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Prognostic impact of impaired left ventricular midwall function during progression of aortic stenosis

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Abstract

Objective: In hypertension, indexes of midwall left ventricular (LV) function may identify patients at higher cardiovascular (CV) risk independent of normal LV ejection fraction (EF). We analyzed the association of baseline and new-onset LV midwall dysfunction with CV outcome in a large population of patients with asymptomatic aortic stenosis (AS).

Methods: 1478 patients with asymptomatic AS and normal EF (≥50%) at baseline in the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study were followed for a median of 4.3 years. LV systolic function was assessed by biplane EF and midwall shortening (MWS, low if <14% in men / 16% in women) at baseline and annual echocardiographic examinations.

Results: 123 CV deaths and heart failure hospitalizations occurred during follow-up. In Cox analyses, adjusting for age, gender, body mass index, hypertension, EF, AS severity, LV hypertrophy and systemic arterial compliance, low baseline MWS predicted 61% higher risk of a major CV event and a 2-fold higher risk of death and heart failure hospitalization ($p < 0.05$). New-onset low MWS developed in 574 patients, particularly in elderly women with higher blood pressure and more severe AS ($p < 0.05$). In time-varying Cox analysis, new-onset low MWS was associated with a 2-fold higher risk of CV death and heart failure hospitalization, independent of changes over time in EF, AS severity, LV hypertrophy and systemic arterial compliance ($p < 0.05$).

Conclusions: Low MWS develops in a large proportion of patients with AS and normal EF during valve disease progression and is a marker of increased CV risk.

Key Words: aortic stenosis, midwall function, prognosis, echocardiography

Abbreviations:

AS =aortic valve stenosis

AVA =aortic valva area

CI =confidence interval

CMR =cardiac magnetic resonance

CV =cardiovascular

EF =ejection fraction

HF =heart failure

LV =left ventricle

MACE = major CV events

MWS =midwall shortening

SAC =systemic arterial compliance

SEAS =Simvastatin and Ezetimibe in Aortic Stenosis

In the management of patients with aortic stenosis (AS), timing of aortic valve replacement depends on assessment of stenosis severity, left ventricular (LV) function and development of cardinal symptoms [1]. Current guidelines recommend aortic valve replacement in patients with severe AS if typical symptoms or LV systolic dysfunction identified as an ejection fraction (EF) less than 50% are present [1,2]. However, evaluation of symptoms is often difficult in elderly AS patients who are sedentary or have comorbidities that cause chest pain or dyspnea or limit physical capacity. Moreover, EF may be normal despite reduced myocardial function, especially in the presence of compensatory concentric LV geometry [3].

Midwall function can easily be assessed by the midwall fractional shortening (MWS) on a standard echocardiogram using validated equations [4]. Presence of low MWS despite preserved LV EF is shown to be a predictor of adverse cardiovascular (CV) outcome in patients with arterial hypertension as well as diabetic patients [5,6]. In AS, studies using cardiac magnetic resonance (CMR) with late gadolinium enhancement have shown an association between presence of midwall fibrosis in AS, lower MWS and worse prognosis [7,8]. However, replacement fibrosis in the LV midwall does not regress after aortic valve replacement [7], being rather a late, irreversible finding. Thus, assessment of replacement fibrosis may be less useful as an earlier marker of myocardial dysfunction in AS patients [9]. The present analysis aims at assessing the prognostic importance of development of LV midwall dysfunction, assessed by baseline and new-onset low MWS, during progression of AS in patients with normal LV EF.

Methods

Study Population: The SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study was a randomized, double-blind, placebo-controlled study which assessed the effect of combined simvastatin and ezetimibe on AS progression and cardiovascular morbidity and mortality on 1873 patients with initially asymptomatic, mild-moderate AS, and without known coronary artery disease, peripheral arterial disease, cerebrovascular disease, diabetes mellitus or any condition requiring lipid-lowering therapy [10]. Patients with significant mitral valve disease, severe or predominant aortic regurgitation, or rheumatic valvular disease were not included in the SEAS trial. In the present analyses, only the 1497 patients in whom LV systolic function could be assessed both by EF and at midwall at baseline and at least one follow-up echocardiogram before occurrence of any CV event were considered. We further excluded the 19 patients with low EF (EF<50%) at baseline, leaving 1478 patients with normal EF for the present analyses. Hypertension was defined as history of hypertension, use of antihypertensive treatment reported by the attending physician or blood pressure ≥140/90 mmHg at the baseline clinical visit. Overweight was considered present when body mass index was ≥25kg/m^2.

