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Diastolic Function Assessed with Speckle Tracking Over a Decade and Its Prognostic Value: The Copenhagen City Heart Study.

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Abstract

Background:

The ratio of transmitral early filling velocity to early diastolic strain rate (E/e'sr) may be a more accurate measure of LV filling pressure then ratio of early filling pressure to early tissue velocity. The aim of the study was to investigate the impact of age, sex, obesity, smoking, hypertension, hypercholesterolemia, diabetes, physical activity level, socioeconomic and psychosocial status on E/e'sr over a decade. Additionally, the predictive value of **ΔE**/e'sr on future major adverse cardiovascular events (MACE) has never been explored.

Method:

The study included 623 participants from the general population, who participated in the 4th and 5th Copenhagen City Heart Study (CCHS4, CCHS5). Examinations were median 10 years apart. MACE was the composite endpoint of heart failure, myocardial infarction, and all-cause death.

Results:

Follow-up time was median 5.7 years and 43 (7%) experienced MACE. Mean age was 51±14 years and 43% were male. Mean ΔE/e'sr was 2.1±23.0cm. After multivariable adjustment for demographic, clinical and biochemistry variables, high age (stand. β-coef.=0.24, P<0.001)

and mean arterial blood pressure (MAP) (stand. β-coef.=0.17, P<0.001) were significantly associated with an accelerated increase in E/e'sr. In multivariable Cox regression, E/e'sr at CCHS5 and ΔE/e'sr were independent predictors of MACE (HR=1.20, 95%CI[1.01;1.42] per 10cm increase for both). ΔE/e'sr did only provide incremental prognostic value to change in left atrial volume index of the conventional diastolic measurements.

Conclusion:

In the general population age and MAP were predictors of an accelerated increase in E/e'sr over a decade. E/e'sr at CCHS5 and ΔE/e'sr were independent predictors of future MACE.

Keywords: Echocardiography, cardiovascular risk factors, major adverse cardiovascular events, diastolic function.

Introduction

The prevalence of cardiac risk factors is increasing worldwide[1]. Cardiac risk factors such as hypercholesterolemia, diabetes, hypertension, obesity, smoking, senescence, physical inactivity, low psychosocial and socioeconomic status are all conditions predisposing to cardiac dysfunction and cardiovascular disease[2–7].

Diastolic dysfunction is characterized by changes in left ventricular (LV) filling including impairment of myocardial relaxation[8]. Diastolic dysfunction is associated with a variety of adverse cardiac disorders and events such as acute myocardial infarction, heart failure, and cardiovascular death[9–11]. Early mitral inflow velocity (E) to peak longitudinal early diastolic velocity (e') – an echocardiographic measure of LV filling pressure has been used and recommended to assess diastolic function[12]. However, E to early diastolic strain rate (E/e'sr) have been demonstrated to correlate more closely to LV filling pressure[13] and be a more sensitive predictor of cardiovascular morbidity and mortality[14–17].

The LV changes in structure and function as we age due to an adaptive response to aging and exposure to cardiac risk factors[18]. The aging heart is associated with an increased prevalence of diastolic dysfunction and an elevated E/e'sr[15,19]. Additionally, diastolic dysfunction is associated with obesity, hypertension, diabetes, and smoking[15,20–22].

There have been no longitudinal studies investigating changes in E/e'sr and/or which cardiac risk factors that accelerate deterioration of diastolic function assessed by change in E/e'sr over time. Hence, the aim of the present study was to investigate the impact of cardiovascular risk factors on E/e'sr in the general population over a decade. Identifying risk factors that are

associated with accelerated changes in E/e'sr could help improve the understanding of the pathophysiology of the failing heart assessed by diastolic measures. In addition, the prognostic value of changes in E/e'sr over time is unknown.

Methods

Population

This study includes 623 members of the general population, who underwent two echocardiographic examinations including 2D-speckle tracking analysis a decade apart. The study is part of the Copenhagen City Heart Study using data obtained from the 4th and 5th round (CCHS4 and CCHS5). The Copenhagen City Heart Study is a prospective longitudinal cohort study on cardiovascular disease and risk factors. All participants included in the present study were part of both CCHS4 and CCHS5. CCHS4 spanned from 2001 to 2003 and CCHS5 from 2011 to 2015. Examinations were median 10.4 (IQR: 10.2;10.7) years apart. The population has been described in detail before[14].
Exclusion criteria were insufficient image quality for 2D-speckle tracking analysis, non-sinus rhythm in either study or prevalent heart failure at the time of CCHS4. A total of 543 participants were excluded due to these criteria. Participants with non-sinus rhythm (primarily atrial fibrillation) were excluded as evaluation of diastolic function including measuring E/e'sr during active atrial fibrillation and/or tachycardia can be inaccurate[23,24]. Exclusion process is illustrated in *Figure 1*.

The study was approved by a regional ethics committee, all participants gave written consent and the study was performed in accordance to the Helsinki Declaration.

Health Examination

At the time of CCHS4 all participants went through a thorough physical examination and answered a self-administered extensive questionnaire. Hypertension, diabetes, and presence of ischemic heart disease were defined as previously described[25]. Hypercholesterolemia was defined as total plasma cholesterol (TPC) ≥ 6.5 mmol/L and/or treatment with cholesterol-lowering medication. Psychosocial score was assessed by vital exhaustion score defined as previously described[26].

Outcome and endpoints

The primary outcome MACE was the combined endpoint of incident heart failure, acute myocardial infarction, and all-cause mortality after CCHS5. Information regarding endpoints was retrieved from The Danish National Board of Health's National Patient Registry and the

Danish Register of Causes of Death using International Classifications of Diseases codes. Follow-up was 100%.

