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Quantification of asymptomatic kidney stone burden by computed tomography for predicting future symptomatic stone events

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Abstract

Objective—To find the optimal characterization of asymptomatic radiographic stone burden on computed tomographic (CT) scans.

Methods—A survey was sent to stone formers who underwent a CT scan while asymptomatic during a stone clinic evaluation. Symptomatic stone passage events after CT scan were detected by survey and medical record review. Radiographic stone burden was quantified by number of stones, largest stone diameter, automated total stone volume (TSV), and bilateral stones and then compared as predictors of stone events.

Results—There were 550 stone formers; 43% had a stone event a median 4.7 years after the CT scan. Stone burden by quartiles was 0–1, 2–3, 4–6, 7 for number of stones; 0–2, 3–4, 5–7, 8 mm for largest stone diameter; and 0–8, 9–78, 79–280, and 281 mm³ for TSV; 48% had bilateral stones. The hazard ratios (HRs) for symptomatic event was 1.30 (p<0.001) for the number of stones per quartile, 1.26 (p<0.001) for largest stone diameter per quartile, 1.38 (p<0.001) for TSV per quartile, and 1.80 (p<0.001) for bilateral stones. On multivariable analysis, only TSV was an independent predictor of symptomatic events (HR=1.35 per quartile, p=0.01). This risk of events

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with TSV was also independent of demographics, urine chemistries, and stone composition. Among the 53 patients with interim events between CT scans, a rapid increase in TSV between CT scans ($>570 \text{ mm}^3/\text{year}$) predicted subsequent events ($\text{HR}=2.8$, $p=0.05$).

Conclusions—Automated TSV is more predictive of symptomatic events than manual methods for quantifying stone burden on CT scan.

Keywords

Computed tomography; kidney stones; total stone volume; hematuria; flank pain

Introduction

Kidney stones affect 1 in 11 people, and have become more prevalent.^{1–4} Besides pain (often described as the worst ever experienced), stones lead to costly surgical interventions, loss of work, and the long-term complication of kidney failure. Preventing future painful stone passage events is the primary concern of these patients. Patients with asymptomatic kidney stones on imaging are known to be at increased risk for future symptomatic stone events.^{5,6} Typically, the number, diameter (of largest stones), and location of stones are assessed on imaging to quantify stone burden.^{7,8}

Computed tomography (CT) scans are routinely used to identify “metabolically active” stone disease as defined by new or larger stones compared to previous scans.⁸ Stone diameter is important for determining which stones will likely require surgery versus pass spontaneously.^{9–11} In addition to the number and diameter of stones, stone burden can be quantified with total stone volume by adapting techniques used for coronary artery calcification.^{12–14}

Patients with asymptomatic stones on CT scan may receive more aggressive dietary and medical therapy. Some may be referred for surgery to remove stones before they cause painful obstruction.^{8,15} Despite these practices, the relationship of radiographic stone formation and growth to symptomatic stone events is poorly understood. Some patients may form and symptomatically pass stones prior to detection on a routine CT scan. Other patients may have stones on a CT scan that never pass or that are passed with mild symptoms that do not result in a recognized stone passage event.

We studied a large cohort of stone formers who underwent surveillance CT scans while asymptomatic. Chart review and survey were used to ascertain their next symptomatic stone event. Goals were to: 1) identify the optimal radiographic characteristics that predict future stone events, and 2) determine if an increase in total kidney stone burden between CT scans was predictive of future stone events.

Methods

Study sample

We identified all patients at a Mayo Clinic kidney stone clinic who underwent a stone protocol CT scan while asymptomatic (i.e., no gross hematuria or abdominal pain) between

October 2005 and December 2009. Subjects who had stone surgery up to 90 days after their CT scan were also excluded in order to ensure that patients who had asymptomatic stones detected and removed because of this scan were not misclassified as having stone events. A survey was mailed to remaining patients in 2012. The study was approved by the Mayo Clinic Institutional Review Board (IRB).

Clinical characteristics at the time of the first CT scan were abstracted from the medical record including age, sex, past symptomatic kidney stone events, stone composition, and other kidney stone disease characteristics. In addition, the closest 24-hour urine supersaturation studies within 6 months of the first CT scan were electronically captured for each patient.¹⁶ The subset of patients who had a second CT scan while they were asymptomatic at a later stone clinic visit were also identified. The total stone volume, number of stones, and largest stone diameter were measured from the CT images and the next symptomatic stone event was identified by the survey and chart review (Supplementary methods).

