1147-1156.

407 doi:10.1176/appi.ajp.160.6.1147

408 17. Bernardini F, Attademo L, Cleary SD, et al. Risk prediction models in psychiatry: Toward a
409 new frontier for the prevention of mental illnesses. *J Clin Psychiatry*. 2016;in press.

410 doi:10.4088/JCP.15r10003

411 18. Cattelani L, Belvederi Murri M, Chesani F, et al. Risk Prediction Model for Late Life
412 Depression: Development and Validation on Three Large European Datasets. *IEEE J*
413 *Biomed Heal informatics*. 2018;PP(c):9. doi:10.1109/JBHI.2018.2884079

414 19. Cuijpers P, Smit F, Patel V, Dias A, Li J, Reynolds CF. Prevention of depressive disorders
415 in older adults: An overview. *PsyCh J*. 2015;4(1):3-10. doi:10.1002/pchj.86

416 20. Hu MX, Turner D, Generaal E, et al. Exercise interventions for the prevention of
417 depression: A systematic review of meta-analyses. *BMC Public Health*. 2020;20(1).

418 doi:10.1186/s12889-020-09323-y

419 21. Biesheuvel-Leliefeld KEM, Kok GD, Bockting CLH, et al. Effectiveness of psychological
420 interventions in preventing recurrence of depressive disorder: Meta-analysis and meta-
421 regression. *J Affect Disord*. 2015;174:400-410. doi:10.1016/j.jad.2014.12.016

422 22. Almeida OP. Prevention of depression in older age. *Maturitas*. 2014;79(2):136-141.

423 doi:10.1016/j.maturitas.2014.03.005

424 23. Xu Z, Zhang Q, Li W, Li M, Yip PSF. Individualized prediction of depressive disorder in the
425 elderly: A multitask deep learning approach. *Int J Med Inform*. 2019.

426 doi:10.1016/j.ijmedinf.2019.103973

427 24. Okamoto K, Harasawa Y. Prediction of symptomatic depression by discriminant analysis in
428 Japanese community-dwelling elderly. *Arch Gerontol Geriatr*. 2011;52(2):177-180.

429 doi:10.1016/j.archger.2010.03.012

430 25. Bogner HR, Morales KH, Reynolds CF, Cary MS, Bruce ML. Course of depression and

- 431 mortality among older primary care patients. *Am J Geriatr Psychiatry*. 2012;20(10):895-
432 903. doi:10.1097/JGP.0b013e3182331104
- 433 26. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable
434 prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement.
435 *BMJ*. 2015. doi:10.1136/bmj.g7594
- 436 27. Börsch-Supan A, Brandt M, Hunkler C, et al. Data resource profile: The survey of health,
437 ageing and retirement in europe (share). *Int J Epidemiol*. 2013;42(4):992-1001.
438 doi:10.1093/ije/dyt088
- 439 28. Prince MJ, Reischies F, Beekman ATF, et al. Development of the EURO-D scale - A
440 European Union initiative to compare symptoms of depression in 14 European centres. *Br*
441 *J Psychiatry*. 1999;174(APR.):330-338. doi:10.1192/bjp.174.4.330
- 442 29. Pagán-Rodríguez R, Pérez S. Depression and self-reported disability among older people
443 in Western Europe. *J Aging Health*. 2012;24(7):1131-1156.
444 doi:10.1177/0898264312453070
- 445 30. Meier L, Van De Geer S, Bühlmann P. The group lasso for logistic regression. *J R Stat Soc*
446 *Ser B Stat Methodol*. 2008;70(1):53-71. doi:10.1111/j.1467-9868.2007.00627.x
- 447 31. Van Calster B, McLernon DJ, Van Smeden M, et al. Calibration: The Achilles heel of
448 predictive analytics. *BMC Med*. 2019;17(1). doi:10.1186/s12916-019-1466-7
- 449 32. Palumbo P, Cattelani L, Chesani F, et al. Manto online risk calculator for late life
450 depression. www.manto.unife.it. Published 2021.
- 451 33. Wynants L, Van Smeden M, McLernon DJ, Timmerman D, Steyerberg EW, Van Calster B.
452 Three myths about risk thresholds for prediction models. *BMC Med*. 2019;17(1):1-7.
453 doi:10.1186/s12916-019-1425-3
- 454 34. Brettschneider C, Heddaeus D, Steinmann M, Härter M, Watzke B, König HH. Cost-

