ORIGINAL PAPER

Prevalence of the Third and Fourth Heart Sound in Asymptomatic Adults

The prevalence of abnormal diastolic heart sounds in asymptomatic adults has been the subject of great debate. The authors determined the prevalence of an electronically detected S_3 and S_4 in 1329 asymptomatic adults between the ages of 18 and 94. The authors also investigated the relationship between abnormal diastolic heart sounds, age, and electrocardiography. The overall prevalence of S_3 was 10.0% (95% confidence interval [CI], 8.1%–12.2%), S_4 was 15.6% (95% CI, 13.2%–18.2%), and both S_3 and S_4 were 3.5% (95% CI, 2.4%–5.0%). Using multinomial logistic regression, increasing age was found to decrease the odds of an S_3 being heard (odds ratio, 0.96; 95% CI, 0.95–0.96) and increase the odds of an S_4 being heard (odds ratio, 1.04; 95% CI, 1.03–1.05). We conclude that the prevalence of an S_3 is increased earlier in life, that an S_4 is less common than previous studies suggest, and that its detection, even in the elderly, should not be ignored. (CHF. 2005;11:242–247) ©2005 CHF, Inc.

Extra diastolic heart sounds are produced as a result of increased stiffness and decreased compliance of the left ventricle (LV). The third heart sound (S_3) occurs 0.12–0.16 seconds after the second heart sound in early diastole (Figure 1).[1] Of the many proposed theories, the most likely explanation is that excessive rapid filling of a stiff ventricle is suddenly halted, causing vibrations that are audible as S_3.[2] The fourth heart sound (S_4) occurs after P wave onset and before the first heart sound in the cardiac cycle. It is produced in late diastole as a result of atrial contraction causing vibrations of the LV muscle, mitral valve apparatus, and LV blood mass.[3] The atrial and ventricular "gallop" has been described in the literature dating back to the late 1800s.[4] The ventricular gallop is recognized as an S_3. The atrial gallop is synonymous with an S_4.

The detection of an S_3 is often considered "normal" in adolescents and young adults, while its detection after the age of 40 is usually considered abnormal and indicative of LV dysfunction.[5–7] The incidence of an S_4 in acute ischemia and acute infarction approaches 100%.[8]

The prevalence of these sounds, especially the S_4, in healthy individuals has been a subject of great debate. Previous phonocardiographic studies have found a prevalence of S_4 from as low as 11%[9] to as high as 75%,[10] as well as many values in between.[11–16] The vast majority of these studies enrolled fewer than 300 subjects and suffered from enrollment bias because many of the subjects had been referred for cardiac workup, including left-sided and right-sided heart catheterization.

The goals of our study are twofold: 1) to determine the prevalence of an S_3 and S_4 in a large asymptomatic population using a computerized algorithm that analyzes acoustical data; and 2) to determine if there is an association between abnormal diastolic heart sounds, age, and electrocardiographic (ECG) findings.

Methods

This study was a cross-sectional observational cohort study of a convenience sample of asymptomatic persons. The Western Institutional Review Board, Olympia, WA, approved the study.

Subject Enrollment. A total of 1511 subjects were recruited from two colleges near Portland, OR; a community center outside Portland; a hospital outpatient clinic (Willamette Valley Medical Center); and several senior citizen centers. Subjects were screened by a research nurse who obtained consent and a brief cardiac history and determined whether the subjects had any acute

Sean P. Collins, MD;[1] Patricia Arand, PhD;[2] Christopher J. Lindsell, PhD;[3] W. Frank Peacock IV, MD;[4,5] Alan B. Storrow, MD[1]
From the Department of Emergency Medicine[1] and the Institute of Health Policy and Health Sciences Research,[3] University of Cincinnati, Cincinnati, OH; Inovise Medical, Inc., Portland, OR;[2] the Department of Emergency Medicine, Ohio State University, Columbus, OH;[4] and The Cleveland Clinic Foundation, Cleveland, OH[5]
Address for correspondence: Sean P. Collins, MD, Assistant Professor, Department of Emergency Medicine, University of Cincinnati, 231 Albert Sabin Way, Cincinnati, OH 45267-0769
E-mail: sean.collins@uc.edu
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cardiovascular complaints. Potential subjects were not enrolled if acute cardiovascular complaints were indicated. Baseline demographic information was recorded on all subjects.