Echocardiography

All participants underwent echocardiographic examinations including 2D-speckle tracking in CCHS4 and CCHS5. Vivid 5 ultrasound systems (GE Healthcare, Horten, Norway) were used in CCHS4, while Vivid 9 ultrasound systems were used in CCHS5. Echocardiograms were analyzed by a single experienced blinded investigator with commercially available post-processing software (EchoPac, GE Heathcare, Horten, Norway: version 8 and 113 respectively).

Conventional Echocardiography

In CCHS4 and CCHS5 LV chamber dimensions (interventricular septal thickness (IVSDd) LV internal diameter (LVIDd), and LV posterior wall thickness (LVPWd), were measured at end-diastole in the parasternal long axis view. LV mass index was calculated from Deveraux' formula. LVEF was assessed by 1 experienced observer based on wall motion score index[27] in CCHS4. In CCHS5, LVEF was measured with a semi-automated function measuring volume in end-diastole and end-systole with the bi-plane methods of discs in the apical 4-chamber and 2-chamber views. Great care was taken to avoid LV foreshortening. Left atrial volumes at end systole were measured by the biplane area-length method in the apical 4-chamber and 2 chamber views and left atrial volume index (LAVi) was calculated. E and A was measured with pulsed-wave Doppler imaging at the tips of the mitral valve leaflets in the apical 4-chamber view in CCHS4 and CCHS5. Color tissue Doppler imaging was used in the apical 4-chamber view to measure e' at the lateral and septal mitral annular segments, subsequently the mean was calculated and indexed to E to calculate E/e' in CCHS4 and CCHS5.

Two-Dimensional Speckle Tracking Echocardiography

The LV was analyzed with 2D-speckle tracking in the apical 2-chamber, 3-chamber, and 4-chamber views in CCHS4 and CCHS5. Mean frames per second were 57±4 in CCHS4 and 64±7 in CCHS5. The LV endocardial border was traced by a semi-automated function that defined a region of interest at end-systole. The investigator had the possibility to adjust the region of interest manually if the region of interest was inaccurate. In each view, the LV wall was divided into 6 segments. Segments could be excluded by the investigator, when image quality of a segment was too poor, if disturbed by intersecting image artifacts, or a segment was not visible throughout the heart cycle. Mean values of all LV segments were used to

calculate a global e'sr. E/e'sr was calculated by dividing E with e'sr. *Figure 2* illustrates how E/e'sr is measured. Images were deemed insufficient for 2D-speckle tracking analysis, when all myocardial walls were not visible, or no segments were trackable throughout the whole cardiac cycle. Our lab has previously demonstrated good reproducibility of E/e'sr with a intraobserver and interobserver variability with low bias[28].

Statistical Analysis

STATA statistics/data analysis, SE 15.0 (StataCorp, College Station, TX, USA) was used for all data work. P-value<0.05 defined statistical significance. Categorical values are expressed as frequencies (percentages) and compared using χ^2-test. Continuous Gaussian distributions are displayed as mean values ± standard deviation, students T-test was used to compare groups. Non-Gaussian continuous variables are expressed as median values along with interquartile range and compared with the Mann Whitney U test.

Pearson' correlation coefficient was calculated to assess the relationship between ΔE/e'sr and ΔE/e'. To determine the impact of the cardiovascular risk factors on ΔE/e'sr linear regression analysis was utilized. Continuous risk factor variables where chosen when available. Two adjustment models were constructed. A demographic model including variables age and sex. An extensive adjustment model, which included age, sex, BMI, smoking status, mean arterial blood pressure (MAP), total plasma cholesterol (TPC), HbA1c, eGFR, proBNP, heart rate, plasma triglyceride and history of previous ischemic heart disease. E/e'sr measured at CCHS4 were included in all linear regressions to adjust for baseline E/e'sr. Standardized β-coefficient (stand. β-coef.) are reported. A sensitivity analysis, which excluded participants suffering acute myocardial infarction or heart failure before CCHS5 was conducted.

To illustrate the relationship between ΔE/e'sr and significant continuous cardiac risk factors restricted cubic spline curves were constructed. The lowest value of Akaike information criterion was used to select the number of knots for each spline (*Figure 3*).

Participants suffering acute myocardial infarction and heart failure before CCHS5 (n = 21) were excluded from comparisons stratified by future MACE in *Table 1* and prognostic tests to avoid reverse causality. The prognostic value of E/e'sr at CCHS5 and ΔE/e'sr was assessed by using Cox proportional hazards regressions. E/e'sr were included in Cox regression models with ΔE/e'sr, to adjust for regression to the mean. The demographic adjustment model and the extensive multivariable adjustment model with the addition of LVEF at CCHS5 were employed for multivariable adjustment. Finally, incidence rates of MACE

according to E/e'sr at CCHS5 and ΔE/e'sr calculated with Poisson spline regressions were illustrated with restricted cubic spline curves (*Figure 4*). Harrell's C-statistics were compared to assess the incremental prognostic value of adding ΔE/e'sr to conventional diastolic function parameters (ΔE/e', ΔLAVi, and ΔE/A). Each parameter was adjusted with its baseline value.