- 455 effectiveness of guideline-based stepped and collaborative care versus treatment as usual
456 for patients with depression - A cluster-randomized trial. *BMC Psychiatry*. 2020;20(1):1-14.
457 doi:10.1186/s12888-020-02829-0
- 458 35. Smit F, Ederveen A, Cuijpers P, Deeg D, Beekman A. Opportunities for Cost-effective
459 Prevention of Late-Life Depression: An Epidemiological Approach. *Arch Gen Psychiatry*.
460 2006;63(3):290-296. doi:10.1001/ARCHPSYC.63.3.290
- 461 36. Belvederi Murri M, Caruso R, Ounalli H, et al. The relationship between demoralization and
462 depressive symptoms among patients from the general hospital: network and exploratory
463 graph analysis: Demoralization and depression symptom network. *J Affect Disord*. 2020.
464 doi:10.1016/j.jad.2020.06.074
- 465 37. Lee YY, Stockings EA, Harris MG, et al. The risk of developing major depression among
466 individuals with subthreshold depression: A systematic review and meta-analysis of
467 longitudinal cohort studies. *Psychol Med*. 2019. doi:10.1017/s0033291718000557
- 468 38. Cremers G, Taylor E, Hodge L, Quigley A. Effectiveness and Acceptability of Low-intensity
469 Psychological Interventions on the Well-being of Older Adults: A Systematic Review. *Clin
470 Gerontol*. 2019. doi:10.1080/07317115.2019.1662867
- 471 39. Blanken TF, Borsboom D, Penninx BW, Van Someren EJ. Network outcome analysis
472 identifies difficulty initiating sleep as a primary target for prevention of depression: a 6-year
473 prospective study. *Sleep*. 2019;(December):1-6. doi:10.1093/sleep/zsz288
- 474 40. Alexopoulos GS, Raue PJ, Banerjee S, et al. Comparing the streamlined psychotherapy
475 “Engage” with problem-solving therapy in late-life major depression. A randomized clinical
476 trial. *Mol Psychiatry*. 2020. doi:10.1038/s41380-020-0832-3
- 477 41. Alexopoulos GS, O’Neil R, Banerjee S, et al. “Engage” therapy Prediction of change of
478 late-life major depression. *J Affect Disord*. 2017;221(NA):192-197.

- 479 doi:10.1016/j.jad.2017.06.037
- 480 42. Solomonov N, Bress JN, Sirey JA, et al. Engagement in Socially and Interpersonally
481 Rewarding Activities as a Predictor of Outcome in “Engage” Behavioral Activation Therapy
482 for Late-Life Depression. *Am J Geriatr Psychiatry*. 2019. doi:10.1016/j.jagp.2018.12.033
- 483 43. Task Force on Community Preventive Services. Interventions To Reduce Depression
484 Among Older Adults: Home-Based Depression Care Management. Guide to Community
485 Preventive Services. [https://www.thecommunityguide.org/findings/mental-health-](https://www.thecommunityguide.org/findings/mental-health-interventions-reduce-depression-among-older-adults-home)
486 [interventions-reduce-depression-among-older-adults-home](https://www.thecommunityguide.org/findings/mental-health-interventions-reduce-depression-among-older-adults-home). Published 2007. Accessed
487 September 16, 2021.
- 488 44. Steinman L, Cristofalo M, Snowden M. Implementation of an Evidence-Based Depression
489 Care Management Program (PEARLS): Perspectives From Staff and Former Clients. *Prev*
490 *Chronic Dis*. 2012;9(4). /pmc/articles/PMC3406738/. Accessed September 16, 2021.
- 491 45. Casado B, Quijano L, Stanley M, Cully J, Steinberg E, Wilson N. Healthy IDEAS:
492 implementation of a depression program through community-based case management.
493 *Gerontologist*. 2008;48(6):828-838. doi:10.1093/GERONT/48.6.828
- 494 46. Substance Abuse and Mental Health Services Administration. Promoting Emotional Health
495 and Preventing Suicide: A Toolkit for Senior Centers.
496 [https://store.samhsa.gov/product/Promoting-Emotional-Health-and-Preventing-](https://store.samhsa.gov/product/Promoting-Emotional-Health-and-Preventing-Suicide/SMA15-4416)
497 [Suicide/SMA15-4416](https://store.samhsa.gov/product/Promoting-Emotional-Health-and-Preventing-Suicide/SMA15-4416). Published 2015.
- 498 47. Malkin G, Hayat T, Amichai-Hamburger Y, Ben-David BM, Regev T, Nakash O. How well
499 do older adults recognise mental illness? A literature review. *Psychogeriatrics*.
500 2019;19(5):491-504. doi:10.1111/psyg.12427
- 501 48. MacKenzie CS, Pagura J, Sareen J. Correlates of perceived need for and use of mental
502 health services by older adults in the collaborative psychiatric epidemiology surveys. *Am J*