Echocardiographic measurements: Echocardiography was performed at baseline and then annually and before valve surgery at the 173 SEAS participating centers following a standard protocol. The last study echocardiogram in the individual patient was defined as the last exam before any CV event occurred or the final study echocardiogram, respectively. All echocardiographic analysis was performed at the SEAS Echocardiography Core Laboratory in Bergen, Norway.

LV hypertrophy was assessed by LV mass/height$^{2.7}$ (cut-off 46.7 g/m$^{2.7}$ in women and 49.2 g/m$^{2.7}$ in men, respectively) [11], and LV concentric geometry by the relative wall thickness (cut-off 0.43). The main measure of AS severity was the aortic valve area (AVA) by the continuity equation [1].

Assessment of LV systolic function and systemic arterial compliance: The main measures of LV systolic function were LV EF and MWS. EF was measured by the Simpson's biplane method and considered low if <50% [12]. LV MWS was calculated using two-dimensional LV diameters and wall thicknesses according to a previously validated formula [4]:

MWS =[(LVIDd+Hd/2)-(LVIDs+Hs/2)] / (LVIDd+Hd/2)

Where d=end-diastolic, s=end-systolic, LVID=LV internal diameter, H=combined septum and posterior wall thickness. Low MWS was defined using gender-specific cut-offs: <16% in women and <14% in men [13].

LVs pump performance was additionally assessed by the stroke volume based on the Doppler method and indexed for body surface area (low if <35ml/m²) [1]. The ratio of stroke volume index and pulse pressure was used to assess systemic arterial compliance (SAC) [14].

Study endpoints: The primary outcome of the SEAS study was major CV events (MACE), a composite endpoint consisting of death from CV causes, aortic valve replacement, heart failure hospitalization (HF) due to progression of AS, non-fatal myocardial infarction, hospitalization for unstable angina pectoris, coronary artery bypass grafting, percutaneous coronary intervention, and non-hemorrhagic stroke [10]. All endpoints were adjudicated by an independent committee. In the present analysis, the endpoints MACE, CV death and combined CV death and HF hospitalization were targeted.

Statistical analyses: Statistical analyses were performed using IBM SPSS version 26.0 (Armonk, NY: IBM Corp). For the purpose of the present study, the population was divided into three groups: patients with low baseline MWS, patients with normal MWS at baseline that developed low MWS during follow-up before any clinical event (new-onset low MWS) and patients with normal MWS throughout the study (hereafter reffered to as normal MWS). No patient with low MWS at baseline had normal MWS at the follow-up study visits. The interaction between study treatment (simvastatin and ezetimibe vs. placebo) and MWS measured at different time points (annual study visits) was tested in a general linear model with repeated measures and Greenhouse-Geisser test of within-subjects effects. Comparisons between the specific means of baseline characteristics of patients with baseline low MWS vs. new-onset low MWS and vs. normal MWS were made by chi-square tests and one-way ANOVA with Sidak´s post hoc test as appropriate. Prevalence of low MWS and low EF at each study visit are reported as crude values with p values based on chi-square tests.

The change in CV risk over time in the three study groups was tested in Kaplan-Meier survival analyses with log-rank test for the overall analysis, as well as in univariable and multivariable time-fixed and time-dependent Cox regression analyses, respectively. The association of baseline low MWS and new-onset low MWS, vs. normal MWS, with higher rate of MACE was tested in univariate Cox analyses in the whole population, as well as separately in clinically relevant subgroups (men and women, normal weight and in

overweight, and hypertensive and normotensive patients). The results are presented as a forest plot including the hazard ratios with 95% CI for low baseline MWS and new-onset low MWS in each clinical subgroup. The multivariable Cox models tested the relationship between MWS and study endpoints, with adjustment for age, sex, body mass index, hypertension, EF, LV hypertrophy, severity of AS by AVA and SAC. In time-varying Cox models, EF, prevalence of LV hypertrophy, AVA and SAC were included as time-varying covariates. A two-tailed $p \leq 0.05$ was considered significant both in univariable and multivariable analyses. Results are reported as hazard ratios with 95% confidence intervals (CI).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

The study protocol conforms to the ethical guidelines of the Declaration of Helsincki and was approved by ethics committees in all SEAS participating countries. All study participants gave written informed consent.

