Contribution of an under-recognized adversity to child health risk: large-scale, population-based ACEs screening.

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2 • What's Known on This Subject

Whereas ACEs correlate with neurodevelopmental and physical health of children at the population level, ACEs scales (e.g., PEARLS) are only weakly predictive at the level of the individual child. Are important elements of early-life adversity missed by these scales? What This Study Adds • Because unpredictable signals constitute a unique ACE, we developed the Questionnaire of Unpredictability in Childhood (QUIC-5). Administering QUIC-5 and PEARLS to 30,000 families identified youth at risk for depression, obesity and other health problems, who would be missed by PEARLS alone.

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Abstract

29 Background and Objectives: Whereas adverse early life experiences (ACEs) correlate with 30 cognitive, emotional and physical health at the population level, existing ACEs screens are only weakly predictive of outcomes for an individual child. This raises the possibility that important 31 32 elements of the early-life experiences that drive vulnerability and resilience are not being 33 captured. We previously demonstrated that unpredictable parental and household signals 34 constitute an ACE with cross-cultural relevance. We created the 5-item Questionnaire of 35 Unpredictability in Childhood (QUIC-5) that can be readily administered in pediatric clinics. 36 Here, we tested if combined screening with the QUIC-5 and an ACEs measure in this real-world 37 setting significantly improved prediction of child health outcomes.

38 Methods: Leveraging existing screening with the Pediatric ACEs and Related Life Events 39 Screener (PEARLS) at annual well-child visits, we implemented QUIC-5 screening in 19 40 pediatric clinics spanning the diverse sociodemographic constituency of Orange County, CA. 41 Children (12yr+) and caregivers (for children 0-17years) completed both screens. Health 42 diagnoses were abstracted from electronic health records (N=29,305 children).

Results: For both screeners, increasing exposures were associated with a higher probability of a mental (ADHD, anxiety, depression, externalizing problems, sleep disorder) or physical (obesity abdominal pain, asthma, headache) health diagnosis. Across most diagnoses, PEARLS and QUIC provided unique predictive contributions. Importantly, for three outcomes (depression, obesity, sleep disorders) QUIC-5 identified vulnerable individuals that were missed by PEARLS alone.

49 Conclusions: Screening for unpredictability as an additional ACE in primary care is feasible,
50 acceptable and provides unique, actionable information about child psychopathology and
51 physical health.

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Introduction

The Centers for Disease Control and Prevention-Kaiser Permanente study¹ focusing on 53 54 Adverse Childhood Experiences (ACEs) documented cumulative effects of exposure to potentially traumatic experiences (e.g. abuse, neglect, violence exposure) on a wide range of 55 physical and mental health conditions. This seminal work prompted studies examining the 56 enduring role of ACEs in health and disease² and it is now estimated the economic burden of 57 exposure to ACEs in the US adult population is \$14.1 trillion annually³. Given the accumulating 58 evidence regarding the human and fiscal toll of ACEs, calls to address the prevalence and 59 consequences of ACEs are rapidly increasing^{4,5} and the vast majority of states have enacted some 60 form of legislation to address the burden of ACEs⁶. At the forefront of these efforts, in 2020, 61 62 California became the first state to implement a publicly supported screening program 63 comprising guidelines for trauma-informed care coupled with reimbursement for ACEs screening for the State's 15 million individuals supported by Medicaid. While California intends to 64 dramatically reduce the burden of ACEs on its citizens through this program^{7,8}, the value of this 65 public health initiative has been questioned on several grounds⁹. First, whereas ACEs screens 66 identify risk at the population level, they are limited in the ability to do so at the level of the 67 individual¹⁰. In addition, in the absence of established means for the prevention or mitigation of 68 the effects of ACEs, the value of screening is $unclear^{11}$. 69

70 There are several potential explanations for why ACEs scores are limited in their ability to
71 detect health risk for an individual child. One possibility is that significant sources of stress and

trauma occurring in childhood are missed with existing screeners¹². One such early life exposure 72 that is not currently included in standard screening instruments is unpredictability of the family 73 and environmental signals received by the child, which activate the brain's stress responses. It 74 75 has now been demonstrated in prospective longitudinal studies across diverse cultures and 76 sociodemographic groups that unpredictable parental care (independent from parental support 77 and sensitivity) and lack of structure in the family and home environment strongly predict cognitive and emotional development¹³. Notably, the concept that unpredictable signals to the 78 developing brain disrupt brain maturation is well supported by experimental animal studies¹⁴⁻¹⁷. 79 Specifically, unpredictability in childhood has been linked to decreased self-regulation, a slower 80 trajectory of cognitive development and poorer memory, as well as increased risk for anxiety, 81 depression, anhedonia, PTSD, and poorer self-reported physical health in children and adults¹⁸⁻²². 82 83 These associations persist after consideration of other well-established ACEs (e.g. poverty, 84 abuse, neglect), suggesting that unpredictable experience is a robust risk factor for adverse developmental and health outcomes, and its absence from existing assessments of early-life 85 86 adversity may account for some of their shortcomings in predicting an individual child's risk profile. 87