Recording the Heart Sounds. Electrodes were placed on each subject in a standard 12-lead configuration, except for Audicor (Inovise Medical, Inc., Portland, OR) sensors (capable of both ECG and acoustic signal detection), which were placed in the V_3 and V_4 positions (Figure 2). The V_3 sensor was positioned in the fourth intercostal space at the midclavicular line. The V_4 sensor was positioned midway between V_3 and V_5, the latter of which was in the fifth intercostal space in the anterior axillary line. Cardiac acoustic and standard 12-lead ECG data were recorded simultaneously. The subject was supine or in a semi-Fowler's position and asked to relax, breath normally, and refrain from speaking during a 10–180-second continuous recording. The data collection was performed with custom data collection systems based on the Hewlett-Packard XLi cardiograph (Hewlett-Packard Company, Palo Alto, CA) with sampling rates at either 4000 or 1000 samples per second and digital files stored for later processing. All of the sound and electrical data were run through the same version of the ECG and sound algorithms, independent of the system on which the data was collected. All recorded data was filtered and downsampled to the same sampling rate (500 samples per second) and then processed through identical data streams.

The 12-lead ECGs were analyzed using a commercial computerized algorithm (Audicor) for the presence of cardiac disease, specifically the presence of LV hypertrophy, prior myocardial infarction (MI), acute MI, and ischemia. Patients with multiple findings on ECG were given only one diagnosis, according to a priority ordering of findings: acute MI, prior MI, ischemia, LV hypertrophy, abnormal, borderline, and normal.

Phonocardiographic evidence of heart sounds was determined by computerized algorithm. The algorithm has been validated in prior studies comparing the detection of S_3 and S_4 to hemodynamic measurements obtained at cardiac catheterization.[17] Briefly, both channels (V_3 and V_4) are analyzed by the algorithm for the presence of abnormal diastolic heart sounds, using the ECG as a timing marker, and frequency content appropriate for the gallops, and the results are combined for the final statements. The results of this analysis are then displayed on the paper printout of the ECG.

Statistical Analysis. Data are described using median and range for age and frequencies and percent for all other variables. For computing prevalence, the sound data constitute a multinomial distribution with mutually exclusive findings of no sounds, S_3 only, S_4 only, or both S_3 and S_4. This distribution arises from a function of the algorithmic interpretation of the heart sounds. The detection of either heart sound is not necessarily an independent event. Both gallops may be identified during a period of potential acoustic overlap. When this occurs, since it is not possible to algorithmically categorize the finding as a discrete S_3 or S_4, it is reported as the combination. For this reason, exact 95% confidence intervals for multinomial proportions have been used to estimate variance of the prevalence estimates. Prevalence estimates of the S_3 and S_4 do not include findings of both S_3 and S_4. Multinomial logistic regression has been used to evaluate relationships between predictor variables and the presence or absence of the various heart sounds. Analyses have been performed using StatXact version 6 (Cytel Software Corporation, Cambridge MA) and SPSS version 12.0 (SPSS Inc., Chicago IL).

Results

We recorded heart sounds in 1511 subjects between 18 and 99 years of age (median, 63 years). There were 182 subjects excluded from the analysis because of: dextrocardia (1), missing demographic information (3), ventricular pacing (47), other ECG abnormalities in which heart sounds were not able to be analyzed

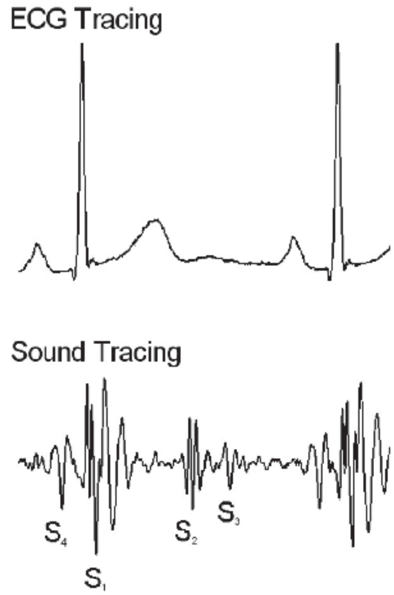

Figure 1. Location of heart sounds in the cardiac cycle. ECG=electrocardiographic