Results

Baseline characteristics

Mean age of the study sample was 51±14 years at the time of CCHS4 and 43% were male. Prevalence of hypertension was 23%, 19% for hypercholesterolemia, and 7% for diabetes. Median E/e'sr at baseline was 60.7cm (IQR: 51.0;73.8) and at CCHS5 63.0 cm (IQR: 53.6;76.7). During the 10-year follow-up, average increase of E/e'sr was 2.1±23.0cm – a relative increase of 3.8%. A moderate correlation between ΔE/e'sr and ΔE/e' was observed (r=0.47, P<0.001). All baseline characteristics are displayed in *Table 1*. Participants included in the final study sample suffered less frequently from cardiovascular risk factors and were less likely to develop MACE compared to those with inadequate image quality for 2D-speckle tracking echocardiographic analysis (*Supplementary table).*

Relationship between cardiovascular risk factors and E/e'sr

In crude linear regression the following variables were all significantly associated with an increase in E/e'sr: Increasing age, length of education, physical activity level, pack-years, high BMI, high MAP, and elevated TPC. Figure 3 shows the unadjusted associations of risk factors with change in ΔE/e'sr. After multivariable adjustments age and MAP remained significantly associated with an accelerated increase of E/e'sr (Age: stand. β-coef.=0.24, P<0.001. MAP: stand. β-coef.=0.17, P<0.001) (*Table 2*). In sensitivity analysis, age and MAP both remained significant associated with an accelerated increase (Age: stand. β-coef.=0.23, P<0.001. MAP: stand. β-coef.=0.17, P<0.001). Crude and multivariable linear regression analysis for all investigated variables are displayed in *Table 2*.

The relationship between E/e'sr at CCHS5, ΔE/e'sr, and MACE.

Of the 602 participants included in prognostic analyses, 12 (2.0%) developed heart failure, 7 (1.2%) suffered acute myocardial infarction, and 27 (4.5%) died during the follow-up period after CCHS5. In total 43 (7.1%) experienced MACE. Median follow-up time was 5.7 (IQR: 4.7;6.1) years. Participants suffering MACE were generally older, had a shorter length of

education, had higher blood pressures, suffered more frequently from hypertension and hypercholesterolemia, and smoked more. They also had higher TPC, plasma triglycerides, plasma proBNP levels and reduced eGFR (*Table 1*). Additionally, participants developing MACE had reduced E/A and increased E/e' at both timepoints, in addition to elevated LAVi and ΔE/e' at CCHS5. There was no difference in baseline E/e'sr. However, E/e'sr at CCHS5 and ΔE/e'sr were significantly higher in participants with future MACE (E/e'sr at CCHS5: 80.0cm (IQR: 70.3;92.4) vs 61.4cm (IQR: 52.4;3.9), P<0.001. ΔE/e'sr: 12.5±29.8cm vs 1.5±22.4cm, P=0.003).

E/e'sr at CCHS5 and ΔE/e'sr demonstrated a significant association with future MACE in crude Cox proportional hazard regressions. The incidence rate of MACE according to E/e'sr at CCHS5 appeared to severely increase from 57 to 92 cm, meanwhile the incidence rate of ΔE/e'sr displayed a linear relationship (*Figure 4*). Following extensive multivariable adjustment E/e'sr at CCHS5 and ΔE/e'sr remained significant independent markers of MACE risk (E/e'sr: HR=1.20, 95%CI[1.01;1.42], P=0.036, per 10cm increase & ΔE/e'sr: HR=1.20, 95%CI[1.01;1.42], P=0.037, per 10cm increase) (*Table 3)*.

Changes in E/e'sr did provide incremental prognostic information when added on top of ΔLAVi (C-statistics: 0.57, 95%CI[0.49;0.66] vs 0.71, 95%CI[0.62;0.79], P=0.001). However, no incremental prognostic gain was observed when ΔE/e'sr was added to ΔE/e (C-statistics: 0.76, 95%CI[0.69;0.83] vs 0.76, 95%CI[0.69;0.83], P=0.66) or ΔE/A (C-statistics: 0.73, 95%CI[0.66;0.80] vs 0.76, 95%CI[0.69;0.83], P=0.001).

Discussion

In this longitudinal prospective study based on citizens from the general population who participated in both the 4th and 5th CCHS, we made several significant findings; (1) high age and MAP were the sole risk factors independently associated with an accelerated increase in E/e'sr over a decade, (2) both E/e'sr at CCHS5 and ΔE/e'sr demonstrated to be independent predictors of MACE in the present study, (3) change in E/e'sr only provided incremental prognostic value to ΔLAVi (and not ΔE/e or ΔE/A) regarding development of MACE.

The present study is the first to assess the temporal relationship between cardiovascular risk factors and E/e'sr. Furthermore, no other study has investigated the association between changes in E/e'sr and MACE.

E/e'sr is a novel marker that has been demonstrated to be strongly correlated to left ventricular filling pressure[13]. The prognostic value of E/e'sr has been examined in several populations. Lassen et al demonstrated E/e'sr to be a superior predictor of heart failure, cardiovascular death, and acute myocardial infarction in the general population[14]. Ersbøll et al, and Lassen et al investigated the predictive value of E/e'sr in patients undergoing coronary intervention[15,29]. Both studies found E/e'sr to be a significant predictor of their investigated composite outcome. E/e'sr has proven to be a superior predictor to conventional echocardiographic measurements in patients with aortic stenosis, heart failure and type 2 diabetes [16,17,30]. The results of the present study are in concordance with current literature. We found high E/e'sr at CCHS5 and an increase in E/e'sr to be significant predictors of future MACE (*Table 3*). We found the HR and 95%CI of E/e'sr at CCHS5 and ΔE/e'sr to be equal after multivariable adjustments. This implies that inclusion of previous measurements of E/e'sr does not provide incremental prognostic information when risk stratifying at least when the previous marker was measured 10 years before. This holds true even though we exclude participants with events prior to CCHS5, which reduces the likelihood of reverse causality as ΔE/e'sr could already be somewhat affected. Finally, unlike the studies by Ersbøll et al[15] and Lassen et al[14] we only found E/e'sr to provide incremental prognostic value to change in LAVi (and not to ΔE/e' or ΔE/A). Thus, we must conclude that in the present population changes in E/e'sr does not provide added value to conventional diastolic parameters.