Statistical Analysis

Kidney stone burden was assessed by presence versus absence of bilateral stones and by quartiles and top 10th percentile for number of stones, largest stone diameter, and total kidney stone volume. Cox proportional hazard models were used to estimate hazard ratios (HR) for stone events by stone burden at the first CT scan (Supplementary Figure 1A). Multivariable models assessed whether total kidney stone volume was an independent predictor of stone events. Separate models adjusted for other measures of stone burden and for other baseline clinical and laboratory characteristics. Interaction terms were also included in models to determine if the risk of stone events with total stone volume differed by number of stones, largest stone diameter, and presence of bilateral stones. In the subset with two CT scans, the rate of change in total kidney stone volume was assessed by both quartiles and by the top 10th percentile. Cox proportional hazard models were used to estimate the HR for symptomatic kidney stone events after the second CT scan as predicted by rate of change in stone volume between the two CT scans (Supplementary Figure 1B). Analysis was further stratified on presence or absence of any interim symptomatic stone event (between the first and second CT scan). All analyses were repeated excluding cystine stone formers since this stone type is rare and more aggressive in causing symptomatic stone events than more common stone types.

Results

There were 1098 patients identified with a kidney stone protocol CT scan while asymptomatic. There were 62 excluded for no clinical history of kidney stones (symptomatic or asymptomatic) at the time of the CT scan. Thirty-two patients who had stone surgery within 3 months after their CT scan were also excluded. A survey was mailed to the remaining 1004 stone formers; the 550 (55%) who completed and mailed back the survey were included in the study. The group that completed the survey was similar to the overall group (Supplementary Table 1). During follow-up, 230 (42%) had a symptomatic stone event a median (25%, 75%) of 4.7 (3.3, 5.9) years after the CT scan.

Table 1 lists the characteristics of the stone formers with and without symptomatic events and hazard ratio for symptomatic events by each characteristic. Notably, younger age, cystine stone composition, higher calcium oxalate supersaturation, lower urinary potassium, and lower urinary sulfate were the only non-radiographic characteristics that predicted future symptomatic stone events. For the first CT scan, the quartiles of stone burden were 0 to 1, 2 to 3, 4 to 6, and 7 for number of stones; 0 to 2, 3 to 4, 5 to 7, and 8 mm for largest stone diameter; and 0 to 8, 9 to 78, 79 to 280, and 281 mm³ for total stone volume. The top 10th percentile threshold was >11 mm for largest stone diameter, >12 for number of stones, and >1000 mm³ for total stone volume. Total stone volume was more correlated with largest stone diameter ($r_s=0.87$) than with number of stones ($r_s=0.69$). Bilateral kidney stones were present in 264 (48%) patients.

Stone formers who had symptomatic events had at baseline more stones (mean 7 vs. 5, $p<.001$), larger largest stone diameter (6.5 vs 4.6 mm, $p<0.001$), bilateral stones (59% vs 40%, $p<0.001$), and larger total stone volume (1200 vs 344 mm³, $p<0.001$). Table 2 summarizes the risk of a symptomatic stone event based on CT scan stone burden. Total stone volume was a stronger predictor of symptomatic events than other measures of stone burden including stone number, stone diameter, and presence of bilateral stones. Figure 1 shows the risk of symptomatic events by total stone volume (0 to 78 mm³, 79 to 1000 mm³, and >1000 mm³). The risk of events by total stone volume per quartile during the first 2 years was stronger (HR=1.67, 95% CI: 1.38 to 2.04) than for follow-up beyond 2 years (HR=1.24, 95% CI: 1.06 to 1.45) ($p=0.02$ for proportional hazards test).