Results

Prevalence of low LV midwall systolic function at baseline and during follow-up: At baseline, 372 patients (25% of the population) had low MWS (Table 1, Figure 1). Compared to the 532 patients with normal MWS throughout the study, those with low baseline MWS were older, included more women and patients with hypertension, and had higher LV mass and relative wall thickness, as well as more severe AS by all recommended criteria of severity (all $p < 0.001$) (Table 1). 574 patients developed low MWS during a median of 4.3 years follow-up (Figure 1). Compared to those with normal MWS, also patients with new-onset low MWS were older, had slightly higher LV mass index and more severe AS (all $p < 0.05$), but comparable blood pressure values, relative wall thickness and stroke volume index (Table 1). No significant interaction was found between study treatment and changes in MWS over time (Greenhouse-Geisser within-subjects test $F=0.14$, $p=0.94$).

EF was normal at study inclusion, but lowest in the group with low baseline MWS ($p < 0.001$). During follow-up, the total prevalence of low MWS increased to 61% ($p < 0.001$, Figure 1), while low EF was rare (2%). The 34 patients that developed low EF during follow-up were predominantly men (85%), had high prevalence of LV hypertrophy (74%), as well as more severe AS at baseline than patients that maintained a normal EF (all $p < 0.05$).

Risk of events by MWS group: A total of 505 MACE, 65 CV deaths and 58 HF hospitalizations occurred during follow-up. 41% of the patients with low baseline MWS experienced at least one MACE during follow-up, vs. 38% of those with new-onset low MWS

and 25% of those with normal MWS (p <0.001). The rate of AS progression of assessed by yearly reduction in AVA was comparable between the three groups: 0.03 cm²/year in patients with normal MWS, 0.05 cm²/year in those with low baseline MWS, and 0.04 cm²/year in patients with new-onset low MWS, respectively (p =0.50).

Presence of low baseline MWS, as well as new-onset low MWS during the study, carried a significantly increased CV risk, with 61% and 45% higher adjusted MACE rate, respectively (Figure 2, Table 2). In particular, the rate of combined CV death and HF hospitalization doubled both in the group with low baseline MWS as well as in patients with new-onset low MWS during the 4 years follow-up, compared to patients with normal MWS, independent of other well-established prognostic factors (Table 2).

When taking into account changes in EF, AVA, LV hypertrophy and SAC during the study period in time-varying Cox models, presence of low MWS throughout the study was associated with a 48% (95% CI 19%-83%) higher hazard of MACE (p <0.001, Table 3) and a 2-fold increase (95% CI 1.16-3.38) in CV death and HF hospitalization (p <0.05).

Additional inclusion of baseline relative wall thickness as well as its changes over time in time-fixed and time-varying Cox analyses, respectively, did not change the results.

When analyzed in clinically relevant subgroups, baseline low MWS and new-onset low MWS were associated with higher risk of MACE during progression of AS in both women and men, in normal weight and in overweight patients, as well as in hypertensive patients with AS (p <0.001), but not in normotensive patients (Figure 3).

Discussion

The present study of a large cohort of AS patients with initially normal LV EF shows that EF is a less sensitive marker of LV systolic function in AS and that assessment of LV midwall function by MWS identifies a significant number of asymptomatic AS patients with more advanced ventricular disease and at increased CV risk. Low MWS was present at baseline in ¼ of AS patients with normal EF, and its prevalence raised 2.4-fold during AS progression. Both low MWS at study baseline, as well as new-onset low MWS during AS progression were associated with subsequent higher MACE rate. It is noteworthy that, despite evidence that low MWS often develops in parallel with concentric LV hypertrophy, baseline and new-onset low MWS were associated with significantly worse CV outcome independent of changing LV geometry during the 4.3 years follow-up.

