

**AUTHORS' MANUSCRIPT ACCEPTED FOR PUBLICATION IN *ECHOCARDIOGRAPHY***

**2019**

**Left atrial diameter, left ventricle filling indices and association with all-cause mortality. Results from the population-based Tromsø Study**

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2 **Left atrial diameter, left ventricle filling indices and association with all-cause mortality. Results**  
3 **from the population-based Tromsø Study**

4 **Running head (Left atrial size, diastolic dysfunction and mortality)**

5 **Authors**

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22

23 **Abstract**

24 **Aims:** To examine the associations between diastolic dysfunction indices and long-term risk of all-  
25 cause mortality in adults over 23 year follow-up.

26 **Methods and results:** Participants (n=2734) of the population-based Tromsø Study of Norway had  
27 echocardiography in 1994-1995. Of these 67% were repeated in 2001 and/or 2007-2008. Mortality  
28 between 1994 and 2016 was determined by linkage to the national death registry. Cox regression was  
29 used to model the hazard of all-cause mortality in relation to left atrial parameters (treated as time-  
30 dependent using repeated measurements) adjusted for traditional risk factors and cardiovascular  
31 disease.

32 During the follow-up 1399 participants died. Indexed left atrial diameter, mitral peak E deceleration  
33 time and mitral peak E to peak A ratio showed an U-shaped association with all-cause mortality.

34 Combining left atrial diameter with mitral peak E deceleration time increased the prognostic accuracy  
35 for all-cause mortality whereas adding mitral peak E to peak A ratio did not increase prognostic value.

36 We estimated new optimal cut-off values of left atrial diameter, mitral peak E deceleration time and  
37 mitral peak E to peak A ratio for all-cause mortality outcome. E/e' had a cubic relation to mortality.

38 **Conclusion:** Both enlarged and small left atrial diameter were associated with increased all-cause  
39 mortality risk. A combination of Doppler-based left ventricle filling parameters had an incremental  
40 effect on all-cause mortality risk. The cut-off values of diastolic dysfunction indices we determined  
41 had similar all-cause mortality prediction ability as those recommended by American Association of  
42 Echocardiography and European Association of Cardiovascular Imaging.

43

44 **Key words:** Left atrial diameter, prognosis, all-cause mortality, diastolic dysfunction, epidemiology,  
45 echocardiography.

46

## 47 **Introduction**

48 Heart failure (HF) is associated with reduced quality of life and premature mortality (1). It is defined  
49 as a clinical syndrome associated with a wide range of left ventricular (LV) structural and functional  
50 abnormalities of different underlying aetiologies (2). Recent data suggest that the incidence of HF with  
51 reduced LV ejection fraction (HFrEF) and HF with mid-range LV ejection fraction (HFmrEF) is  
52 decreasing while incidence of HF with preserved LV ejection fraction (HFpEF) is increasing (1).

53 Detection of asymptomatic diastolic dysfunction is a strong risk factor for developing HFpEF (3). Left  
54 atrial (LA) diameter measured in M-mode and mitral flow measurements such as the ratio of the  
55 maximal E wave to the maximal A wave (E/A ratio) and the deceleration time of the E wave (DT) has  
56 been commonly used as indices of diastolic dysfunction. Enlarged LA diameter is a significant  
57 predictor of adverse cardiovascular events (4). Additionally, LA enlargement has been found to be an  
58 independent predictor of HF development, atrial fibrillation, coronary heart disease, stroke and all-  
59 cause mortality (5-8).

60 A short as well as long DT are associated with poor cardiovascular outcomes (9). E/A ratio is used for  
61 evaluating filling pressure and degree of diastolic dysfunction and also provides prognostic  
62 information (10).

63 The number of studies on the diagnostic impact of LA size and function through the last decades  
64 indicates its importance for cardiovascular health (11). However, there is a lack of data on associations  
65 between lower ranges of LA size and all-cause mortality rates. The American Society of  
66 Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) has put  
67 forward a series of LA diameter cut-offs that are defined purely in terms of percentiles of the  
68 distribution. Their ability to predict mortality has not so far been ascertained (12).

69 The recent ASE and EACVI guidelines define diastolic dysfunction in terms of a combination of  
70 statistically “normal” values of mitral flow indices derived from a small sample of healthy individuals  
71 and predictions of mortality by LA diameter from a surveys of the general population (13). These  
72 guidelines have not validated the combination of these indices as predictors of disease development or

73 mortality (10, 13). In the latest guidelines septal and lateral e' peaks, average E/e' ratio, LA volume  
74 index and peak tricuspid regurgitation velocity are recommended for use as indices for identification  
75 of diastolic dysfunction (10). However, no current population-based cohort has yet the power to  
76 examine the predictive value of these newest indices, but several including the Tromsø Study have the  
77 possibility to validate the older guidelines, but so far this has not been done. Redfield et al. validated a  
78 tissue Doppler, mitral and pulmonary vein flow derived definition of diastolic dysfunction against  
79 total mortality in a general population, but only tissue Doppler indices is still part of guideline defined  
80 diastolic dysfunction (14). The latest guideline have been validated against left ventricular end-  
81 diastolic pressure with a high negative predictive value 93% and area under the curve (AUC) of 0.78  
82 (15), but only the individual components of the 2009 and 2016 guidelines have been validated against  
83 mortality and morbidity (16).

84 Our aim was to study the long-term risk of all-cause mortality according to diastolic dysfunction  
85 measured as LA diameter and the mitral flow Doppler markers such as DT and E/A ratio using a  
86 population-based cohort. In addition, we tested the hypothesis that outcome derived cut-off values of  
87 diastolic dysfunction indices are more accurate for predicting fatal outcomes than normal cut-off  
88 values derived from a general population.

## 89 **Methods**

### 90 **Study population**

91 The Tromsø Study was initiated in 1974 as a prospective cohort study with the primary aim of  
92 assessing the role of modifiable risk factors for cardiovascular diseases. The study design has been  
93 described in detail previously (17). At present, seven consecutive surveys have been conducted. Both  
94 total birth cohorts and random samples from the general population of the Tromsø municipality were  
95 invited to participate, and many of the participants attended several surveys. Echocardiography was  
96 performed on a random selection of participants in the Tromsø 4 (1994-1995), Tromsø 5 (2001) and  
97 Tromsø 6 (2007-2008) surveys.

98 A total of 3272 participants of the Tromsø 4 survey underwent echocardiographic examination. Of  
99 these, 1946 and 1462 had another echocardiographic examination in the Tromsø 5 and/or Tromsø 6  
100 surveys, respectively (Fig. 1). The reason that some participants at Tromsø 4 did not have further  
101 echocardiography examinations at Tromsø 5 and Tromsø 6 are various. They include moving away  
102 from the Tromsø municipality (n=155, out of them n=21 died afterwards), emigration from Norway  
103 (n=18), non-attendance despite being invited (n=368) and death (n=457) between Tromsø 4 and  
104 Tromsø 6 survey dates.

105 For the purposes of this analysis we excluded those aged 50 years or younger (n=470), those with  
106 atrial fibrillation (n=39) during echocardiographic examination to prevent potential inaccuracy of DT  
107 measurements and those who had LVEF<50% (n=37) in the Tromsø 4 survey. Following these  
108 exclusions, 2734 participants were included in the analyses, each having had echocardiography at  
109 Tromsø 4 and possibly at later sweeps. The numbers included in analyses of specific endpoints were  
110 slightly smaller due to missing data on these parameters: 2616 participants for LA diameter analysis,  
111 2691 participants for DT analysis, and 2699 participants for E/A ratio analysis. We included 1875  
112 participants from the Tromsø 6 survey in additional analysis of the ratio of mitral peak velocity of  
113 early filling (E) to early diastolic mitral annular velocity (e') (E/e' ratio).