The risk of symptomatic events with total stone volume did not change substantively with adjustment for other measures of stone burden or adjustment for clinical characteristics that predicted stone events in Table 1. None of the other measures of stone burden (number of stones quartile, largest stone diameter quartile, or bilateral stones) were statistically significant predictors of stone events after adjustment for stone volume (Table 2). There was no evidence of effect modification between total stone volume and each of the other measures of stone burden ($p>0.05$ for statistical interaction for each). These findings were similar after exclusion of the 16 cystine stone formers (not shown). In a multivariable model, the independent predictors of symptomatic stone events were larger total stone volume, younger age, higher calcium oxalate supersaturation, and cystine composition ($p \leq 0.01$ for all). Supplementary Figure 2 shows the risk of symptomatic events by total stone volume in younger (age <56 years) and older (age ≥ 56 years) patients. The 3-year risk of events in younger patients was 20%, 35% and 58% for total stone volumes of 0 to 78 mm³, 79 to 1000 mm³, and >1000 mm³, respectively. The 3-year risk of events in older patients was 8%, 17% and 43% for total stone volumes of 0 to 78 mm³, 79 to 1000 mm³, and >1000 mm³, respectively.

Of the 550 stone formers, 249 had a second CT scan while asymptomatic a median (25%, 75%) 1.1 (1.0, 2.0) years after the first CT scan. An interim symptomatic stone event between the two CT scans occurred in 53 patients, of which 32 (60%) had a subsequent event after the second CT scan. Among the 196 without an interim stone event, 61 (31%) had a subsequent event after the second CT scan. The quartiles for change in total stone volume were: less than -1, -1 to 18, 18 to 132, and >132 mm³ per year; rapid increase in

stone volume (top 10th percentile) was >570 mm³ per year. The risk of symptomatic events was not statistically significant per quartile of stone volume change (HR=1.16, 95% CI: 0.96 to 1.40, p=0.12) or between stone formers with versus without a rapid increase in stone volume (HR=1.70, 95% CI: 0.82 to 3.12, p=0.14). However, a rapid increase in total stone volume was associated with an increased risk of symptomatic stone events in patients with an interim stone event (HR=2.83, 95% CI: 1.02 to 6.8, p=0.046) (Figure 2), but not for those without an interim stone event (HR=1.00, 95% CI: 0.30 to 2.44, p=0.99). The 3-year risk of recurrence in patients with interim stone events and with a rapid versus without a rapid increase in stone volume was 84% versus 46%. The test for interaction (effect modification) between the interim stone event and rapid increase in total stone volume in the prediction of events after the second CT scan was not statistically significant (p=0.094), except when cystine stone formers were excluded (p=0.015).

Discussion

There were several key findings in this study of asymptomatic stone formers with CT imaging. First, total kidney stone volume is the optimal radiographic measure for predicting future symptomatic stone events and is superior to other common radiographic measures (number of stones, largest stone diameter, or presence of bilateral stones). This is likely due to total stone volume being a more comprehensive characterization of stone burden than these other radiographic measures. Also, total stone volume is more accurately measured because it is based on an automated image processing algorithm as opposed to manual review of CT images by individuals. Other radiographic measures did not inform prediction of future symptomatic stone events beyond what was already captured by total stone volume alone. Second, the increased risk of symptomatic events with total stone volume cannot readily be accounted for by other clinical characteristics. Specifically, the prognostic information from stone burden on a CT scan is independent of urine chemistries and other clinical factors. Finally, a rapid increase in stone volume appears to be predictive of future stone events in patients who had an interim stone event between their CT scans. These findings demonstrate the importance of total stone volume for optimally interpreting CT scans, monitoring risk of future stone events in stone formers, and suggest a possible role in treatment decisions.

Many of our findings are consistent with other investigations that have also characterized the risk of future stone events from asymptomatic radiographic stones. Glowacki and colleagues found symptomatic stone events increased with the number of asymptomatic stones.⁵ Kang and colleagues found that after identifying an asymptomatic kidney stone about half of these patients had progression (defined as stone passage, pain, stone growth, or surgical intervention).⁶ Inci and colleagues followed asymptomatic lower pole stones for progression (defined as pain, stone growth, or surgical intervention) with stone growth specifically observed in a third of these patients.¹⁷ Burgher and colleagues found that a larger stone diameter was predictive of disease progression (defined as pain, stone growth, or surgical intervention).¹⁵

While our study also found asymptomatic kidney stone burden increases the risk of future stone events, there is an important difference compared to these prior studies. We defined

our event as symptomatic passage or symptomatic attempted passage with surgical interventions. We did not consider radiographic stone growth in the absence of symptoms to be a clinical event. Further, in the absence of stone-related symptoms, we did not consider surgical intervention to be an event. Our justification was that stone passage or attempted passage that results in pain or hematuria is the relevant clinical event to the patient.