In the present study, we also investigated the impact of cardiovascular risk factors on E/e'sr. We found high age and MAP to be significantly associated with an accelerated increase in E/e'sr. The published literature on the relationship between age and E/e'sr is inconclusive. In studies by Hsu et al[31], Dahl et al[16], and Ersbøll et al[15] investigating the prognostic value of E/e'sr in patients with atrial fibrillation, aortic stenosis, and acute myocardial infarction respectively, the authors assessed the differences between groups with high E/e'sr and normal E/e'sr. Hsu et al (n = 190) and Dahl et al (n = 121) found no significant differences in age between tertiles or medians of E/e'sr respectively. Meanwhile, Ersbøll et al (n = 1048) found significant higher age in increasing quartiles of E/e'sr. There are several differences between the mentioned studies and ours. Most importantly, we investigated a sample of the general population, while the described studies investigate different patient cohorts with a generally older sample with more comorbidities.

Elevated E/e'sr has been established as a marker of LV diastolic dysfunction[12] and several studies have investigated the association between age and LV diastolic dysfunction. In 2011 Kane et al investigated predictors of diastolic dysfunction in the general population in a

prospective longitudinal study based on two exams 4 years apart[32]. Kane et al assessed diastolic dysfunction through Doppler echocardiography. The authors found age to be a significant predictor of diastolic dysfunction assessed 4 years later even after multivariable adjustment. The results are similar to our findings as we found increasing age to be an independent predictor of an accelerated increase in E/e'sr after multivariable adjustments.

Hsu et al[31], Dahl et al[16] and Ersbøll et al[15] also examined the differences in systolic and diastolic blood pressure and prevalence of hypertension between medians or tertiles of E/e'sr. Hsu et al and Dahl et al did not find any significant differences. Ersbøll et al found an increasing prevalence of hypertension as E/e'sr increased. However, Ersbøll et al did not find any differences in systolic or diastolic blood pressure. Though, it must be stressed that these studies report cross-sectional associations and not temporal relationships. In the prospective longitudinal study by Kane et al, they also investigated the predictive value of hypertension in the development of diastolic dysfunction in the general population[32]. The authors found hypertension to be a significant predictor of diastolic dysfunction in multivariable logistic regression. These findings are in concordance with the present results as we found high MAP to be an independent predictor of an accelerated increase in E/e'sr.

Strengths and limitation

A noteworthy strength of the present prospective longitudinal study is the community-based composition of a homogenous population of male and female across all adult ages. There are also several limitations to the study. The study sample is primarily Caucasian, which limits the generalizability of our results to other ethnicities and races. We also had a change in ultrasound instruments between the two echocardiograms of CCHS4 (Vivid 5, GE Healthcare) and CCHS5 (Vivid 9, GE Healthcare) as well as different echocardiographic software versions (Echopac version 8 vs 113). This can raise some questions of comparability. However, this issue would likely affect all investigated cardiovascular risk factors similarly. Consequently, different equipment and software are unlikely to change the results of the present study.

A significant portion of the initial study sample was excluded due to inadequate image quality for echocardiographic analysis particularly at CCHS4. This results in a degree of selection bias, as these participants suffered more frequently from cardiovascular risk factors and developed MACE at a higher frequency. Finally, there may also be a minor amount of healthy retention bias. Additionally, some participants of CCHS4 likely died before agreeing to participate in CCHS5 and others might have developed serious health conditions and

consequently declined to participate. However, the fact that we found a signal despite of these presences only underscore the strength of our results.

Conclusion

In a sample of the general population of Denmark, high age and MAP significantly accelerate the deterioration of E/e'sr over a decade. Additionally, E/e'sr measured at CCHS5 and an increase in E/e'sr are both independent predictors of future MACE.

Conflict of Interest

TBS reports receiving research grants from Sanofi Pasteur, and GE Healthcare, is a Steering Committee member of the Amgen financed GALACTIC-HF trial, on advisory boards for Sanofi Pasteur and Amgen, and speaker honorariums from Novartis and Sanofi Pasteur. The remaining authors have nothing to disclose.

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Data availability statement

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

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Figure legends

Figure 1: Title: Flow chart illustrating exclusion process

Caption: A flow chart displaying the flow of participants CCHS4 to finale sample included in the present study

Abbreviation: CCHS4 = 4th Copenhagen City Heart Study. CCHS5 = 5th Copenhagen City Heart Study. E/e'sr = ratio of transmitral early filling pressure to early diastolic strain rate.

Figure 2: Title: Example of analysis of E/e'sr.

Caption: Pictures of echocardiographic analysis of E and e'sr. E is measured with pulsed-wave Doppler imaging at the tips of the mitral valve leaflets in the apical 4-chamber view (upper image). e'sr is measured with 2D-speckle tracking echocardiography in the apical 4-chamber view in this example (lower image).

Abbreviations: E = transmitral early filling velocity, e'sr = early diastolic strain rate.

Figure 3: Title: Relationship between cardiac risk factors and ΔE/e'sr .

Caption: Restricted cubic spline curves displaying the relationship between ΔE/e'sr and age, BMI, MAP, and TPC P-value for significance of the investigated cardiac risk factor and 95% confidence intervals.