(52) (e.g., Wolff-Parkinson-White syndrome, second-degree heart block), and atrial fibrillation or flutter (79). Of the remaining 1329 subjects included in analyses, 35.7% (474) were ambulatory seniors, 31.5% (418) were from the hospital outpatient clinic, 20.2% (269) were asymptomatic adults, 11.4% (152) were college students, and 1.2% (16) did not fit into any of these categories. Women comprised 59.1% (786) of the subjects. Population characteristics are given in Table I for the entire cohort and for subjects within each group.

The overall prevalence of S_3 was 10.0% (95% confidence interval [CI], 8.1%–12.2%); the prevalence of S_4 was 15.6% (95% CI, 13.2%–18.2%), and the prevalence of both S_3 and S_4 was 3.5% (95% CI, 2.4%–5.0%). Table II gives point estimates of the prevalence of heart sounds stratified by decade and subject group. Figure 3 shows the prevalence of S_3, S_4, and both S_3 and S_4, stratified by age. In the multinomial logistic regression model (Table III), increasing age was associated with decreased odds of an S_3 being detected (odds ratio [OR], 0.96; 95% CI, 0.95–0.96) but increased odds of an S_4 being detected (OR, 1.04; 95% CI, 1.03–1.05). There was no influence of

Table I. Characteristics of Subjects in the Study

	Asymptomatic Adults N=269	Ambulatory Seniors N=474	College Students N=152	Outpatients N=418	Other N=16	Total N=1329
Women (n [%])	185 (68.8)	324 (68.4)	72 (47.4)	191 (45.7)	14 (87.5)	786 (59.1)
Men (n [%])	84 (31.2)	150 (31.6)	80 (52.6)	227 (54.3)	2 (12.5)	543 (40.9)
Age (yr) (median [range])	48 (30–59)	74 (60–94)	21 (18–29)	66 (21–94)	27 (22–29)	63 (18–94)
Age (yr) distribution (n [%])						
<30	4 (1.5)	–	152 (100.0)	4 (1.0)	16 (100)	176 (13.2)
31–40	77 (28.6)	–	–	13 (3.1)	–	90 (6.8)
41–50	72 (26.8)	–	–	50 (12.0)	–	122 (9.2)
51–60	116 (43.1)	13 (2.7)	–	98 (23.4)	–	227 (17.1)
61–70	–	140 (29.5)	–	81 (19.4)	–	221 (16.6)
71–80	–	221 (46.6)	–	113 (27.0)	–	334 (25.1)
>80	–	100 (21.1)	–	59 (14.1)	–	159 (12.0)

Table II. Prevalence of S_3 and S_4, Stratified by Patient Group and Decade of Age