Our study found that total stone volume is the optimal metric to quantify stone burden for the purposes of predicting stone events. Stone number, stone diameter, and bilateral location are important characteristics for planning surgical intervention, but we found no evidence that these factors added anything to stone event risk stratification beyond total stone volume. Predictive discrimination of stone events by total stone volume was stronger in the first 2 years. Thus, total stone volume appears to be more useful for identifying which patients have an early risk of stone events compared to patients with a late risk of stone events. This is consistent with the early risk of stone events being due to the existing stone burden, whereas the late risk of stone events being due to other factors that lead to new stone formation.

There are also several problems with using stone number and stone diameter to quantify stone burden. There can be disagreement between radiologists as to the number of stones as tiny stones are difficult to identify with certainty.¹⁸ Stone diameter is usually defined by maximal transverse diameter, but this diameter is a poor indicator of the stone's volume since stones are rarely spheres and are often complicated three-dimensional shapes.¹⁹ Of note, total stone volume was much more correlated with largest stone diameter than number of stones. A large stone may be more likely to detach and cause symptoms than the often numerous and possibly less relevant "tiny calyceal tip stones." Large stones (>11 mm in diameter) in this stone clinic population were associated with an increased risk of symptomatic stone events. However, any patient with very large stones (i.e., staghorn) had them surgically removed right after the first CT scan and thus were excluded from the analysis.

There are several advantages to using total stone volume to quantify stone burden. Current 64-channel CT scanners are able to obtain images of the urinary system with a high degree of spatial resolution which defines the smallest object that can be accurately resolved by an imaging system. CT is recommended as study of choice for evaluation of stone disease (sensitivity 97%, specificity 95%).²⁰ Ultrasound shows lower sensitivity and specificity (40% and 84%, respectively) for detection of stones. In addition, inaccurate measurement of stone material by ultrasound is seen in at least 30% of patients.²¹ The superior spatial resolution with CT scan allows accurate assessment of the volume of calcification in a standardized manner (>130 HU).¹⁹ Changes in stone volume allow for an accurate determination of whether a patient's kidney stone burden is increasing in number and size (i.e. metabolically active).^{8,22,23} Patel and colleagues compared stone burden by both manual stone diameter and by automated renal stone volume measurement on non-contrast renal CT scans. They found stone volume was a more accurate and reproducible quantification of stone burden than stone diameter.²² In addition to predicting future stone events, total stone volume helps identify patients who will respond well to certain surgical interventions such as shock wave lithotripsy (SWL). Two recent studies found patients who

were stone free after a SWL procedure had a lower pre-treatment total kidney stone volume than those with residual stones (274 vs. 464 mm³)²⁴ and (360 vs. 770 mm³).²⁵ Patients at higher risk may benefit from more intensive medical and dietary management to prevent further increases in total stone volume.

We also found that only a few non-radiographic characteristics (younger age, cystine composition, high urinary calcium oxalate supersaturation, and low urinary potassium and sulfate) were predictive of future symptomatic stone events. The non-radiographic characteristics likely play more of a role in preventing new stone formation and growth as opposed to detachment of existing stones with subsequent symptoms from an obstructive uropathy. Longer follow-up in a stone former population without baseline asymptomatic radiographic stones is needed to better define how clinical and urine chemistry characteristics and stone composition predict future symptomatic stone events. However, we were able to verify that radiographic stone burden strongly predicts the risk of symptomatic stone events and does so independent of these other clinical characteristics including urine chemistries and stone composition. This is an important point when considering the utility of surveillance imaging of stone burden in stone formers.