- 503 *Geriatr Psychiatry*. 2010;18(12):1103-1115. doi:10.1097/JGP.0b013e3181dd1c06
- 504 49. Alexopoulos GS, Manning K, Kanellopoulos D, et al. Cognitive control, reward-related
505 decision making and outcomes of late-life depression treated with an antidepressant.
506 *Psychol Med*. 2015;45(14):3111-3120. doi:10.1017/S0033291715001075
- 507 50. Cattelani L, Chesani F, Palmerini L, Palumbo P, Chiari L, Bandinelli S. A rule-based
508 framework for risk assessment in the health domain. *Int J Approx Reason*. 2020;119:242-
509 259. doi:10.1016/j.ijar.2019.12.018
- 510
- 511 .

Table 1. Total sample characteristics

	Not depressed at baseline (N = 29,116)	Depressed and Non-Depressed at baseline (N= 39,439)
Age, mean (SD), y	67.0 (8.3)	67.9 (8.6)
Female sex, No. (%)	14,897 (51.2)	22,028 (55.9)
Education, median (IQR), y	12 (9 – 14)	12 (8 - 14)
Current job situation, No. (%)		
Retired	18,799 (64.4)	25,290 (64.1)
Employed or self-employed	6,890 (23.7)	8,463 (21.5)
Unemployed	620 (2.1)	921 (2.3)
Permanently sick or disabled	493 (1.7)	1 082 (2.7)
Homemaker	1,889 (6.5)	2,989 (7.6)
Other	272 (0.9)	405 (1.0)
Marital status, (%)		
Married and living together with spouse	7,111 (73.7)	9,001 (70.4)
Married, living separated from spouse	103 (1.1)	40 (0.4)
Never married	408 (4.2)	538 (4.2)
Divorced	736 (7.6)	1,017 (8.0)
Widowed	1,205 (12.5)	1,975 (15.4)
Poor physical performance/ disability (any), (%)	11,928 (41.0)	18,991 (49.1)
Functional limitations (any), No. (%)	3,588 (12.3)	7,175 (18.5)