	Abnormal Heart Sounds (n [%])			
Age (yr)	None	S_3	Both	S_4
Asymptomatic Adults				
<30	3 (75.0)	0 (0.0)	1 (25.0)	0 (0.0)
31–40	62 (80.5)	10 (13.0)	4 (5.2)	1 (1.3)
41–50	51 (70.8)	9 (12.5)	3 (4.2)	9 (12.5)
51–60	89 (76.7)	7 (6.0)	3 (2.6)	17 (14.7)
Total	205 (76.2)	26 (9.7)	11 (4.1)	27 (10.0)
Ambulatory Seniors				
51–60	11 (84.6)	1 (7.7)	0 (0.0)	1 (7.7)
61–70	109 (77.9)	4 (2.9)	3 (2.1)	24 (17.1)
71–80	165 (74.7)	6 (2.7)	9 (4.1)	41 (18.6)
>80	69 (69.0)	4 (4.0)	1 (1.0)	26 (26.0)
Total	354 (74.7)	15 (3.2)	13 (2.7)	92 (19.4)
College Students				
<30 (Total)	84 (55.3)	59 (38.8)	5 (3.3)	4 (2.6)
Outpatients				
<30	2 (50.0)	2 (50.0)	0 (0.0)	0 (0.0)
31–40	12 (92.3)	1 (7.7)	0 (0.0)	0 (0.0)
41–50	41 (82.0)	5 (10.0)	2 (4.0)	2 (4.0)
51–60	67 (68.4)	5 (5.1)	8 (8.2)	18 (18.4)
61–70	58 (71.6)	5 (6.2)	2 (2.5)	16 (19.8)
71–80	76 (67.3)	6 (5.3)	3 (2.7)	28 (24.8)
>80	31 (52.5)	5 (8.5)	3 (5.1)	20 (33.9)
<30 to >80	287 (68.7)	29 (6.9)	18 (4.3)	84 (20.1)
Other				
<30	12 (75.0)	4 (25.0)	0 (0.0)	0 (0.0)

age on the prevalence of a combined S_3 and S_4 (OR, 1.00; 95% CI, 0.98–1.01).

Figure 4 shows prevalence of the heart sounds separately for men and women. The model showed that women were less likely than men to have a detectable combined S_3 and S_4. There was no measurable influence of gender on the presence of an S_4. Table III shows the relationship between ECG findings and the presence of an S_3 or S_4. The univariable multinomial regression showed no significant relationships between ECG findings and heart sounds. ECG findings have not been included in the multivariable model.

Table III. Multinomial Logistic Regression Models Showing the Relationship Between Abnormal Heart Sounds, Age, Gender, and Electrocardiographic (ECG) Findings

		S_3		Both		S_4	
Univariable Models	n	OR	95% CI	OR	95% CI	OR	95% CI
Age		0.955	0.946–0.964	0.996	0.981–1.011	1.037	1.026–1.048
Women vs. men		0.757	0.525–1.090	0.398	0.218–0.727	0.920	0.677–1.250
ECG findings*							
Acute myocardial infarction	8		**		**	3.008	0.704–12.858
Prior myocardial infarction	174	0.641	0.324–1.269	0.686	0.227–2.076	1.166	0.730–1.862
Ischemia	32	0.342	0.045–2.591	3.016	0.822–11.072	1.367	0.536–3.487
Left ventricular hypertrophy	46	0.778	0.229–2.648	2.288	0.634–8.264	1.902	0.910–3.974
Abnormal	331	0.996	0.618–1.605	1.418	0.695–2.893	1.093	0.739–1.616
Borderline	220	1.893	1.188–3.016	0.752	0.273–2.076	1.057	0.667–1.675
Multivariable Model							
Age		0.955	0.946–0.965	0.997	0.982–1.012	1.037	1.026–1.048
Women vs. men		0.851	0.579–1.251	0.400	0.219–0.732	0.877	0.641–1.200

*normal ECG is the reference category in all cases; **no findings of acute myocardial infarction among patients with an S_3 or both an S_3 and S_4

Discussion

Our results suggest that an S_3 is common in the asymptomatic individual younger than 40, with its presence decreasing in the decades of life thereafter. This underlying prevalence (approximately 10%) has implications in the management of those patients with a suspected acute coronary syndrome. The American College of Cardiology/American Heart Association guidelines recommend that patients with unstable angina and a concurrent auscultated S_3 be classified in the group at highest risk for adverse outcomes and considered candidates for an early invasive strategy.[18] Accurate knowledge of the true underlying frequency of the S_3 may impact these recommendations. Consequently, the implications of our findings require further corroboration with clinical outcomes.

The low prevalence of S_3 in asymptomatic subjects over the age of 50 strengthens previous findings that a detectable S_3 in older subjects may be highly specific for cardiac pathology, although the age above which an S_3 is predictive of LV dysfunction may be slightly higher than 40 years, as previously reported.[5–7]

In contrast to the S_3, detection of an S_4 was quite uncommon in subjects younger than 50 (under 10%), with increasing prevalence thereafter.