There are several strengths to this study. These include a relatively large sample size, prospective follow-up for stone events with a mailed survey, and longitudinal analysis of asymptomatic stone burden changes. We also compared total stone volume to other radiographic and clinical factors that are used to predict risk in stone formers. There are also several potential limitations of this study. We relied on self-reported symptomatic stone events that we could not independently verify. However, stone formers pass stones without receiving medical care and these events are only detectable by surveying the patient. Other than identifying bilateral stone disease, we did not collect data on stone location within each kidney (e.g., lower pole vs. upper pole) as a prognostic factor. The image processing protocol did not determine individual stone volume (only total stone volume). This was a referral based patient population at a tertiary medical center; CT scans were for clinical care of patients already believed to be at increased risk of future stone events. Our findings are most valid for comparing different methods of quantifying radiographic stone burden in predicting stone events in a high risk population. Prospective study of the average stone former from the general community is needed to better clarify the relative contribution of existing radiographic stone burden, stone composition, urine chemistries, and other clinical characteristics to future stone events.

Conclusions

Total stone volume is the optimal method of quantifying stone burden for the purpose of predicting future stone events. We would recommend a baseline CT scan be obtained in stone formers that need sub-specialty care for the purposes of risk stratification. A total stone volume >1000 mm³ has a 3-year risk of events in younger stone formers of 58% and older stone formers of 43%. Whereas a total stone volume of <79 mm³ has a 3-year risk of events in younger stone formers of 20% and older stone formers of 8%. Follow-up CT scans in patients who have had a stone event since their last CT scan does inform the risk of future events. In particular, those with versus without a >570 mm³ per year increase in total stone

volume have a 84% versus 46% risk of stone events in the next 3 years. Whether this prognostic information justifies the additional radiation exposure and expense of follow-up CT scans is unclear. Follow-up CT scans in stone formers who are not having interim stone events may not be as prognostically useful.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Risk of symptomatic stone events by total kidney stone volume group: less than the median (78 mm³), median to 90th percentile (1000 mm³), or greater than the 90th percentile.

Figure 2.
Risk of symptomatic stone events in patients with a rapid rate of increase in total stone volume ($>570 \text{ mm}^3/\text{year}$) among patients with an interim stone event between CT scans.

Table 1

Characteristics of stone formers and risk of symptomatic events at follow-up

Characteristic	Follow-up stone event (n=230)		No follow-up stone event (n=320)		Hazard ratio (per SD if continuous)	P-value
Clinical	N (%) or mean ± SD	N (%) or mean ± SD				
Mean Age at 1 st CT scan (years)	50 + 15	57 + 14	0.70 (0.62 to 0.80)			
Male	117 (51%)	185 (58%)	0.78 (0.60 to 1.01)			
White	216 (94%)	306 (96%)	0.88 (0.54 to 1.59)			
Primary Stone composition *						
Unknown	65 (28%)	129 (40%)	0.67 (0.50 to 0.88)			
Calcium Oxalate	116 (50%)	138 (43%)	1.22 (0.94 to 1.58)			
Calcium Phosphate	23 (10%)	26 (8.2%)	1.27 (0.80 to 1.91)			
Uric Acid	12 (5.2%)	21 (6.6%)	0.78 (0.41 to 1.34)			
Cystine	12 (5.2%)	4 (1.3%)	2.84 (1.50 to 4.86)			
Struvite	2 (0.9%)	2 (0.6%)	1.76 (0.29 to 5.50)			
Malabsorption disease						
Bariatric surgery	13 (5.7%)	14 (4.4%)	1.37 (0.74 to 2.31)			
Inflammatory bowel disease	12 (5.2%)	16 (5.0%)	0.98 (0.52 to 1.68)			
Bowel resection	7 (3.0%)	16 (5.0%)	0.59 (0.25 to 1.16)			
Chronic Diarrhea	8 (3.5%)	12 (3.8%)	1.00 (0.45 to 1.89)			
Chronic Pancreatitis	3 (1.3%)	1 (0.31%)	2.15 (0.53 to 5.64)			
Renal Tubular Acidosis	5 (2.2%)	4 (1.3%)	1.57 (0.56 to 3.42)			
Primary Hyperoxaluria	4 (1.7%)	10 (3.1%)	0.49 (0.15 to 1.16)			
Medullary Sponge Kidney	12 (5.2%)	20 (6.3%)	0.84 (0.45 to 1.44)			
Urine Chemistries						
pH	6.1 ± 0.6	6.1 ± 0.7	1.06 (0.94 to 1.19)			
Volume (ml/day)	2048 ± 953	2092 ± 882	0.95 (0.82 to 1.10)			
Calcium Oxalate (CaOx) supersaturation (DG)	1.72 ± 0.68	1.49 ± 0.85	1.27 (1.10 to 1.48)			
Brushite supersaturation (DG)	-0.10 ± 1.31	-0.50 ± 1.46	1.27 (1.10 to 1.48)			