Abbreviations: E/e'sr = ratio of transmitral early filling velocity to early diastolic strain rate. BMI = body mass index. MAP = Mean arterial blood pressure. TPC = Total plasma cholesterol concentration.

Figure 4: Title: Relationship between E/e'sr, ΔE/e'sr and MACE.

Caption: Restricted cubic spline curves displaying the incidence rate of MACE per 1,000 person according to E/e'sr at CCHS5, and ΔE/e'sr with 95% confidence intervals. ΔE/e'sr adjusted for baseline E/e'sr.

Abbreviation: MACE = Major adverse cardiovascular event. E/e'sr = ratio of transmitral early filling pressure to early diastolic strain rate.

Table 1. Baseline characteristics.

	Whole study sample (n = 623)	Event-free sample (n = 559)	MACE after CCHS5 (n = 43)	P-value
Demographics at CCHS4				
Age, years	50.8±13.5	49.6±13.2	62.6 ± 11.1	< 0.001
Male sex, n (%)	269 (43.2)	234 (41.9)	18 (41.9)	1.0
Education length, years	12 [10;12]	12 [10;12]	10 [7;10]	< 0.001
Clinical data at CCHS4				
Vital exhaustion score	3 [1;5]	3 [1;5]	2 [1;4]	0.16
BMI, kg/m^2	24.5±3.2	24.4±3.2	25.0±3.5	0.21
Heart rate, beats per minute	64.3±10.1	64.1±10.1	64.9±11.0	0.62
Mean arterial blood pressure, mmHg	92.7±12.6	91.9±12.1	99.0±12.5	< 0.001
Systolic blood pressure, mmHg	126.5±19.5	125.0±18.7	138.1±21.2	< 0.001
Diastolic blood pressure, mmHg	75.9±10.9	75.4±10.6	79.4±10.0	0.016
Hypertension, n (%)	142 (22.9)	114 (20.5)	15 (34.9)	0.027
Hypercholesterolemia, n (%)	105 (18.8)	84 (16.9)	15 (35.7)	0.002
Diabetes, n (%)	44 (7.1)	39 (7.0)	2 (4.7)	0.56
Previous ischemic heart disease, n (%)	15 (2.4)	8 (1.4)	2 (4.7)	0.11
Smoking status at CCHS4				
Never, n (%)	234 (37.8)	215 (39.2)	12 (27.9)	0.083
Previous, n (%)	210 (33.9)	191 (34.8)	12 (27.9.3)	

Current, n (%)	175 (28.3)	143 (26.0)	19 (44.2)	
Pack years, 12.5 g tobacco/day x years smoked	1.5 [0;15]	1.15 [0;13.3]	15.0 [0;33.8]	< 0.001
Physical activity level at CCHS4				
Inactive, n (%)	35 (5.7)	30 (5.4)	3 (7.1)	0.18
Low, n (%)	262 (42.3)	229 (41.2)	22 (52.4)	
Moderate, n (%)	278 (44.9)	254 (45.7)	17 (40.5)	
High, n (%)	44 (7.1)	43 (7.7)	0 (0.0)	
Blood work at CCHS4				
Hemoglobin A1c, mmol/mol	39.6±7.3	39.5±7.4	39.6±6.7	0.93
Total plasma cholesterol, mmol/L	5.3 [4.6;6.1]	5.2 [4.6;6.1]	5.7 [4.8;7.0]	0.021
Plasma triglyceride mmol/L	1.2 [0.9;1.7]	1.2 [0.8;1.7]	1.5 [1.1;1.8]	0.031
eGFR, mL/min/1.73 m^2	91.0 [74.7;108.2]	93.0 [76.0;108.2]	80.5 [61.4;100.2]	0.005
Plasma proBNP, pmol/L	17.1±18.4	16.2±15.0	24.8±27.9	< 0.001
Echocardiography				
IVSDd, cm	0.9±0.2	0.9±0.2	1.0±0.2	0.002
LVIDd, cm	4.9±0.5	4.9±0.5	4.7±0.6	0.079
LVPWd, cm	0.9±0.2	0.9±0.1	0.9±0.2	0.37
LV mass index, g/m^2	78.7 [69.0;91.9]	78.2 [68.7;91.4]	82.6 [69.0;94.1]	0.64
LV mass index at CCHS5, g/m^2	80.7 [69.7;95.0]	79.8 [69.6;93.6]	81 [67.1;100.5]	0.50

LVEF, %	59.8±1.7	59.9±0.8	59.4±2.2	0.003
LVEF at CCHS5, %	56.6±5.7	56.9±5.6	55.4±5.7	0.089
E/A	1.2 [0.9;1.5]	1.2 [1.0;1.5]	0.9 [0.7;1.2]	< 0.001
E/A at CCHS5	1.1 [0.8;1.4]	1.1 [0.9;1.4]	0.9 [0.7;1.0]	< 0.001
LAVi, ml/m^2	18.8±5.3	18.8±5.3	19.3±4.9	0.58
LAVi at CCHS5, ml/m^2	27.1±8.1	26.9±8.0	30.0±8.7	0.014
E/e'	8.8 [7.5;10.7]	8.6 [7.4; 10.5]	10.4 [8.7;13.1]	< 0.001
E/e' at CCHS5	10.1 [8.2;12.8]	10.0 [8.1; 12.2]	14.3 [10.9;18.7]	< 0.001
ΔE/e'	1.6±3.1	1.4±2.9	3.9±4.6	< 0.001
E/e'sr, cm	60.7 [50.5;73.8]	60.0 [50.3;70.9]	64.2 [50.2;85.2]	0.18
E/e'sr at CCHS5, cm	63.0 [53.6;76.7]	61.1 [52.4;73.9]	80.0 [70.3;92.4]	< 0.001
ΔE/e'sr, cm	2.1±23.0	1.5±22.4	12.5±29.8	0.003

Table 2. Linear regression analysis investigating the relationship between cardiac risk factors and changes in E/e'sr.