Here we test the relative and cumulative contributions of both ACES and unpredictability as risk factors for child mental and physical health in a large, diverse pediatric population. We leverage the existing ACEs screening implemented in the Children's Hospital of Orange County (CHOC) primary care network²³ together with a well-validated 5-item screening instrument for unpredictability to address the following critical questions: 1. When employed in routine pediatric primary care, does ACEs screening identify children at increased risk of mental and

94	physical health problems? 2. Does screening for unpredictability in the home environment
95	provide additional predictive power to current ACEs screening recommendations?
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Methods

99 Study Setting and Participants

100 This study took place in 19 pediatric primary care clinics affiliated with Children's Hospital of 101 Orange County (CHOC), which serve a diverse community of children in Orange County, CA 102 (see Table 1 for an overview of demographics). In 2020, the primary care clinics implemented 103 routine ACEs screening for all children at their annual well-child visits. As part of the California Initiative to Advance Precision Medicine²⁴, in 2021, optional screening for unpredictability was 104 initiated. For both screens all caregivers provided information and the screens were also 105 106 administered to children aged 12 and over. Inclusion criteria for the current study included: 1. 107 Completion of the QUIC-5 screener. 2. Child ages 0 to 17 years. 3. English or Spanish language 108 preference. Here we present data for the first 29,305 children screened for ACEs and 109 unpredictability. All study procedures were approved by the CHOC institutional review board.

110 Assessment of ACEs

ACEs were assessed with the face-valid Pediatric and Related Life Events Scale (PEARLS²⁵). Following current state screening recommendations, we examined the score for Part 1, which focuses on 10 ACEs yielding a potential score of 0 to 10. Current protocols at the CHOC Pediatric Primary care clinics utilize the aggregated or deidentified version of the

PEARLS in which the respondent provides a count of the number of items positively endorsed
without specification of the individual items contributing to these scores. PEARLS scores are
available in electronic health records (EHR).

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120 Assessment of Unpredictability

121 Unpredictability was assessed with the 5-item version of the Questionnaire of Unpredictability in Childhood (QUIC-5^{20,26}). At the well-child visit, caregiver and child (as 122 123 appropriate based on age) were given the opportunity to complete the unpredictability screen. 124 The OUIC, which broadly assesses unpredictability in the social, emotional and physical 125 environments demonstrates robust psychometric properties. The scale was validated against prospective longitudinal assessments of early life unpredictability and exhibits strong content 126 and discriminant validity as well as excellent test-retest reliability²⁰. The OUIC-5, on which 127 128 scores range from 0 to 5, is correlated on average .84 with the full-length version and predicts mental health outcomes effects sizes comparable to the original scale 26 . 129

130 *Child Health*

Mental and Physical health conditions were selected based on those that have strong stressrelated and behavioral components and have been previously identified as common outcomes of exposure to early life adversity in pediatric populations²⁷. Presence or absence of the following conditions in each child's EHR prior to or concurrent with the well-child visit at which the screen was conducted were obtained: abdominal pain, ADHD, anxiety, asthma, depression,

externalizing problems, headache, obesity and sleep disorders. Specific ICD-10 codes for eachdiagnosis can be seen in Table S1 and the incidence of each diagnosis in Table S2.

138 Analysis Plan

139 First, distributions of caregiver and youth endorsements on the PEARLS and QUIC were 140 examined. Bivariate correlations were then used to determine the degree of association between 141 youth and caregiver reports for each screener, as well as the correlation between the PEARLS 142 For both QUIC-5 and PEARLS separate binary logistic regressions were and OUIC-5. 143 conducted to examine the associations between caregiver and youth reports with mental and 144 physical health outcomes. In these regressions, scores on both screeners were categorized as 0, 145 1, 2, 3 and 4+. To determine whether the QUIC adds predictive power to the PEARLS, we 146 employed two approaches: 1. QUIC and PEARLS scores (continuous) were entered 147 simultaneously into binary logistic regressions predicting mental and physical health outcomes. 148 2. In a second set of binary logistic regressions, we examined the independent contributions of 149 all possible combinations of QUIC (0, 1, 2, 3 and 4+) and PEARLS scores (0, 1, 2, 3 and 4+)150 with 0-0 as the reference for mental and physical health outcomes. All regression models 151 adjusted for child gender and age (with both linear and quadratic age terms considered as 152 appropriate).