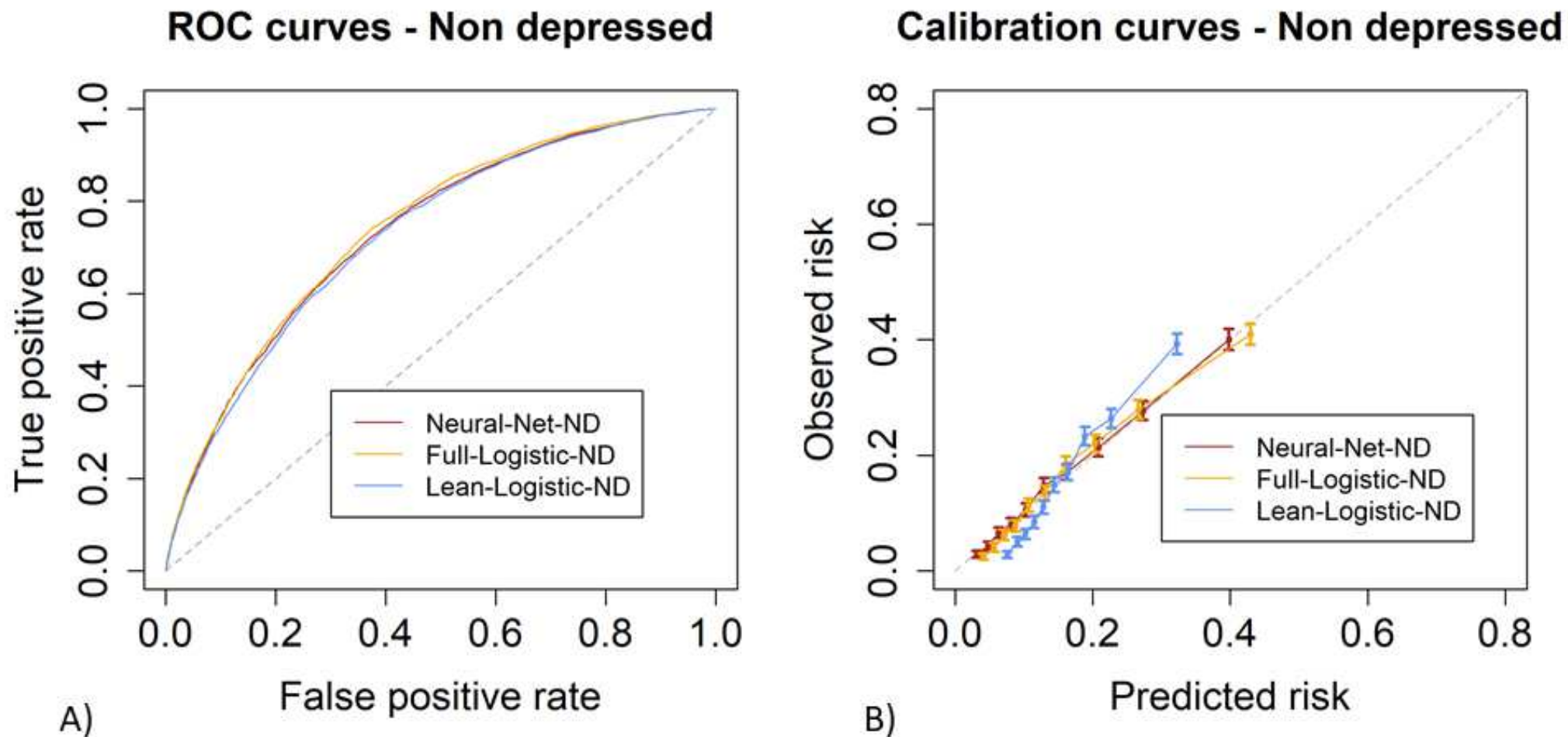
BMI 30 and above - obese, No. (%)	5,828 (20.0)	8,349 (21.5)
Use of drugs for anxiety or depression, No. (%)	934 (3.2)	2,356 (6.2)
Depression at baseline (EURO-D \geq 4), No. (%)	-	9,688 (24.6)
Depression at follow-up (EURO-D \geq 4), No. (%)	4,471 (15.4)	9,904 (25.8)
Depressive symptoms at baseline, %		
Depression	22.9	38.5
Pessimism	9.2	15.5
Suicidality	1.4	6.5
Guilt	3.2	7.9
Sleep	23.0	35.0
Interest	2.3	8.3
Irritability	16.6	27.9
Appetite	2.5	7.4
Fatigue	21.8	35.3
Concentration	7.9	15.6
Enjoyment	6.0	10.9
Tearfulness	11.7	22.7

Table 2. Performance of Risk Prediction Models

	Not depressed at baseline (N=29 591) ^a		
	ANN	Full-LR	Lean-LR
N. risk factors	124	58	34
AUC (95% CI)	0.737 (0.730-0.745)	0.743 (0.718-0.766)	0.730 (0.706-0.754)
MSE (95% CI)	0.117 (0.115-0.120)	0.118 (0.110-0.126)	0.121 (0.113-0.129)
Population below the selected risk threshold (20%)	73.6%	74.4%	78.8%
Sensitivity	53.3%	53.0%	44.6%
Specificity	78.4%	79.5%	83.0%
PPV	31.1%	32.1%	32.5%
NPV	90.3%	90.2%	89.1%
Accuracy	74.6%	75.4%	77.1%
	Total sample (N=39,439)		
	ANN	Full-LR	Lean-LR
N. risk factors	35	70	32
AUC (95% CI)	0.807 (0.799 - 0.815)	0.809 (0.794 - 0.824)	0.805 (0.790 - 0.821)
MSE (95% CI)	0.144 (0.140 - 0.147)	0.143 (0.137 - 0.149)	0.146 (0.139 - 0.152)
Population below the selected risk threshold (20%)	53.3%	53.2%	47.4%
Sensitivity	80.3%	80.2%	84.3%
Specificity	65.0%	64.7%	58.4%
PPV	44.3%	44.1%	41.3%
NPV	90.5%	90.4%	91.5%
Accuracy	69.0%	68.7%	65.1%

AUC, Area Under the Curve; MSE, Mean Square Error; PPV, Positive Predictive Value; NPV, Negative Predictive Value. Reported values of Sensitivity, Specificity, PPV and NPV are based on a risk threshold of 20%, which optimizes sensitivity ($\geq 80\%$). The full set of values at each risk threshold are reported in the supplement. a. Participants with EURO-D total score < 4.