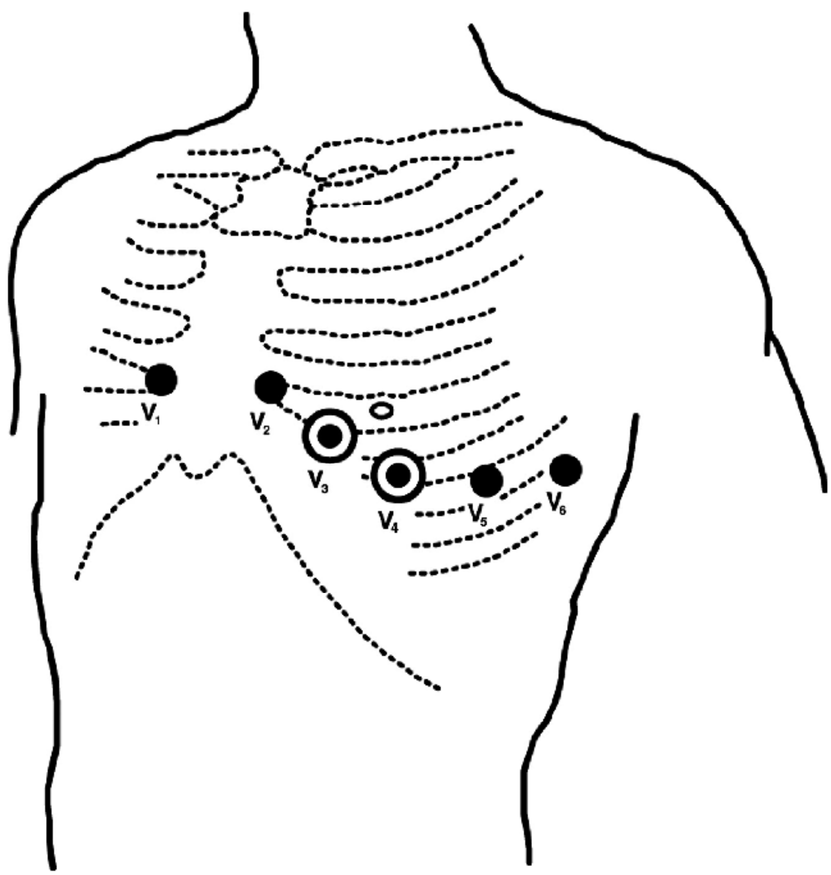

Figure 2. Schematic of the placement of the chest leads with acoustical leads in the V_3 and V_4 positions

An S_4 detected by auscultation has long been considered indicative of ventricular dysfunction.[19,20] Previous studies have demonstrated the presence of an S_4 during episodes of angina, in patients with coronary artery disease,