### 114 **Data collection**

115 Information on risk factors and comorbidities was obtained from self-administered questionnaires.  
116 Participants provided information on their date of birth, sex, current smoking (yes/no), leisure time  
117 physical activity and current use of antihypertensive treatment (yes/no), history of angina (yes/no),  
118 myocardial infarction (yes/no), stroke (yes/no) (17). Body mass index was defined as weight  
119 (kg)/height (m<sup>2</sup>). Blood pressure was measured using an automated device Dinamap Pro care 300  
120 Monitor (GE Medical Systems Information Technologies, Tampa, FL, USA). Three readings were  
121 made after 2 minutes' rest and separated by 1-minute intervals. The mean of the last two readings was  
122 used in the analysis. Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg, diastolic  
123 blood pressure  $\geq 90$  mm Hg or self-reported use of antihypertensive medication. Non-fasting serum  
124 levels of total cholesterol and glycated haemoglobin (HbA1c) were measured according to the  
125 previously described procedure (17, 18).

#### 126 **Echocardiography imaging**

127 The echocardiography in the Tromsø 4 survey was performed by two expert cardiologists using a  
128 Vingmed CFM 750 ultrasound scanner (Vingmed Sound A/S, Horten, Norway), and details have been  
129 described previously (7). In the Tromsø 5 and 6 surveys, Acuson Sequoia C258 or C512 scanner  
130 (Acuson, Mountain view, California, USA) were used (19). Coefficients of variation for intra- and  
131 interobserver variability in the Tromsø 4-6 surveys were less than 10% for chamber dimensions and  
132 Doppler-derived values (19, 20).

133 Echocardiographic assessment was performed with the use of standard imaging planes in the left  
134 lateral decubitus position according to ASE and EACVI recommendations (12). All of the  
135 echocardiographic measurements were performed online once per examination, but remeasured online  
136 if deviating from eye-balled estimates. M-mode echocardiography was used for LA diameter  
137 measurement. LA was measured from the posterior aortic wall to the posterior LA wall using both the  
138 parasternal long-axis and short axis view perpendicular to the aortic root long axis at the level of the  
139 aortic sinuses by using the leading-edge to leading-edge convention. LA diameter measurement was  
140 performed during end ventricular systole. Body surface area indexed LA diameter (LA BSA) as 1.5-  
141 2.3 cm/m<sup>2</sup> was considered as normal cut-off value range both for men and women. BSA was

142 calculated by the Du Bois formula ( $BSA = [\text{weight } \{\text{kg}\}^{0.425} \times \text{height } \{\text{cm}\}^{0.725}] \times 0.007184$ )  
143 (21).

144 Doppler examination was performed using the apical 4-chamber view with placing of the 2-mm  
145 Doppler sample volume between the mitral leaflet tips. For Doppler measurements the insonation  
146 angle was kept as perpendicular as possible toward the mitral inflow to obtain maximal velocity flow  
147 in early diastole. Spectral gain was adjusted until the flow curve became clear relatively to the  
148 background (22). Normal values of DT were considered as 140-220 ms. E/A ratio between 0.8-1.5  
149 characterize a normal filling pattern (10). Values of E/e' ratio used in analysis were within 4-25.

### 150 **Follow-up and outcome data**

151 Subjects included in the analysis contributed to risk from the date of attendance of the Tromsø 4  
152 survey until date of death, date of emigration from Norway or the end of follow-up on 31<sup>st</sup> December  
153 2016, whichever came first. Of the 2734 aged > 50 years who had echocardiography at the Tromsø 4  
154 survey, 1399 died during the follow-up period. Table I shows the numbers of participants and deaths  
155 according to which sweeps they were examined in. In the Cox model we treated the indices of  
156 diastolic dysfunction as time varying covariates. Those participants who had repeat echocardiography  
157 examinations in T5 or T6, were still free of atrial fibrillation, and had LVEF $\geq$ 50%, had their indices of  
158 diastolic dysfunction and values for other covariates updated. E/e' ratio was measured only in the  
159 Tromsø 6 survey, giving a follow-up of only 10 years for this parameter.

160 The all-cause mortality endpoint was identified by linkage of the participants to the National Causes of  
161 Death Registry at the Norwegian Institute of Public Health using personal identification number.  
162 Information on the participants who had emigrated from Tromsø was obtained through the Population  
163 Register of Norway.

### 164 **Statistical methods**

165 Means with standard deviations and proportions were used to describe baseline characteristics of the  
166 study participants according to the three categories of LA diameter (<1.5 cm/m<sup>2</sup>; 1.5-2.3 cm/m<sup>2</sup>; >2.3



167 cm/m<sup>2</sup>), DT (<140 ms; 140-220 ms; >220 ms), and E/A ratio (<0.8; 0.8-1.5; >1.5). Means (except for  
168 age) and proportions were adjusted for age using linear or logistic regression, respectively.

169 Associations of the three echocardiographic variables with all-cause mortality were assessed using  
170 time dependent Cox proportional hazards regression models with fractional polynomials of LA  
171 diameter, DT and E/A ratio as the main predictors. Baseline information for the participants can  
172 change during a follow-up period of 23 years. To take into account these changes we updated baseline  
173 information for those participants who also attended following surveys using time-dependent Cox  
174 regression. Models were tested for possible interactions between sex and LA diameter, DT, E/A ratio  
175 and E/e' ratio. We found no interaction between sex and LA diameter, sex and DT, sex and E/A ratio,  
176 or sex and E/e' ratio (p=0.489, p=0.696, p=0.199 and 0.730 respectively), and therefore results were  
177 presented for men and women combined. We chose the best-fitting fractional polynomials of LA  
178 diameter, DT, E/A ratio and E/e' ratio while adjusting for sex and fractional polynomials of age using  
179 the Akaike information criterion (23). Hazard ratios (HRs) were estimated for a range of LA diameter  
180 values from 1.1 to 4.0 cm/m<sup>2</sup>, using 1.8 cm/m<sup>2</sup> as the reference value, for a range of DT levels from 80  
181 to 300 ms with 155 ms as the reference value, for a range of E/A ratio levels from 0.3 to 4.0 with 1.1  
182 as the reference value and for a range of E/e' ratio from 4 to 25 with 4 as the reference value. HRs  
183 with 95% confidence intervals (CIs) were adjusted for sex and fractional polynomials of age because  
184 we expected non-linear associations between age and endpoint. In order to estimate the independent  
185 effect of left ventricular filling indices on all-cause mortality we adjusted the model for systolic blood  
186 pressure, total cholesterol, body mass index, smoking, antihypertensive treatment, history of stroke,  
187 angina and myocardial infarction. Likelihood ratio test between a model with and model without  
188 fractional polynomial terms of LA diameter, DT, E/A ratio or E/e' ratio were used to test the  
189 associations. The proportional hazard assumption was met in all models.

190 The best cut-off values for LA diameter, DT and E/A ratio were estimated using receiver operating  
191 characteristic (ROC) curves and AUCs. We used the maximum value of Youden's index as a criterion  
192 for selecting the optimal cut-off points for LA diameter, DT and E/A ratio (24). For the two latter with

193 an U-shaped relation to risk, ROC curves were estimated for the upper and lower part of values  
194 separately.

195 A two-sided  $p < 0.05$  was considered statistically significant. All statistical analyses were performed  
196 using SAS statistical package, version 9.4 (SAS Institute, Cary, NC).

197 **Ethical considerations**

198 The study conformed to the principles outlined in the Declaration of Helsinki, and the Tromsø Study  
199 protocol was approved by the Regional Committee for Medical and Health Research Ethics, North  
200 Norway (2009/2536/REK North). Informed consent was obtained from all individual participants  
201 included in the study.

## 202 **Results**

### 203 **Baseline characteristics**

204 The baseline clinical and echocardiographic characteristics of the study participants are presented  
205 according to the three ASE and EACVI categories of LA diameter (Table II), DT (Table III), and E/A  
206 ratio (Table IV).