	Crude regression		Adjustment for demographics		Multivariable adjustment model	
	Standardized β-coefficient	**P-value**	**Standardized β-coefficient**	**P-value**	**Standardized β-coefficient**	**P-value**
Age	0.34	<0.001	0.34	<0.001	0.24	<0.001
Male sex	0.03	0.27	0.07	0.011	0.01	0.74
Years of education	-0.19	<0.001	-0.03	0.28	-0.04	0.27
Vital Exhaustion	-0.04	0.17	0.01	0.80	0.00	1.0
Physical activity level	-0.07	0.034	-0.03	0.30	-0.05	0.12
BMI	0.16	<0.001	0.08	0.009	0.05	0.19
Pack years	0.12	<0.001	0.04	0.14	0.04	0.15
MAP	0.27	<0.001	0.15	<0.001	0.17	<0.001
TPC	0.17	<0.001	0.03	0.35	0.04	0.22
HbA1c	0.04	0.24	0.01	0.61	-0.01	0.80

Demographic adjustments include age and sex.

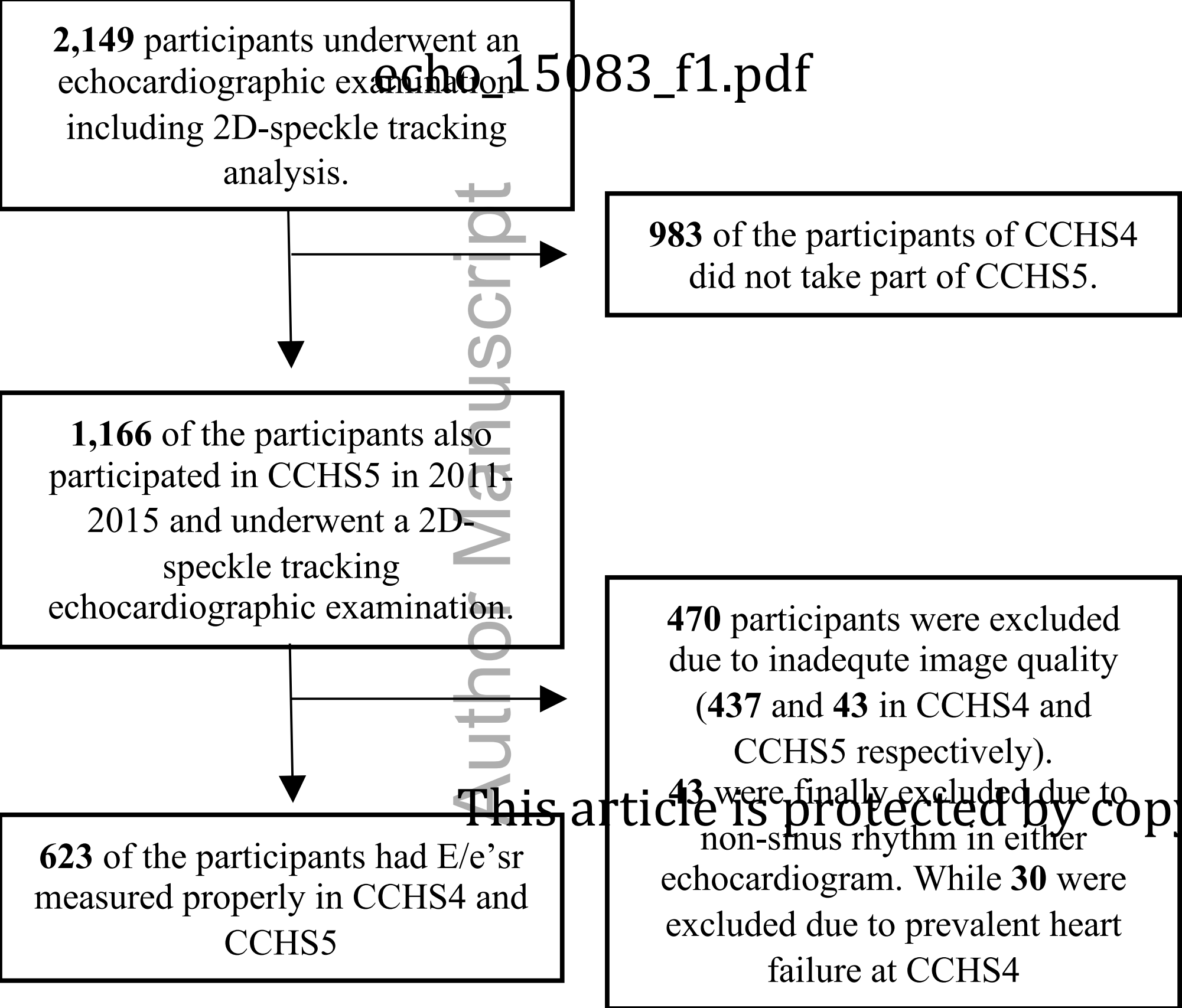
Multivariable adjustment includes sex, age, BMI, smoking status, systolic blood pressure, diastolic blood pressure, total plasma cholesterol, HbA1**c,** eGFR, proBNP, heart rate, plasma triglyceride and previous ischemic heart disease.