Guidelines indications for assessment of LV function in AS: Assessment of LV function by EF is part of the routine clinical evaluation of patients with AS. According to present European as well as American guidelines for management of AS, evaluation of EF is particularly important in patients with asymptomatic, severe AS where an EF <50% is a class I indication for surgical treatment (1,2). This recommendation is based on small-scale, retrospective investigations [15,16], while large prospective studies to support this indication are lacking. There is a growing body of evidence that low EF is a late manifestation of LV dysfunction, especially in the presence of concentric LV geometry that may allow a good endocardial motion despite low LV myocardial contractility [17,18]. Studies on myocardial deformation by tissue Doppler imaging and speckle tracking have indeed shown that patients with AS and normal EF often have depressed LV myocardial deformation, both of the longitudinal fibers [19-21] as well as of the midwall layer [22].

Assessment of midwall function in AS: In chronic LV overload due to hypertension, it is recognized that LV midwall dysfunction is often present despite normal EF and associated with worse CV outcome [5]. In previous publications from the SEAS study, LV midwall dysfunction was particularly common in patients with more advanced valvuloarterial disease [17] and also in those with inappropriately high left ventricular mass relative to the LV load [23]. Lower MWS was significantly associated with severity of AS and presence of symptoms in a retrospective study by Ballo et al. [24]. The present analysis adds to current knowledge by demonstrating that LV midwall dysfunction is found in ¼ of asymptomatic mild-moderate AS patients with normal LV EF, becomes increasingly prevalent with stenosis progression and has independent prognostic value that may improve risk assessment based solely on AS severity, LV hypertrophy and SAC. A recent CMR study in a cohort of 166 AS patient [25] has found that AS progression is accompanied by a gradual increase in total extracellular myocardial volume, with midwall replacement fibrosis present mostly in the most advanced stages of AS. The increasing extracellular volume by CMR was correlated with increasing LV mass, diastolic dysfunction and higher serum troponin level, but not accompanied by a fall in EF or stroke volume [25]. The prevalence and incidence of low MWS in our larger echocardiographic study demonstrates that more advanced LV myocardial disease may be present in milder stages of AS, probably reflecting the impact of comorbidities like hypertension and obesity [26,27]. Furthermore, the echocardiographic MWS allows rapid, non-invasive assessment of midwall function with excellent inter- and intraobserver reproducibility: intraclass correlation coefficient 0.92 (95% CI: 0.87 to 0.96) for intraobserver variability, and 0.98 (95% CI: 0.89 to 0.99) for interobserver variability (both $p < 0.001$) in

the SEAS population [17]. The formula for MWS calculation can easily be saved on the echocardiograph and thus be integrated in the standard serial echocardiographic follow-up of AS patients [17].

Midwall LV failure and associated CV risk: Low MWS predicted significant higher MACE risk and a 2-fold higher risk of CV death and HF hospitalization in this study population, independent of both AVA, LV hypertrophy and arterial load assessed by SAC, possibly reflecting more advanced LV myocardial disease of multifactorial causes. It is previously demonstrated, both in general populations [13] as well as in hypertensive patients [28] and at baseline in SEAS [29], that women have higher MWS than men. By using sex-specific cut-offs, low MWS is more common among elderly women than men during AS progression [30]. However, its prognostic value was comparable in women and men in the present SEAS population. Low MWS increases in parallel with increasing prevalence of adverse geometric LV remodelling, probably at least in part explaining the higher peri- and postoperative mortality reported in these patients [31].

A recent study in 102 AS patients found that patients with ECG strain pattern had lower MWS, and more midwall fibrosis identified by late gadolinium enhancement at CMR [8]. In another cohort of 140 AS patients, the 20 patients with ECG strain pattern had a higher rate of AVR or CV death during a 10.6 years follow-up [8]. Histopathologically it has been demonstrated that in severe AS there is a change in the oxidative stress in the myocardium that contributes to adverse remodeling and correlates with low midwall function [32]. Serial assessment of MWS during patient follow-up has the potential of identifying AS patients with falling myocardial contractility despite unchanged EF [18], but before irreversible midwall fibrosis detectable by CMR has developed [9].