### 207 **LA diameter, DT, E/A and E/e' ratio's and all-cause mortality**

208 We found that models with LA diameter, DT and E/A ratio adjusted for age and sex showed the very  
209 similar pattern of HRs compared to the fully adjusted models. We identified a U-shaped association  
210 between LA diameter and all-cause death (Fig. 2). When adjusted for sex and age, participants with  
211 LA diameter of 1.1 cm/m<sup>2</sup> had a higher risk of death compared with those with LA diameter of 1.8  
212 cm/m<sup>2</sup> (HR=4.35; 95% CI 1.84 to 10.30). For values above the reference significant increase in the  
213 risk of death was observed starting from 2.1 cm/m<sup>2</sup> (HR=1.09; 95% CI 1.01 to 1.18). In the fully  
214 adjusted model, risk of death was 4.60 and 5.72 times higher for those with LA diameter of 1.1 cm/m<sup>2</sup>  
215 and 4.0 cm/m<sup>2</sup>, respectively when compared to LA diameter of 1.8 cm/m<sup>2</sup>.

216 LA diameter of 1.8 cm/m<sup>2</sup> corresponded to the lowest HR in both age- and sex-adjusted and fully  
217 adjusted models (Fig. 2) and accordingly we estimated the optimal cut-off points based on ROC curve  
218 analysis above and below this value. The AUC for LA diameter values  $\leq 1.8$  cm/m<sup>2</sup> was 0.56  
219 ( $p=0.117$ ). The optimal lower cut-off value for LA diameter was estimated as 1.7 cm/m<sup>2</sup>. For those  
220 with LA diameter  $> 1.8$  cm/m<sup>2</sup> the AUC value was 0.60 ( $p<0.001$ ) with an optimal upper cut-off point  
221 for LA diameter of 2.3 cm/m<sup>2</sup> (Table V).

222

223 Association between mitral peak E DT and risk of all-cause death was U-shaped (Fig. 3). In the sex-  
224 and age-adjusted model, those with DT of 80 ms had approximately four times higher risk of death  
225 compared with the reference value of 155 ms (HR=4.65; 95% CI 2.37 to 9.12). Those with DT of 300  
226 ms had a 55% increased risk of death compared with the reference value. In the fully adjusted model,  
227 when compared to the reference DT of 155 ms, HRs for DT of 80 ms and DT of 300 ms were 5.37

228 (95% CI 2.64 to 10.94) and 1.44 (95% CI 1.23 to 1.68), respectively. DT less than the reference of 155  
229 ms was associated with increased risk of death starting from DT of 130 ms (HR=1.09; 95% CI 1.02 to  
230 1.17) (Fig. 3).

231 The DT value of 155 ms conferred the lowest risk and the population was accordingly divided at this  
232 value. For those with DT levels  $\leq 155$  ms (AUC=0.56,  $p=0.030$ ) an optimal cut-off point was 150 ms.  
233 AUC for those with DT  $>155$  ms was 0.60,  $p<0.001$ . Here a value of 200 ms was the best cut-off point  
234 with 67% sensitivity and 50% specificity (Table V).

235 Similarly to LA and DT, the association between mitral valve E/A ratio and risk of death was U-  
236 shaped. Sex- and age-adjusted HRs of death for E/A ratio of 0.3 and for E/A ratio of 4.0 compared  
237 with E/A ratio of 1.1 was 4.63 and 5.00, respectively. In the fully adjusted model HRs for E/A ratio of  
238 0.3 and of 4.0 in comparison with the reference value were 4.12 (95% CI 2.66 to 6.40) and 4.50 (95%  
239 CI 2.64 to 7.67), respectively (Fig. 4).

240 Results of the analysis of E/A ratio's and HR's showed that a value of 1.1 had the lowest HR and at  
241 this value the population was divided in two groups. Lower part of values with E/A ratio  $\leq 1.1$  had an  
242 AUC of 0.54,  $p<0.001$ . An optimal cut-off was considered as 0.6. Results of ROC curve analysis for  
243 those with E/A ratio  $> 1.1$  showed that AUC was 0.58,  $p<0.001$ . The best cut-off value for E/A ratio  
244  $>1.1$  equals 1.2 with levels of sensitivity of 67% and specificity of 46% (Table V).

245

246 Optimal cut-off values for all-cause mortality derived from time-dependent Cox regression models  
247 adjusted for age and sex were 1.4-2.1 cm/m<sup>2</sup> for LA diameter, 120-185 ms for DT and 0.8-1.4 for E/A  
248 ratio (Table V).

249

250 Comparison between ROC curves and AUC's of models with new outcome derived, maximal Youden  
251 index based reference values with different variables showed that the largest AUC of 0.63 was  
252 estimated when LA diameter cut-off was combined with similarly derived cut-offs for DT and E/A  
253 ratio. Combination of LA diameter with DT gave similar AUC. Other combinations of LA diameter

254 with left ventricular filling indices did not result in increase of AUC. HR derived cutoffs produced  
255 identical AUC's and were not presented.

256 ROC analysis using ASE and EACVI recommended cut-offs revealed the highest AUCs when LA  
257 diameter was combined with DT and with DT+E/A ratio. These combinations gave AUCs of 0.63.

258

259 We revealed a cubic association between E/e' ratio and all-cause mortality (Fig. 5). In the age- and  
260 sex-adjusted model those with E/e' of 25 had 3.48-fold increase of overall mortality risk in

261 comparison with reference value of 4. In the fully-adjusted model the risk of all-cause mortality in  
262 those with the extreme E/e' value compared with E/e' of 4 was 4.54 (95% CI 1.80 to 11.44).

263 The AUC for models with E/e' ratio, LA diameter, DT, or E/A ratio as predictor of all-cause mortality  
264 from 2007 and onwards were 0.59 (95% CI 0.54-0.63), 0.60 (95% CI 0.55-0.64), 0.62 (95% CI 0.58-  
265 0.66), 0.60 (95% CI 0.56-0.64) respectively. No significant difference was found between the models  
266 with echocardiographic determinants of diastolic dysfunction and all-cause mortality.

**267 Discussion****268 Results overview**

269 Our study reveals that echocardiographic markers of diastolic dysfunction such as LA diameter, DT  
270 and E/A ratio can be used for prediction of all-cause mortality risk. We were able to estimate HRs for  
271 all of the described parameters, assess new outcome derived cut-off points for them and describe the  
272 best combinations of echocardiographic markers for all-cause mortality outcome prediction. The  
273 association remained U-shaped after additional adjustment for systolic blood pressure, body mass  
274 index, total cholesterol, smoking, antihypertensive treatment, history of stroke, angina and myocardial  
275 infarction. It shows that LA diameter, DT and E/A ratio each have independent effects on all-cause  
276 mortality also after adjustment for sex, age and cardiovascular risk factors. We also used all-cause  
277 mortality risk estimation models for assessing optimal cut-offs of the left ventricular filling indices.  
278 These cut-offs were slightly different from those obtained with maximal Youden index but gave  
279 identical prediction ability for all-cause mortality outcome.

**280 Comparison with other studies****281 Left atrial diameter**

282 LA diameter has been shown to be an important prognostic parameter of mortality in several but not  
283 all studies conducted in general population samples (5, 25). Pritchett et al. reported that BSA-indexed  
284 LA volume was not associated with all-cause mortality when adjusted for age, gender, ejection  
285 fraction and diastolic dysfunction grade (26). Diversity in results may be explained by differences in  
286 the study populations, methods of LA diameter measurement and indexation.