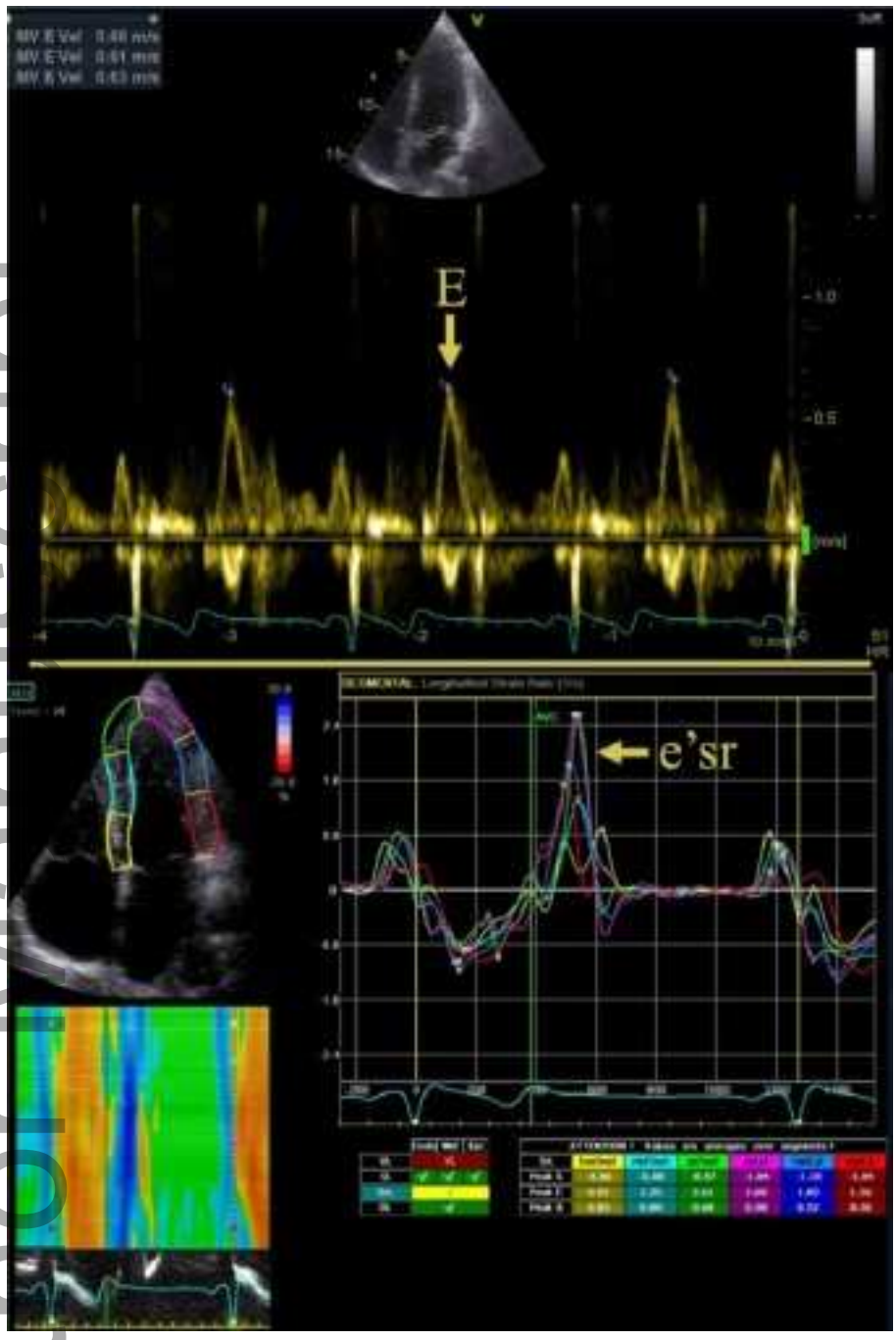
Table 3. Crude and multivariable Cox proportional hazard models investigating the prognostic value of E/e'sr and changes in E/e'sr.

	Crude regression			Adjustment for demographics			Multivariable adjustments*		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
E/e'sr at CCHS5, per 10 cm increase	1.45	1.27-1.64	<0.001	1.23	1.06-1.41	0.005	1.20	1.01-1.42	0.036
ΔE/e'sr, per 10 cm increase	1.43	1.26-1.64	<0.001	1.22	1.02-1.48	0.006	1.20	1.01-1.42	0.037

Demographic adjustments include age and sex.

Multivariable adjustments include sex, age, BMI, smoking status, systolic blood pressure, diastolic blood pressure, total plasma cholesterol, HbA1**c,** eGFR, proBNP, heart rate, plasma triglyceride, previous ischemic heart disease and LVEF* at CCHS5.