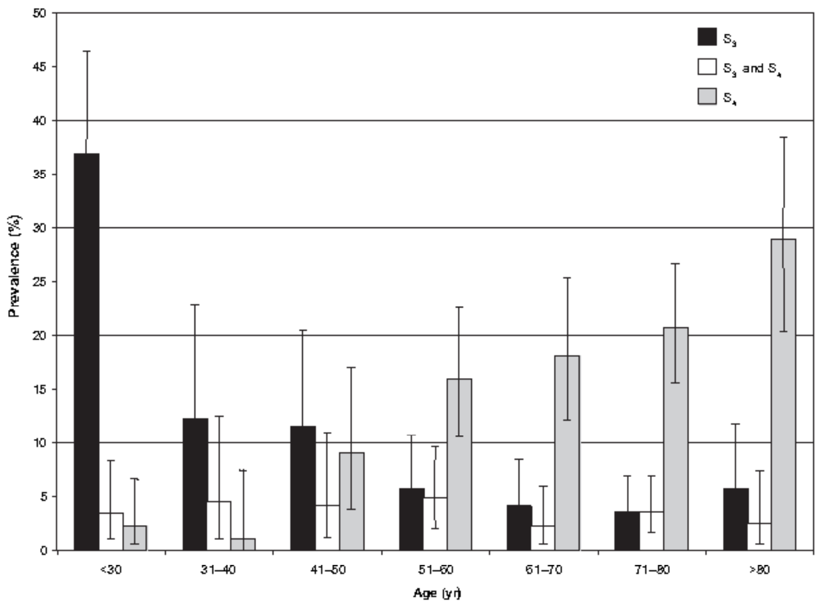

Figure 3. Prevalence of S_3 and S_4 heart sounds stratified by age. Subjects with a finding of S_3 and S_4 are not included in those with findings of S_3 or S_4 only; findings are mutually exclusive. Error bars represent 95% confidence intervals.

and during ischemic stress tests.[16,21,22] Several studies in the early and mid-1970s questioned the validity of this belief. Spodick and Quarry,[12] examining 250 consecutive ambulatory subjects in the Framingham Heart Study, found a phonocardiographic S_4 to be present in 73.1% of healthy patients and 74.3% of patients with CV disease. In a subsequent study of 100 patients of whom half were healthy and half had hypertension, these investigators found a similar 70% prevalence of S_4 in healthy subjects as well as those with hypertension.[15] Erikssen and Rasmussen[11] detected an S_4 using phonocardiography in over 50% of 1714 healthy middle-aged men. Other studies have reported a similar prevalence of S_4 in healthy individuals, although they are limited by a small total enrollment and referral bias.[10,13,14]

At the center of the S_4 controversy may be the difference between an auscultated vs. a phonocardiographically detected S_4. Previous studies on diagnostic and prognostic significance have traditionally focused on an S_4 detected by auscultation.[19,20] With the advent of new technology being incorporated into the bedside ECG, it is necessary to determine the diagnostic and prognostic significance of a phonocardiographic S_4 that may not have been evident on auscultation.

Technology available in the 1970s, when studies suggested a high prevalence of S_4 in healthy individuals, may have inaccurately detected S_4. The low frequency range sound of the S_4 (10–50 Hz)[23,24] overlaps the frequencies of the S_1 (30–150 Hz), making it difficult to differentiate from a split S_1. Our more modern phonocardiographic technique showed a prevalence more consistent with auscultation—Aronow and colleagues[16] found an S_4 to be present at rest in 14% of healthy subjects (n=100) and 43% of subjects with angina (n=100). While the studies discussed here indicate there may be an S_4 present in a subset of asymptomatic patients, it is uncertain whether this is pathologic. Future studies addressing the diagnostic and prognostic significance of a phonocardiographically detected S_4 are fundamental to resolving these discrepant findings.

Detection of either the S_3 or S_4 did not seem to be related to ECG findings in our subjects. Patients with borderline ECG results did demonstrate increased odds of having a detectable S_3, but in the absence of a relationship between definite ECG findings and heart sounds, it might be concluded that the significant result may be spurious. If a true result, the clinical implications are somewhat unclear. Further, the automated interpretation of the ECG may not be sufficiently accurate to determine relationships between heart sounds and ECG findings. For example, the eight patients with automated readings of acute MI were visually over-read by a board-certified cardiologist. Two of the ECGs had paced rhythms that the algorithm missed, resulting in a misclassification. One patient was in atrial flutter and the algorithm did not apply the confounder adjustment, resulting in a misclassification as probable acute ST-segment elevation. One subject had ST depression that was confirmed by visual over-read. Three subjects had borderline ST-segment elevation that was confirmed visually. One subject had ST elevation that was confirmed by visual over-read.

Our intent was to determine the prevalence of an S_3 and S_4 in asymptomatic subjects. Our cohort reported no acute complaints but did not undergo further workup to determine the presence of occult cardiac disease. Other medical conditions, such as hypertension, have been identified as producing S_4 in otherwise asymptomatic individuals, and there may have been hypertensive subjects in our cohort, resulting in an overestimate of the prevalence of S_4. Exclusion of hypertension would be expected to exaggerate our finding that S_4 may not be as common as previously considered. The short sampling timeframe may also limit our findings; the majority of patients had only 10 seconds of data sampled, and measurements were made only once. Repeat measurements or longer samples may result in an increased prevalence, as a greater opportunity is provided to detect a quiet or intermittent S_3 or S_4. The automated ECG reading was algorithmically generated and not based on manual interpretation. While this ensures consistency across readings, subtle changes or atypical findings may have been missed.