287 In our study, the HRs for LA diameter above the reference of 1.8 cm/m<sup>2</sup> increased from 1.12 (1.01-  
288 1.23) to 5.72 (3.65-8.95) in the fully adjusted model corresponding to previous publications (25). The  
289 underlying mechanisms linking an enlarged LA diameter with increased all-cause mortality have been  
290 described previously (27). Elevated LA filling pressures, decreased flow velocities in LA appendages,  
291 atrial fibrillation as well as structural heart disease and hypertension are among those mechanisms  
292 which result in all-cause mortality risk increase.

293 A novel finding of our study is that LA diameter below  $1.5 \text{ cm/m}^2$  independently increases risk of all-  
294 cause death. This finding is supported by a few recent studies, however with several limitations.

295 Aviram et al. found that decreased LA volume was associated with increased mortality risk in patients  
296 with acute pulmonary embolism (28). Rozenbaum et al. also reported that patients with very small LA  
297 volume index  $<24 \text{ ml/m}^2$  had HR of 3.6 (95% CI: 1.46-8.87) for all-cause mortality (29). Limitations  
298 of these studies were small sample sizes and short follow-up periods. Acquisition of images in these  
299 studies were based on computed tomography. To our knowledge, there is no literature data on the  
300 association of small atrial diameters and all-cause mortality rates based on two-dimensional  
301 echocardiography.

302 One of the possible explanation of association between small LA size and mortality could be a  
303 decrease of LA emptying fraction, a functional parameter, which is independently associated with LA  
304 remodeling and mortality prediction (30).

305 According to our findings 11 individuals with LA diameter  $<1.5 \text{ cm/m}^2$  died during the follow-up.  
306 Cause of death of two individuals was not established. Only one person had myocardial infarction as  
307 cause of death indicating a maximal possible proportion of cardiovascular death to 30%. In patients  
308 with LA diameter  $>2.3 \text{ cm/m}^2$ , most of the mortality were due to myocardial infarction 191 (40.1%)  
309 and ischemic heart disease 78 (16.4%). Other causes of death in this group were; stroke 48 (10.1%),  
310 sudden death 10 (2.1%) and subarachnoid haemorrhage 1 (0.2%) indicating less than half the risk of  
311 CVD death for small atria compared to enlarged.

312 We defined lower and upper cut-offs with optimal sensitivity and specificity levels using the Youden  
313 index. Thus, lower reference cut-off value for LA diameter was  $1.7 \text{ cm/m}^2$  (ROC curve p-  
314 value=0.117) which is higher than the ASE and EACVI recommended value of  $1.5 \text{ cm/m}^2$ . According  
315 to our findings the value of  $1.5 \text{ cm/m}^2$  has a higher sensitivity level of 81% which corresponds to the  
316 higher negative predictive value. The upper cut-off point was  $2.3 \text{ cm/m}^2$  with a 46% sensitivity and  
317 71% specificity and had significantly higher risk than  $2.1 \text{ cm/m}^2$ , which conforms to recent  
318 recommendations (12).

**319 Mitral peak E deceleration time**

320 In our study the optimal cut-off level for lower DT reference value was defined as 150 ms which is  
321 higher than the current normality-based cut-off of 140 ms (10). It was a key parameter in Redfield  
322 definition (14) and has shown strong independent predictive ability in patient population with  
323 myocardial infarction (31). Our results demonstrate that risk of all-cause mortality increased gradually  
324 with decreasing DT starting from 130 ms when compared with the reference value of 155 ms in the  
325 fully adjusted model. Our findings can be explained by the inverse relation of DT to the left ventricle  
326 filling pressure and association of a short DT with restrictive filling pattern, which increases the risk of  
327 left ventricular dilatation.

328 We found an optimal upper cut-off value of 200 ms with 67% sensitivity and 50% specificity for  
329 identification of a fatal outcome. Prolonged DT is associated with low left ventricular filling pressures  
330 and impaired ventricular relaxation, which lead to progression of diastolic dysfunction and heart  
331 failure. Although the prognostic value of elevated DT has been documented before (32), this is the  
332 first estimation of the diagnostic accuracy of different DT values for prediction of all-cause mortality  
333 in a general population.

334 Unlike the U-shaped relationships between all-cause mortality and LA size or E/A ratio with a narrow  
335 normal range, DT effect is linked to extreme values at each end of a wide normal range in  
336 concordance with ASE and EACVI normality cut-offs. However, our approach of using outcome-  
337 derived values allowed narrowing the fraction of DT middle values and improves risk assessment non-  
338 significantly.

**339 E/A ratio**

340 Results from the second wave in the Strong Heart Study indicated that in middle-aged and elderly  
341 participants, an E/A ratio level above 1.5 was independently associated with a 2-fold increase in all-  
342 cause mortality risk (33). E/A levels below 0.6 were similarly associated with increased mortality risk.  
343 In our study the risk of all-cause mortality increased gradually for E/A values above 1.3. Risk of all-  
344 cause mortality increased also with decreasing E/A ratios starting from 0.8.



345 Analysis of the predictive ability of E/A ratio showed that optimal cut-offs differed from those  
346 recommended by ASE and EACVI. Thus, the lower optimal cut-off was found as 0.6 with a  
347 corresponding 17% sensitivity and 89% specificity. Upper cut-off value of 1.2 had a specificity level  
348 of 46% which is lower than ASE and EACVI guideline based E/A ratio value of 1.5 (specificity 59%)  
349 with all-cause mortality as outcome.

### 350 **E/e' ratio**

351 Our findings suggest that an elevated E/e' ratio is independently associated with increased risk of all-  
352 cause mortality in a general population. This is in contrast to Mogelvang et al. in the Copenhagen City  
353 Heart Study who found no association of E/e' with overall mortality (34). Kuznetsova et al. reported  
354 borderline association of E/e' ratio and risk of cardiac events (16). These studies had 90 and 59 cases  
355 respectively and half the follow up time of our study where 240 cases and 10 years follow up increases  
356 power in support of our finding. Interestingly E/e' did not have a superior predictive ability for overall  
357 mortality when compared with other diastolic dysfunction markers.

### 358 **Comparison of prognostic values of LA diameter, DT and E/A**

359 We aimed to explore the hypothesis that reference values based on outcome data would predict all-  
360 cause mortality better than those recommended by ASE and EACVI. The outcome-derived model,  
361 which combines LA diameter, DT and E/A ratio showed the best prediction on all-cause mortality, but  
362 not significantly different from the model with only LA diameter and DT included.

363 Using the cut-off values from current ASE and EACVI classification of diastolic dysfunction gave the  
364 same AUCs for LA diameter as Youden index based outcome derived cut-offs. For models with the  
365 three variables combined the largest AUC was detected in LA diameter+DT+E/A ratio model  
366 (AUC=0.63,  $p<0.001$ ) which was the same as in a model with ASE and EACVI cut-off values. When  
367 assessing the incremental value of each parameter both DT and E/A ratio added prognostic value to  
368 LA diameter, but E/A ratio did not add to the prognostic accuracy of LA diameter in combination with  
369 DT.

### 370 **Study strengths and limitations**

371 This was a large prospective population-based study with a long follow-up period. The prospective  
372 design of the Tromsø study and a random sample of a large age span from the general population with  
373 a high attendance rate increases generalizability to other Caucasian populations. Another strength was  
374 the updating of baseline values as the participants attended following surveys. Although biplane or 3D  
375 echocardiography are now regarded as the most accurate methods of LA volume estimation, M-mode  
376 anteroposterior LA diameter has higher intra- and interobserver reproducibility especially while  
377 assessing minimal atrial dimensions (35).