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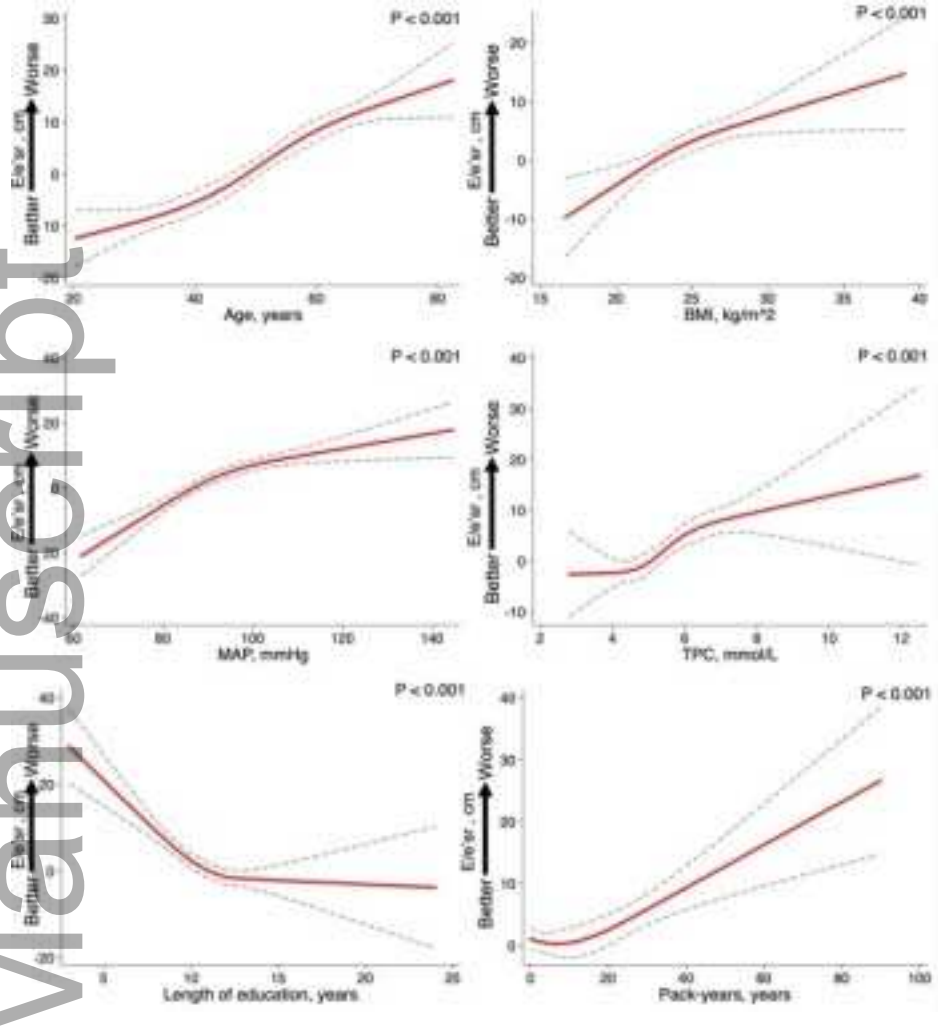

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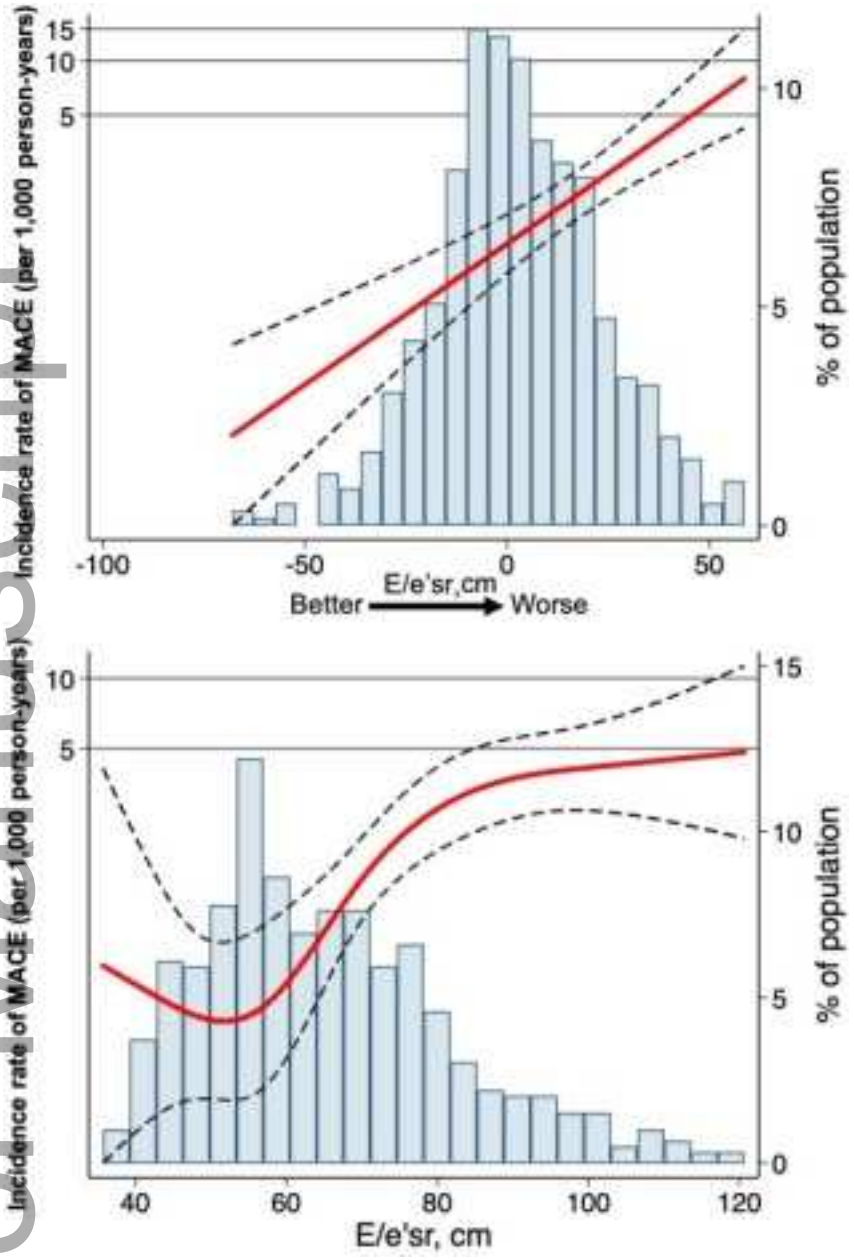

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