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Results

154 Exposures to ACEs and Unpredictability

Figure 1 shows the distribution of caregiver endorsement for exposures on PEARLS and QUIC among children ages 0 to 17 years. On average older children experienced more exposures to both ACEs and unpredictability, as expected. However, exposures to at least one

ACE (13%) or at least one form of unpredictability (23%) were observed even among the youngest children ages 0-4 (means and standard deviations by age group are provided in Table S3).

161 Comparing self-report by the children to caregiver reports within the same dyads, youths 162 reported more exposures to both ACEs and unpredictability than did caregivers (Figure 2; means 163 and standard deviations provided in Table S4). The correlation between youth and caregiver 164 reports on the PEARLS was .64 and for the QUIC the association was .54 (both p's = .00). The 165 two scales were also associated: among youth, the correlation between the QUIC-5 and PEARLS 166 was .51, and the correlation of caregiver reports on the two screeners was of a similar magnitude 167 (r = .43; both p's = .00).

168 *Exposures To ACEs and Unpredictability Predict Child Mental and Physical Health*

169 For both ACEs assessed with PEARLS and unpredictability measured with QUIC-5, 170 increasing exposures were associated with a higher probability of a mental (ADHD, anxiety, 171 depression, externalizing problems, sleep disorder) or physical (abdominal pain, asthma, 172 headache, obesity) health diagnosis. This was true for reports by both caregiver and youth 173 (Figures 3 and 4). Across diagnoses, the associations were generally dose-dependent, with odds 174 ratios increasing with each additional exposure (ORs and CIs are provided in Tables S5-8). For 175 caregiver report of mental health outcomes, the odds ratios for those with 4 or more exposures 176 compared to those with zero ranged from 2.4 to 5.9 for the PEARLS and 1.9 to 3.4 for the QUIC. 177 Similarly, the odds ratios for the physical health outcomes ranged from 1.4 to 1.9 and 1.8 to 2.0 178 for PEARLS and QUIC, respectively. The range of odds ratios for the youth self-reports were 179 similar in magnitude (see Table S8).

180 *Testing the Added Value of Unpredictability*

181 The correlation between PEARLS and QUIC-5 scores raised the question of whether 182 including the assessment of unpredictability adds value for predicting child health outcomes 183 beyond that obtained for PEARLS alone. Therefore, we determined the adjusted ORs for both 184 the QUIC and PEARLS in logistic regressions in which continuous scores for both were 185 concurrently included as predictors of youth mental and physical health (Figure 5; Tables S9 and 186 S10). For most mental and physical health diagnoses examined, both the PEARLS and QUIC 187 provided unique predictive contributions, and the predictive power (odds ratios) were similar, 188 whether reported by caregiver or youth. For sleep disorders and obesity the QUIC was a stronger 189 predictor of the increased probability of a diagnosis than was the PEARLS (Figure 5).

190 The QUIC identified significant risk for health problems that is not captured by the 191 PEARLS screen alone also when a second analytic approach was used (Figure 6). For example, 192 examining risk for depression, Figure 6 shows the odds ratios associated with all possible 193 combinations of QUIC and PEARLS scores. Children with a score of 4 or more on the PEARLS 194 had an increased risk of depression. For example, the odds ratio for a PEARLS score of 4 or 195 more and a QUIC score of zero was 7.9. However, a child with a score of zero on the PEARLS 196 and 4 on the QUIC is 11.8 more likely to have a depression diagnosis than a child who scores a 197 zero on both screens. This indicates that the QUIC-5 identifies a significant population of 198 children with mental health vulnerabilities derived from unpredictable environments that would 199 be missed by restricting screening to current ACEs tools.

This observation was not unique to depression. For example, a child with a "high score" on the PEARLS (4 or more) and with a score of 1 on the QUIC, is not at increased risk of a sleep disorder. However, a child who meets this criterion on the PEARLS and has a QUIC score of 4

or more is 5.4 times more likely to have a sleep disorder diagnosis than a child with a zero scoreon both screens (similar heatmaps for all diagnoses can be found in Table S11).

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Discussion

206 The principal findings of this study conducted in more than 29,000 children at 19 pediatric 207 primary care clinics are: (a) Widespread, systematic screening for ACEs and early-life 208 unpredictability is feasible in primary care clinics serving diverse communities. (b) Exposure to 209 adversity measured with both the QUIC and PEARLS is prevalent even among the youngest 210 children and increases with age. (c) Although parent and youth reports are in general agreement 211 and both predict health risks, youth report more exposures. (d) The unpredictability screen 212 (QUIC-5) portends child outcomes at least as well, and in some cases better, than currently 213 recommended ACEs screens. (e) Crucially, for some health problems (e.g. depression, obesity), 214 the QUIC-5 identifies risk for mental and physical health problems that is not captured by the 215 PEARLS screen.