378 A main limitation of the study is that we used M-mode based linear measurements of LA which is less  
379 accurate than those based on LA volumes performed by biplane method. Unfortunately, LA  
380 echocardiographic data from the Tromsø 4-6 surveys contain only M-mode measurements. Our  
381 findings need validation using LA volumes which will be explored in future studies. The raw images  
382 from Tromsø 4-6 surveys are available as well as measurements of volumes from the latest Tromsø 7  
383 survey (2015-2016) which when enough endpoints have occurred, will give us the possibility to  
384 perform further analysis of LA volumes and diastolic dysfunction patterns according to the recent  
385 recommendations. Tricuspid regurgitation was not measured in the Tromsø 4-6 surveys. E/A ratio  
386 pseudonormal filling pattern was not considered in our study. However, individuals with severe left  
387 ventricular dysfunction were excluded from the study, and we suppose that influence of  
388 pseudonormalisation was relatively small. Information on smoking, current use of antihypertensive  
389 treatment, and history of angina, myocardial infarction and stroke was self-reported. It could  
390 potentially result in the presence of information bias. Models were not adjusted for laboratory markers  
391 such as N-terminal pro brain natriuretic peptide due to inconsistent presence of these parameters in all  
392 studied waves of the Tromsø Study. The maximal Youden index as classic data-driven approach for  
393 optimal cut-off estimation has its own disadvantages. The main is that Youden index is not sensitive  
394 for differences in the sensitivity and specificity of the test. To avoid the limitation we presented  
395 optimal cut-off points based on HR's along with cut-off values based on maximal Youdex index. The  
396 study only assesses the ability to predict mortality. As presence of diastolic dysfunction is associated  
397 with an increased risk of developing heart failure as well as death, estimation of cut-off values based

398 on a composite endpoint of death and heart failure could have yielded different results and potentially  
399 a higher predictive accuracy.

#### 400 **Conclusions**

401 Our study concludes that not only enlarged but also small LA diameter is associated with increased  
402 all-cause mortality risk. Using our new outcome derived cut-offs of LA diameter, DT and E/A ratio  
403 did not result in a better predictive ability for all-cause mortality in comparison with current ASE and  
404 EACVI recommended cut-off points. A combination of the Doppler based LV filling parameter DT  
405 with LA diameter is preferable while assessing risk of all-cause mortality, while E/A ratio did not add  
406 incremental value.

#### 407 **Acknowledgements**

408 This work was supported by UiT-The Arctic University of Norway, Tromsø; International Project on  
409 Cardiovascular Disease in Russia (IPCDR) and Heart to Heart collaboration project (H2H), London  
410 School of Hygiene and Tropical Medicine, London, UK. We acknowledge with gratitude the  
411 contribution of Simon Fougner Hartman's Family Foundation for providing support for purchasing the  
412 Vivid E9 ultrasound scanner.

#### 413 **Conflict of Interest**

414 The authors declare that they have no conflict of interest.

#### 415 **Author contributions**

416 Michael Stylidis – Conceptualization, Study design, Statistical analysis, Methodology, Writing –  
417 original draft preparation; Ekaterina Sharashova – Methodology, Study design, Statistical analysis,  
418 Investigation, Writing – review and editing; Tom Wilsgaard – Methodology, Study design, Statistical  
419 Analysis, Validation, Writing – review and editing; David A. Leon – Formal analysis, Methodology,  
420 Validation, Supervision, Project administration, Writing – review and editing; Geir Heggelund – Data  
421 curation, Methodology, Writing – review and editing; Assami Rösner - Formal analysis, Methodology,  
422 Validation, Writing – review and editing; Inger Njølstad – Methodology, Data curation, Validation,  
423 Writing – review and editing; Maja-Lisa Løchen - Methodology, Data curation, Validation,  
424 Investigation, Writing – review and editing; Henrik Schirmer – Conceptualization, Study design, Data

425 curation, Formal analysis, Methodology, Supervision, Project administration, Validation, Writing –  
426 review and editing.

427

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538

## Tables

**Table I** Numbers of participants and deaths included in analyses according to the sweeps of the Tromsø Study in which they had echocardiographic examinations

	Number of participants	Number of deaths
Tromsø 4 only	914	710
Tromsø 4 + Tromsø 5	694	459
Tromsø 5 + Tromsø 6	252	61
Tromsø 4 + Tromsø 5 + Tromsø 6	874	169
Total	2734	1399



**Table II** Baseline characteristics of study participants by left atrial diameter (n=2616); the Tromsø Study 1994-1995

Characteristics	Left atrial diameter, cm/m <sup>2</sup>			P value
	< 1.5 (n=24)	1.5 – 2.3 (n=1685)	> 2.3 (n=907)	
Death	11 (45.8)	780 (46.3)	524 (57.8)	<0.001
Sex (M-male, F-female)	M-12 (50.0)	M-895 (53.1)	M-392 (43.2)	<0.001
	F-12 (50.0)	F-790 (46.9)	F-515 (56.8)	
Age, years	62.3 (7.1)	62.2 (6.1)	64.7 (6.3)	<0.001
BMI, kg/m <sup>2</sup>	25.5 (3.4)	26.2 (3.9)	26.1 (4.0)	0.630
DBP, mm Hg	85.4 (9.6)	84.2 (12.1)	84.5 (13.1)	0.428
SBP, mm Hg	148.7 (21.0)	145.9 (21.4)	149.4 (23.0)	<0.001
Total cholesterol, mmol/L	6.40 (1.12)	6.84 (1.25)	6.81 (1.19)	0.215
HbA1c, %	5.27 (0.36)	5.49 (0.68)	5.49 (0.81)	0.199
History of stroke	1 (3.7)	34 (1.9)	30 (2.5)	0.486
History of angina	2 (7.7)	125 (7.1)	133 (11.8)	<0.001
History of myocardial infarction	0 (0.0)	91 (5.4)	79 (7.6)	0.076
Smoking	9 (36.7)	551 (31.9)	250 (28.6)	0.195
Physical activity				0.742
Low	3 (13.8)	196 (11.9)	122 (12.3)	

Moderate	5 (21.9)	645 (38.1)	336 (38.8)	
Active	13 (59.4)	749 (45.3)	394 (43.5)	
Highly active	1 (4.4)	73 (4.3)	42 (4.9)	
Antihypertensive treatment	4 (16.4)	173 (10.2)	200 (19.7)	<0.001
DT, ms	226.6 (64.5)	204.6 (43.2)	201.1 (46.7)	0.067
E/A ratio	0.85 (0.23)	0.96 (0.27)	1.02 (0.36)	0.086

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Values in the table are mean (standard deviation) or number (%). Means (except for age) and proportions were adjusted for age using linear or logistic regression, respectively

*BMI* body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *HbA1c* glycated haemoglobin, *DT* mitral peak E deceleration time, *E/A* mitral peak E to peak A ratio, *LA* left atrium

**Table III** Baseline characteristics of study participants by deceleration time (n=2691); the Tromsø Study 1994-1995

Characteristics	Deceleration time, ms			P value
	< 140 (n=71)	140 - 220 (n=1912)	> 220 (n=708)	
Death	39 (54.9)	863 (45.1)	464 (65.5)	<0.001
Sex (M-male, F-female)	M-27 (38.0)	M-902 (47.2)	M-404 (57.0)	<0.001
	W-44 (62.0)	W-1010 (52.8)	W-304 (43.0)	
Age, years	62.8 (6.6)	62.4 (6.1)	65.1 (6.2)	<0.001
BMI, kg/m <sup>2</sup>	26.7 (3.4)	26.1 (4.0)	26.3 (3.9)	0.307
DBP, mm Hg	86.2 (13.5)	83.7 (12.1)	86.0 (13.1)	<0.001
SBP, mm Hg	151.7 (23.0)	146.8 (21.7)	148.2 (22.9)	<0.001
Total cholesterol, mmol/L	7.00 (1.36)	6.88 (1.23)	6.68 (1.23)	0.006
HbA1c, %	5.52 (0.60)	5.48 (0.69)	5.52 (0.84)	0.073
History of stroke	2 (2.5)	41 (2.0)	26 (2.7)	0.441
History of angina	10 (12.5)	198 (9.6)	65 (6.7)	0.024
History of myocardial infarction	11 (14.8)	117 (6.0)	48 (5.6)	0.010
Smoking	17 (23.5)	588 (30.0)	243 (36.1)	0.006
Physical activity				0.225
Low	13 (18.0)	217 (11.5)	102 (13.3)	