Figure 1. Receiver operation curves and calibration curves



Red: Artificial Neural Network model (ANN); Yellow: full Logistic Regression model (full-LR); Blue: lean Logistic Regression model (lean-LR)

Table 3. Predictors retained in the risk prediction models (participants without baseline depression)

Predictor	ANN (n=124)	Full-LR (n=58)	Lean-LR (n=34)	Predictor	ANN (n=124)	Full-LR (n=58)	Lean-LR (n=34)
SOCIODEMOGRAPHIC				History of Parkinson's disease			
Age				History of hip or femoral fracture			
Sex				Recent diagnosis of cancer			
Ethnicity				Recent diagnosis of hip fracture			
Education				Use of glucocorticoids or steroids			
Marital status				Perceived Health			
LIVING CONDITIONS				BIOLOGICAL PARAMETERS			
Rural/Urban residence				History of hypercholesterolemia			
Household size				HEALTHCARE RELATED			
Relocation				Seeing a medical doctor			
Widowhood				Previous hospitalization			
Recent bereavement				Entering a nursing home			
SOCIAL CONTACTS				Unable to afford medical visit			
Help from outside household				Unable to see doctor due to waiting times			
Given help				Satisfaction with the health system			
Number of children				Use of drugs for hypercholesterolemia			
Number of grandchildren				Use of drugs for osteoporosis			
Presence of siblings				Use of drugs for stomach burns			
EMPLOYMENT/ ECONOMIC				Use of drugs for chronic bronchitis			
Current occupation status				Use of antihypertensives			
Financial stability				Use of drugs for coronary diseases			
Able to regularly buy groceries				Use of drugs for heart diseases			
ACTIVITIES				Use of drugs for diabetes			
Participation in voluntary or charity work				Use of drugs for joint pain			
Playing cards or games				Use of analgesics			
Educational or training course				Use of hypnotics			
Sport or a social or other kind of club				No use of Drugs			
activities in religious organizations				Use of Drugs for other conditions			
activities in political organizations				PHYSICAL CONDITION			
Reading books or newspapers				Visual function			
Playing word or number games				Reading ability			
No activities in last year ^a				Hearing function			

Computer skills				Dental problems			
MENTAL HEALTH				BMI			
Depression				Weight loss			
Concentration				Difficulties in walking 100m			
Enjoyment				Difficulties in picking up a small coin from table			
Tearfulness				Difficulties in sitting for two hours			
Pessimism				Difficulties in getting up from a chair			
Suicidality				Difficulties several flights of stairs			
Guilt				Difficulties one flight of stairs			
Sleep				Difficulties stooping, kneeling, crouching			
Interest				Difficulties extending arms above shoulder			
Irritability				Difficulties pulling or pushing large objects			
Appetite				Difficulties carrying weights over 5kg			
Fatigue				No difficulties ^b			
Age of onset of affective disorders				Difficulties dressing			
Use of drugs for anxiety or depression				Difficulties using the telephone			
COGNITIVE				Difficulties taking medications			
History of Alzheimer's disease or other dementia				Difficulties doing work in house			
PSYCHOLOGICAL DIMENSIONS				Difficulties in managing money			
Life's satisfaction/Quality of life				Difficulties walking across a room			
Loneliness				Difficulties bathing or showering			
Age prevents from doing things				Difficulties eating, cutting up food			
Out of control				Difficulties getting in or out of bed			
Feel left out of things				Difficulties using toilet			
Do the things you want to do				Difficulties using a map in a strange place			
Family responsibilities prevent from doing things				Difficulties preparing hot meal			
Shortage of money stops				Difficulties shopping for groceries			
Look forward to each day				No difficulties ^c			
Life has meaning				Experience of falls			
Look back on life with happiness				Fear of falling			
Feel full of energy				Dizziness, faints or blackouts			
Full of opportunities				PHYSICAL SYMPTOMS			
Future looks good				Presence of pain			
PHYSICAL ILLNESSES				Fatigue			

History of heart attack				HABITS / LIFESTYLE			
Recent diagnosis of heart attack				Smoking			
History of stroke				Vigorous physical activity			
Recent diagnosis of stroke or cerebral vascular disease				Moderate physical activity			
History of diabetes or hyperglycaemia				Alcohol consumption			
History of chronic lung disease				Physical inactivity			

a. from a list of 10 activities; b. from a list of 10 ADLs; c. from a list of 13 ALDs