Characteristic	Follow-up stone event (n=230)		No follow-up stone event (n=320)		Hazard ratio (per SD if continuous)	P-value
	N (%) or mean ± SD		N (%) or mean ± SD		HR (95% CI)	
Apatite supersaturation (DG)	3.98 ± 2.15		3.55 ± 2.29		1.18 (1.02 to 1.37)	0.02
Uric acid crystal supersaturation (DG)	−0.44 ± 3.30		−0.44 ± 3.27		1.00 (0.87 to 1.15)	0.97
Sodium (mmol/day)	181 ± 89		175 ± 70		1.05 (0.92 to 1.20)	0.47
Potassium (mmol/day)	62 ± 30		69 ± 29		0.84 (0.72 to 0.97)	0.02
Calcium (mg/day)	224 ± 122		205 ± 122		1.12 (0.98 to 1.27)	0.09
Magnesium (mg/day)	109 ± 47		107 ± 43		1.00 (0.87 to 1.15)	0.99
Chloride (mmol/day)	168 ± 84		164 ± 68		1.03 (0.89 to 1.18)	0.72
Phosphorus (mg/day)	960 ± 379		918 ± 333		1.05 (0.92 to 1.21)	0.46
Sulfate (mmol/day)	19 ± 9		21 ± 9		0.86 (0.75 to 0.99)	0.04
Citrate (mg/day)	603 ± 352		610 ± 334		0.99 (0.86 to 1.14)	0.94
Oxalate (mmol/day)	0.38 ± 0.29		0.38 ± 0.23		1.01 (0.85 to 1.17)	0.89
Uric acid (mg/day)	565 ± 233		558 ± 205		1.03 (0.89 to 1.18)	0.71
Creatinine (mg/day)	1508 ± 505		1438 ± 452		1.07 (0.93 to 1.22)	0.35

* Reference is all other stone compositions

Table 2

Risk of future symptomatic stone events by baseline asymptomatic CT stone burden

CT Stone burden Characteristic	Hazard Ratio (95% CI)	P-value
Total stone volume by each quartile		
1 st Quartile (0–8 mm ³)	Reference	
2 nd Quartile (9–78 mm ³)	1.12 (0.72 to 1.73)	0.60
3 rd Quartile (79–280 mm ³)	1.96 (1.34 to 2.90)	<0.001
4 th Quartile (281 mm ³)	2.53 (1.74 to 3.73)	<0.001
Each method of assessing CT stone burden (unadjusted)		
Total stone volume per quartile	1.40 (1.24 to 1.58)	<0.001
Number of stones per quartile	1.31 (1.17 to 1.46)	<0.001
Largest stone diameter per quartile	1.27 (1.13 to 1.42)	<0.001
Total stone volume >1000 mm ³ (top decile)	2.44 (1.67 to 3.45)	<0.001
Number of stones > 12 (top decile)	1.70 (1.15 to 2.43)	0.009
Largest stone diameter >11 mm (top decile)	2.11 (1.43 to 3.02)	<0.001
Bilateral stone	1.81 (1.39 to 2.35)	<0.001
Multivariable model with radiographic stone burden measures		
Total stone volume per quartile	1.35 (1.06 to 1.70)	0.01
Number of stones per quartile	1.07 (0.89 to 1.28)	0.49
Largest stone diameter per quartile	0.95 (0.78 to 1.16)	0.60
Bilateral stone	1.17 (0.78 to 1.74)	0.45
Multivariable model with total stone volume and clinical and urinary characteristics		
Total stone volume per quartile	1.46 (1.28 to 1.66)	<0.001
Age per SD (15 years)	0.70 (0.61 to 0.81)	<0.001
Male	0.93 (0.70 to 1.24)	0.62
Cystine stone type	12 (1.3 to 40)	0.01
Calcium oxalate supersaturation per SD	1.26 (1.08 to 1.48)	0.003