Moderate	28 (39.3)	754 (39.5)	232 (34.7)	
Active	28 (39.5)	834 (44.2)	325 (46.7)	
Highly active	2 (2.8)	85 (4.4)	32 (4.8)	
Antihypertensive treatment	19 (26.5)	254 (13.0)	124 (14.6)	0.006
LA diameter, cm/m <sup>2</sup>	2.29 (0.30)	2.21 (0.32)	2.17 (0.33)	0.070
E/A ratio	1.16 (0.49)	1.01 (0.29)	0.87 (0.24)	<0.001

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Values in the table are mean (standard deviation) or number (%). Means (except for age) and proportions were adjusted for age using linear or logistic regression, respectively

*BMI* body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *HbA1c* glycated haemoglobin, *DT* mitral peak E deceleration time, *E/A* mitral peak E to peak A ratio, *LA* left atrium

**Table IV** Baseline characteristics of study participants by mitral peak E to peak A ratio (n=2699); the Tromsø Study 1994-1995

Characteristics	E/A ratio			P value
	< 0.8 (n=786)	0.8 – 1.5 (n=1800)	> 1.5 (n=113)	
Death	510 (64.9)	811 (45.1)	50 (44.3)	<0.001
Sex (M-male, F-female)	M-367 (46.7) W-419 (53.3)	M-899 (49.9) W-901 (50.1)	M-68 (60.2) W-45 (39.8)	0.021
Age, years	65.9 (6.0)	62.1 (6.0)	62 (6.3)	<0.001
BMI, kg/m <sup>2</sup>	26.8 (4.1)	25.9 (3.9)	24.9 (3.6)	<0.001
DBP, mm Hg	88.3 (13.3)	82.9 (11.8)	80.2 (11.5)	<0.001
SBP, mm Hg	152.3 (22.9)	145.4 (21.0)	143.1 (21.4)	<0.001
Total cholesterol, mmol/L	6.86 (1.25)	6.83 (1.23)	6.59 (1.13)	0.039
HbA1c, %	5.54 (0.87)	5.47 (0.67)	5.39 (0.50)	<0.001
History of stroke	31 (2.8)	35 (1.9)	3 (3.0)	0.209
History of angina	94 (8.4)	157(8.3)	19 (19.1)	0.002
History of myocardial infarction	63 (6.3)	94 (5.2)	18 (18.0)	<0.001
Smoking	238 (32.5)	581(31.3)	31 (25.1)	0.288
Physical activity				0.242
Low	122 (13.9)	208 (11.9)	7 (6.8)	

Moderate	280 (37.9)	687 (38.1)	46 (39.2)	
Active	348 (44.3)	790 (44.7)	53 (47.9)	
Highly active	24 (3.2)	89 (4.9)	6 (5.1)	
Blood pressure treatment	153 (15.9)	228 (12.7)	16 (15.8)	0.077
DT, ms	221.5 (52.1)	197.8 (38.6)	179.3 (35.5)	<0.001
LA diameter, cm/m <sup>2</sup>	2.16 (0.32)	2.21 (0.31)	2.36 (0.41)	<0.001

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Values in the table are mean (standard deviation) or number (%). Means (except for age) and proportions were adjusted for age using linear or logistic regression, respectively

*BMI* body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *HbA1c* glycated haemoglobin, *DT* mitral peak E deceleration time, *E/A* mitral peak E to peak A ratio, *LA* left atrium

**Table V** Optimal cut-off values of left ventricular filling indices associated with all-cause mortality outcome; the Tromsø Study

		Optimal cut-off values <sup>a</sup>	Sensitivity/ Specificity, %	Youden index	AUC* (95% CI)	ROC curve p-value	Optimal cut-off values <sup>b</sup>
LA diameter, cm/m <sup>2</sup>	Upper cut-off	2.3	46/71	0.17	0.60 (0.58-0.62)	<0.001	2.1
	Lower cut-off	1.7	71/46	0.16	0.56 (0.49-0.63)	0.117	1.4
DT, ms	Upper cut-off	200	67/50	0.17	0.60 (0.58-0.63)	<0.001	185
	Lower cut-off	150	98/18	0.16	0.56 (0.51-0.62)	0.030	120
E/A ratio	Upper cut-off	1.2	67/46	0.14	0.58 (0.53-0.63)	<0.001	1.4
	Lower cut-off	0.6	17/89	0.06	0.54 (0.52-0.57)	<0.001	0.8

<sup>a</sup>Optimal cut-off values for all-cause mortality outcome estimated according to the highest Youden index

<sup>b</sup>Optimal cut-off values for all-cause mortality outcome derived from time-dependent Cox regression models adjusted for age and sex

\*AUCs for ranges which include optimal (maximal Youden index based) upper and lower cut-off values. Ranges are estimated above and below the values with lowest HRs for LA diameter: 1.8 cm/m<sup>2</sup>; for DT: 155 ms; for E/A ratio: 1.1

*LA* left atrium, *DT* mitral peak E deceleration time, *E/A* mitral peak E to peak A ratio, *AUC* area under the curve, *ROC* receiver operating characteristic



## Figure legends

**Fig. 1** Flowchart of the participants with performed echocardiographic examination. The Tromsø Study

<sup>a</sup>Numbers in boxes represent numbers of subjects examined with echocardiography in each wave of the Tromsø Study

**Fig. 2** Left atrial (LA) diameter and all-cause mortality. The Tromsø Study

p-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of LA diameter

\*Adjusted for sex and fractional polynomials of age

\*\*Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, antihypertensive treatment

*HR* hazard ratio, *LCI* lower 95% confidence interval, *UCI* upper 95% confidence interval

**Fig. 3** Mitral peak E deceleration time (DT) and all-cause mortality. The Tromsø Study

p-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of DT

\*Adjusted for sex and fractional polynomials of age

\*\*Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, antihypertensive treatment

*HR* hazard ratio, *LCI* lower 95% confidence interval, *UCI* upper 95% confidence interval

**Fig. 4** Mitral peak E to peak A ratio and all-cause mortality. The Tromsø Study

p-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of E/A ratio

\*Adjusted for sex and fractional polynomials of age

\*\*Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, antihypertensive treatment

*HR* hazard ratio, *LCI* lower 95% confidence interval, *UCI* upper 95% confidence interval