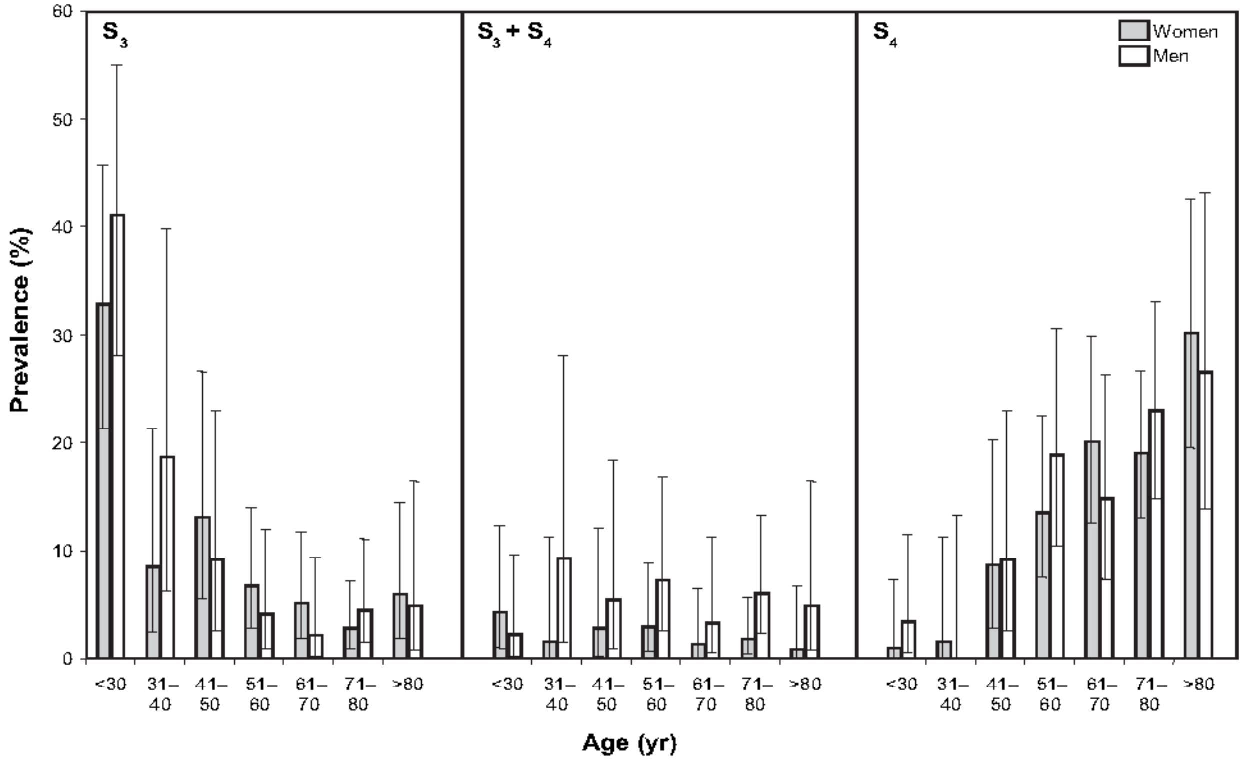

Figure 4. Prevalence of heart sounds stratified by gender and age category. Subjects with a finding of S_3 and S_4 are not included in those with findings of S_3 or S_4 only; findings are mutually exclusive. Error bars represent 95% confidence intervals.

Conclusions

Our study suggests that the prevalence of an S_3 is increased earlier in life, while an S_4 in asymptomatic individuals is much more common in the later decades in life. The prevalence of an S_3 in younger individuals is consistent with previous studies. However, the prevalence of S_4 may be less common than previous phonocardiographic studies suggest, and its detection, even in the elderly, should perhaps not be ignored.

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