Clinical implications: Assessment of CV risk in AS remains challenging. The present data support routine echocardiographic evaluation of LV systolic myocardial function by MWS in AS, for improved identification of patients at increased CV risk including higher risk of CV death and HF hospitalization. MWS can easily be derived from routine measurements of LV wall thickness and dimension, and when the formula is included in the measurement package, it will be automatically reported. The trial was however not designed to compare the benefit of early aortic valve replacement vs. watchful waiting in patients with low vs. normal MWS. Future studies testing the prognostic benefit of early valve replacement in patients with asymptomatic AS and midwall dysfunction are needed. However, identification of low midwall function by MWS or other sensitive echocardiographic techniques as myocardial deformation analyses should help the clinician in detecting myocardial dysfunction. In

patients with comorbidities like hypertension or obesity, better control of these CV risk factors is indicated [33]. A thorough patient evaluation and careful clinical decision making by the heart valve team may be warranted.

Limitations: MWS was calculated by an equation previously validated in hypertensive patients [4]. This equation assumes homogenous wall thickness in the LV, a limitation that we attempted to avoid by measuring the average septal thickness in patients with asymmetrical hypertrophy of the septum [34]. Due to the fact that the majority of echocardiograms in the SEAS study were forwarded to the core laboratory on VHS video tapes, analyses of myocardial strain were not available in this trial population. Furthermore, systematic stress testing and evaluation of cardiac biomarkers, including NT-proBNP, were not part of the SEAS study protocol.

Author contributions: Doctors Cramariuc, Bahlmann, Ray, Kesaniemi, Nienaber and Gerdts were involved in the conception and design, data collection, as well as analysis and interpretation of data. All coauthors have revised the manuscript critically and have approved it for submission.

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Figure legends

Figure 1. Proportion of patients with low MWS at each study visit (orange bars) and separately proportion of patients with new-onset low MWS at each follow-up visit (red bars).

Figure 2. Kaplan-Meier hazard of MACE (2a) and combined HF and CV death (2b) in patients with low baseline MWS, new-onset low MWS and normal MWS. The p value is the level of significance for the log-rank test.

Figure 3. Forest plot presenting the hazard ratios with 95% CI for low baseline MWS and new-onset low MWS, respectively, as predictors of MACE in clinical subgroups (overweight vs. normal weight patients, hypertensive vs. normotensive patients and men vs. women). The red lines represent the 95% CI, and the blue dots the hazard ratio based on univariate Cox analyses.

Table 1. Baseline characteristics of patients with normal MWS vs. low MWS.

	Normal MWS (n=532)	**Low baseline MWS (n=372)**	**New-onset low MWS (n=574)**	**P value**
Age (yrs)	66±10	68±9	68±10	<0.001
Female gender	24%	50%	45%	<0.001
Body mass index (kg/m²)	26.4±3.9	27.2±4.5	26.6±4.1	0.008
Systolic blood pressure (mmHg)	145±20	149±21	147±19	0.01
Diastolic blood pressure (mmHg)	81±10	83±10	82±9	0.005
Hypertension	82%	91%	86%	0.001
Heart rate (bmp)	64±11	68±11	66±11	<0.001
LV mass index ($g/m^{2.7}$)	42±12	52±17	44±13	<0.001
Relative wall thickness (%)	32±6	44±9	33±7	<0.001
Peak aortic jet velocity (m/s)	2.99±0.52	3.16±0.52	3.14±0.55	<0.001
Mean transaortic gradient (mmHg)	21±8	24±9	24±9	<0.001
Aortic valve area (cm²)	1.37±0.47	1.20±0.41	1.24±0.48	<0.001

EF (%)	68±6	65±6	67±6	<0.001
MWS (%)	18.6±2.6	13.2±1.6	18.4±2.5	<0.001
Stroke volume index (ml/m^2)	46.1	44.2	44.5	0.25
SAC ($ml/m^2/mmHg$)	0.78±0.33	0.74±0.34	0.74±0.28	0.08

Data are mean ± standard deviation or percentage. P value for comparison between groups is based on chi-square test for categorical variables and one-way ANOVA for continuous variables.

Table 2. Hazard of MACE, as well as of combined HF or CV death, in patients with low baseline MWS and in patients with new-onset low MWS during the study follow-up, compared to patients with normal MWS. Hazards are presented both as unadjusted (univariable Cox) and as adjusted ratios (multivariable Cox analyses).