**Fig. 5** Mitral peak E to peak e' ratio and all-cause mortality. The Tromsø Study

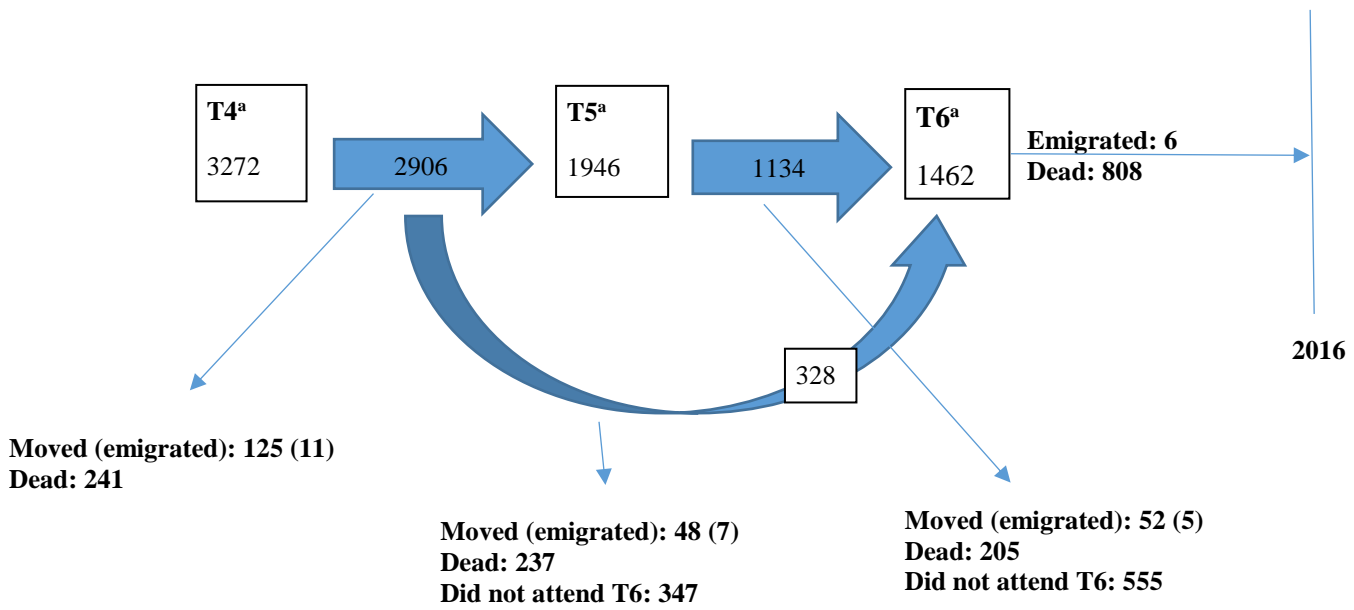
p-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of E/e' ratio

\*Adjusted for sex and fractional polynomials of age

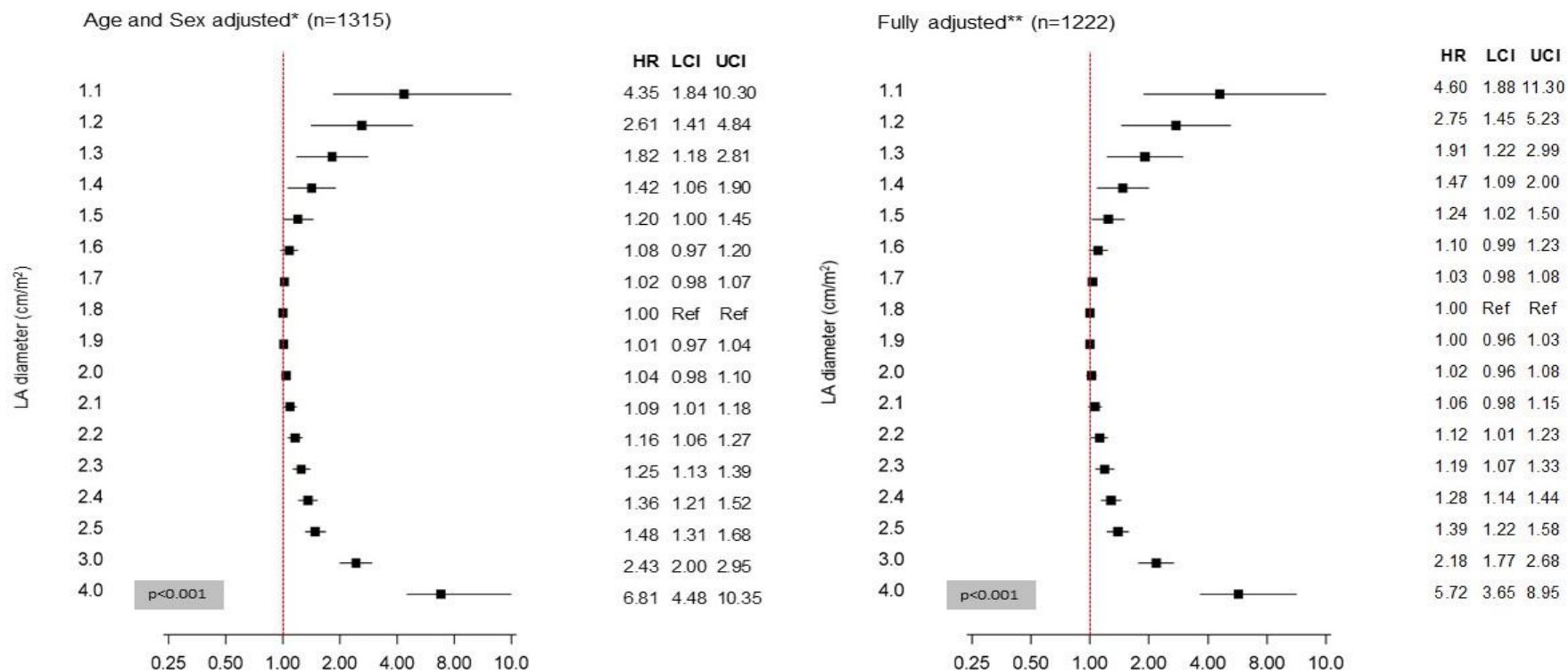
\*\*Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, antihypertensive treatment

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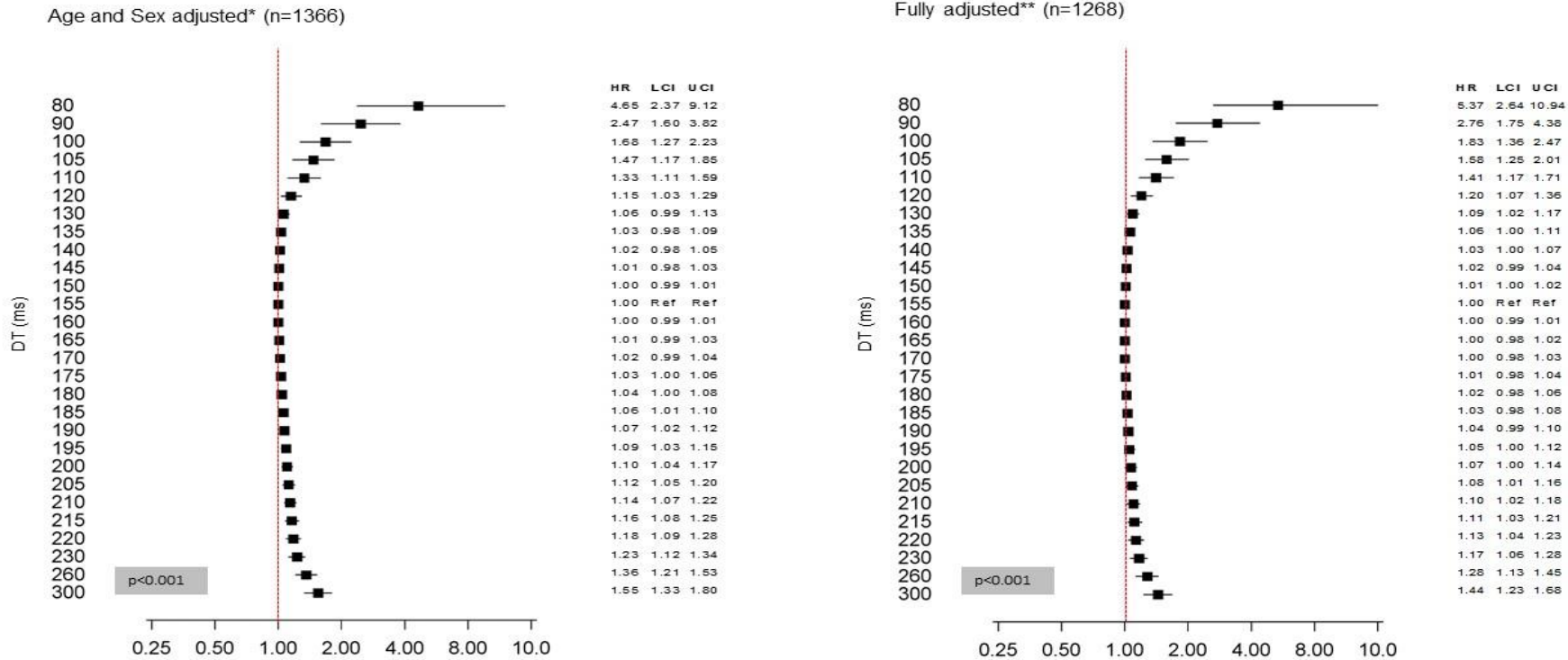
p-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of LA diameter