		Unadjusted HR [95% CI]	Adjusted HR [95% CI]
Low baseline MWS	MACE (n=151)	1.90 [1.51-2.40] *	1.61 [1.24-2.08] *
	HF or CV death (n=38)	3.16 [1.80-5.54] *	2.02 [1.10-3.72] ‡
	CV death (n=24)	2.23 [1.18-4.19]†	1.49 [0.74-2.98]
New-onset low MWS	MACE (n=221)	1.67 [1.35-2.08] *	1.45 [1.16-1.82] *
	HF or CV death (n=50)	2.62 [1.53-4.50] *	2.08 [1.18-3.67]‡
	CV death (n=25)	1.44 [0.77-2.70]	1.15 [0.59-2.23]

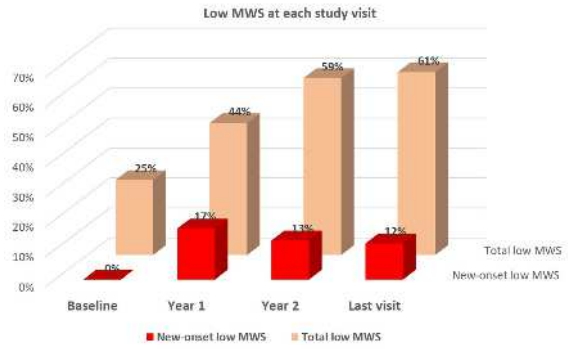
*p <0.001, †p <0.01 and ‡p <0.05.

Adjustment in Cox multivariate analyses for: age, gender, body mass index, hypertension, EF, LV hypertrophy, systemic arterial compliance and severity of AS by AVA.

Table 3. Presence of low MWS (baseline and new-onset) was associated with increased hazard of MACE independent of changes over time in other known prognosticators in AS (multivariable time-varying Cox analysis).

	HR [95% CI]	**p**
Low MWS (baseline and new-onset)	1.48 [1.19-1.83]	<0.001

Time-varying EF	0.98 [0.97-0.99]	0.008
Time-varying LV hypertrophy	1.15 [0.95-1.40]	0.15
Time-varying AVA	0.41 [0.31-0.52]	<0.001
Time-varying SAC	0.84 [0.52-1.37]	0.49
Age (years)	1.00 [0.99-1.01]	0.72
Gender	1.32 [1.09-1.60]	0.005
Body mass index	1.00 [0.98-1.03]	0.72
Hypertension	0.96 [0.73-1.25]	0.74



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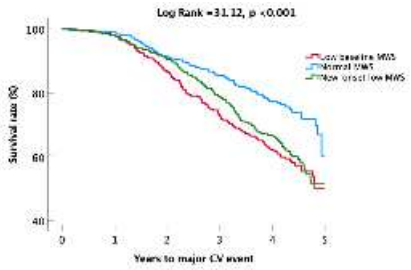

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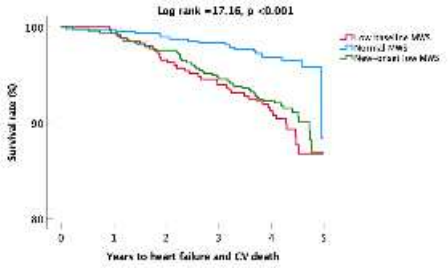

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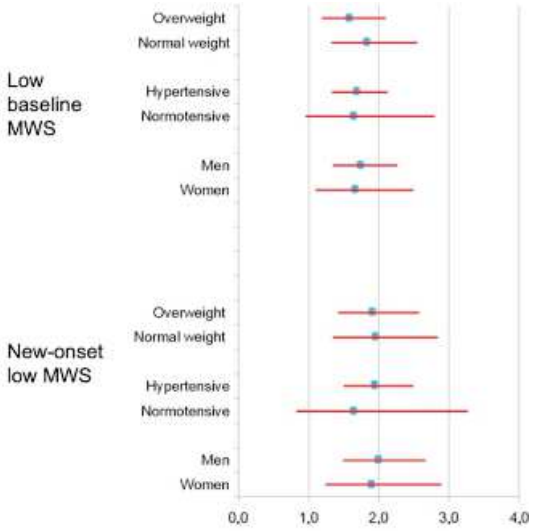

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