\*Adjusted for sex and fractional polynomials of age

\*\*Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, antihypertensive treatment

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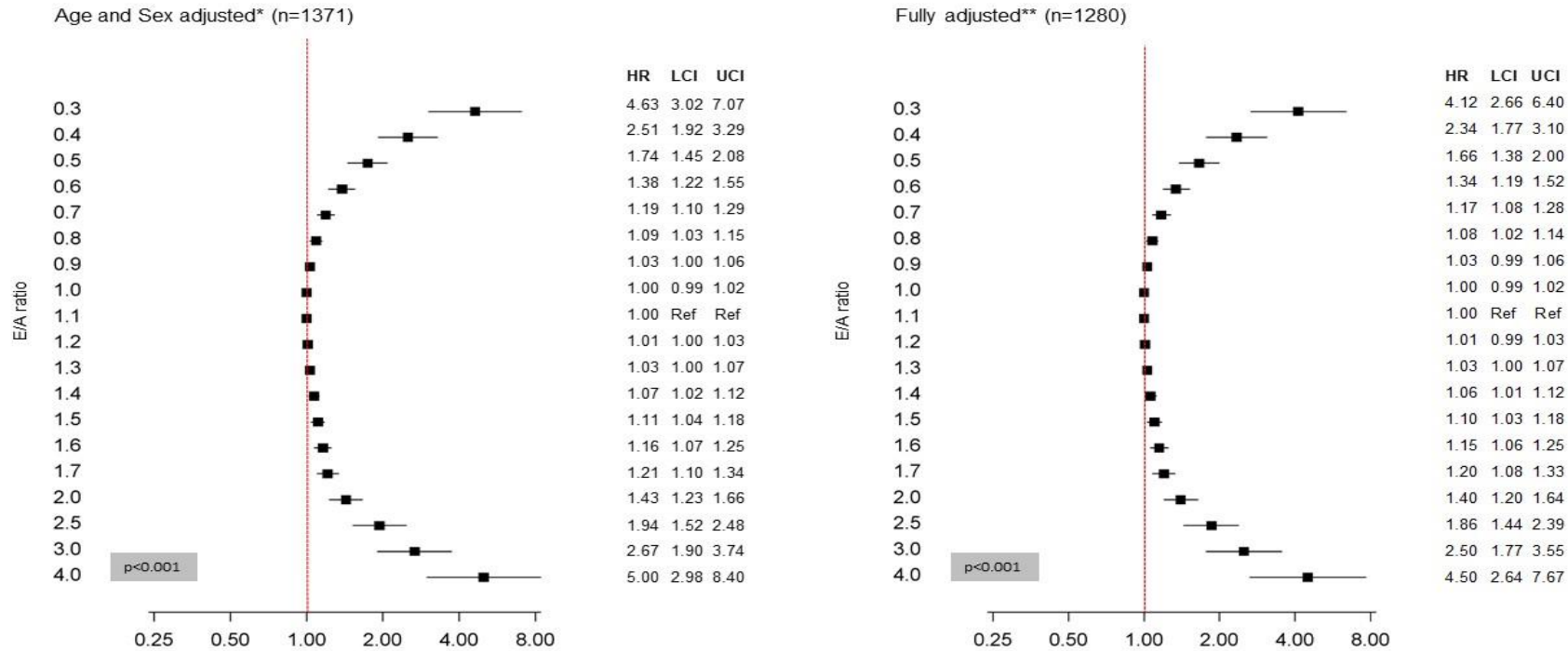
p-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of DT

\* Adjusted for sex and fractional polynomials of age

\*\* Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, antihypertensive treatment

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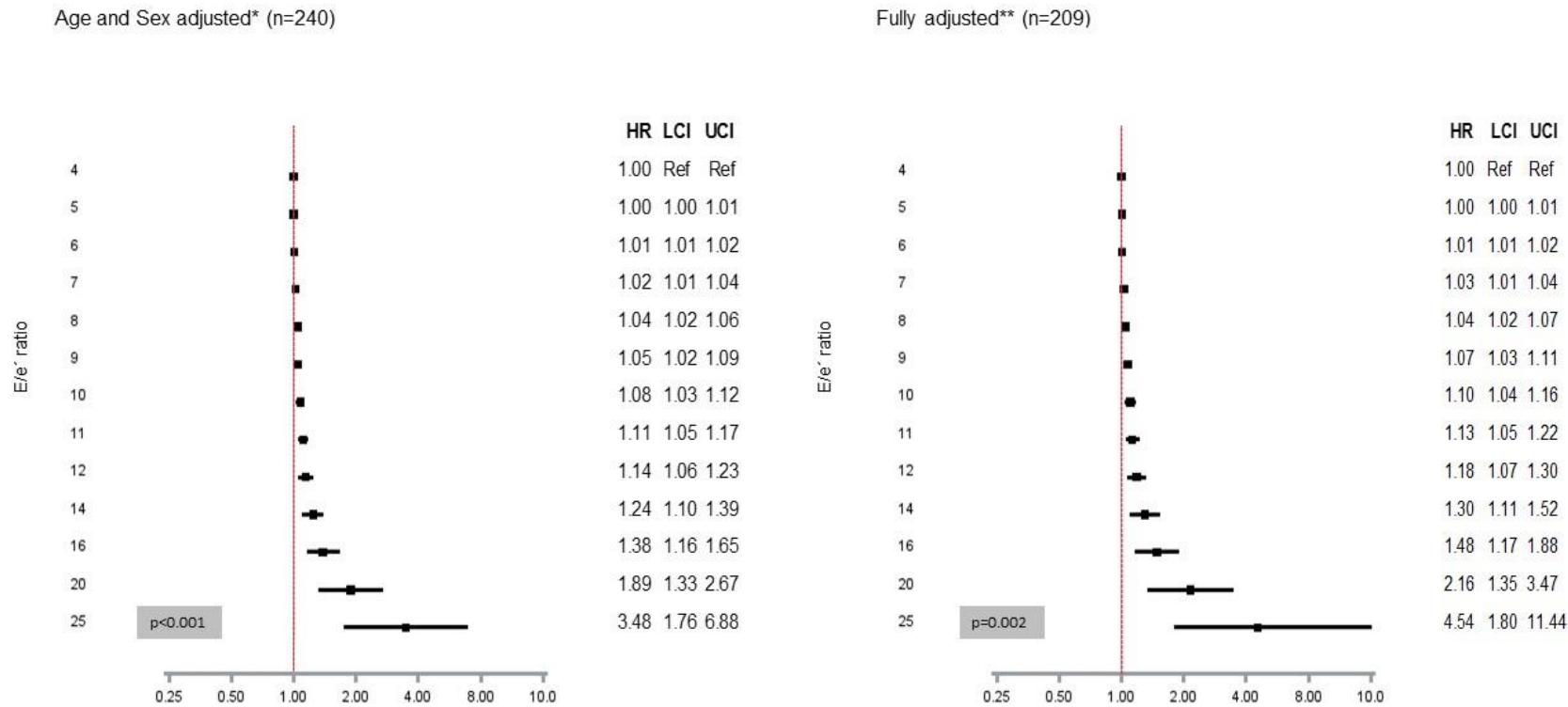
p-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of E/A ratio

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p-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of E/e' ratio

\*Adjusted for sex and fractional polynomials of age

\*\*Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, antihypertensive treatment

HR hazard ratio, LCI lower 95% confidence interval, UCI upper 95% confidence interval