Our study was conducted in Orange County, California (CA) which is home to the third largest child population in the state (after Los Angeles and San Diego counties). The youth served by CHOC are representative of the diverse socioeconomic, ethnic and cultural constituency of both the county and of California more broadly. Underscoring the representative nature of the sample is the fact that our race and ethnic distributions largely mirror that of both the county and state²⁸. This indicates that both the feasibility and uptake of the screening as well as the associations we observed with child health outcomes are highly likely to generalize.

A concerning observation was the prevalence of adversity exposures even among the youngest children, with 13 percent already having experienced at least one ACE and 27 percent exposed to at least one form of unpredictability before 5 years of age. As children aged, both caregivers and youth reported more exposures. On average, youths reported more exposures to both ACEs and unpredictability than did caregivers, highlighting the importance of obtaining youth self-report in addition to caregiver report when possible. According to self-reports, by late adolescence 27 percent of youth had been exposed to one or more ACE and 49 percent at least one form of unpredictability.

231 For both mental and physical health outcomes, exposure to more ACEs and unpredictability 232 exhibited a graded relationship with risk of diagnosis. Additionally, the predictive power of 233 unpredictability was similar in magnitude to ACEs for the range of mental and physical health 234 outcomes examined. The results strongly suggest that consideration of unpredictability enhances 235 the ability to identify children at risk of a mental or physical health condition beyond that of the 236 PEARLS: First, when modeling the two screens together, each predicted risk independently from 237 the other for the mental and physical health outcomes examined. Furthermore, high QUIC scores 238 predicted significant risk for many diagnoses even when the PEARLS score was low. These risks 239 (in some cases, odds ratios greater than 10) would be missed if PEARLS scores alone were used 240 for screening.

For two health conditions, obesity and sleep disorders, the QUIC was superior in risk identification compared to the PEARLS. This observation regarding obesity mirrors findings from a study of 367 children receiving care at a safety net practice in Northern California that documented positive associations between caregiver reports with the PEARLS and asthma, but not obesity²⁹. This is not entirely surprising as healthy eating and sleep hygiene are both dependent on structure and routines^{30,31}. Delineating both the shared and unique contributions of different forms of early life adversity to individual disease burden, as done here, paves the path

for more precise understanding of individual exposures, and the mechanisms through whichthose exposures operate, enabling true precision medicine.

250 An additional strength of the current study was the examination of the utility of youth self-251 report of exposure to adversity. Following State of California recommendations for the PEARLS, 252 children aged 12 and above completed both screens. In general, the dose-response patterns 253 associated with both mental and physical health outcomes were comparable for youth and 254 caregiver reports, including the findings that the QUIC was a better predictor of sleep disorders 255 and obesity than the PEARLS. These similarities underscore the validity of youth report on the 256 QUIC and PEARLS and increase confidence in the validity of both screening instruments. A 257 limitation of the study lies in the reliance on child health diagnoses derived from electronic 258 health records. Given the study design, it is not possible to disentangle the temporal relations 259 between exposures and diagnoses. Further, particularly for the mental health outcomes, we are 260 unable to probe the associations between exposures and subclinical symptom profiles, which are 261 highly likely. Future studies will explore how structural and social determinants of health 262 influence exposures to unpredictability and their associations with health, to better identify 263 inequities which exist. This is of particular importance because structural determinants of ACEs 264 and unpredictability are not evenly distributed and individuals of historically and currently 265 marginalized and systematically excluded backgrounds are at disproportionate risk for these exposures³²⁻³⁶. 266

There are several features of unpredictability that distinguish it from many other forms of early life adversity, rendering it a promising target for prevention and intervention: (1) There are multiple opportunities for prevention and intervention, including the prospect of multilevel intervention^{37,38}. These range from the level of the individual (e.g. altering caregiver attitudes

271 regarding the importance of predictability), to the family systems level (e.g. implementing family 272 routines) and at the public policy level (e.g. adoption of Fair Workweek regulations that address 273 precarious parental work schedules). Addressing the full range of ACEs such as poverty and 274 abuse should be a top priority to improve the well-being of children and families. However, a parallel and attainable goal is increasing predictability in children's lives, for example through 275 276 the encouragement of family routines, which have the additional advantage of being relatively 277 low cost. (2) In conceptualizing high unpredictability as a form of early life adversity, it is 278 notable that low unpredictability (i.e., predictable environments) may exert protective influences 279 on child development and buffer children from adversity. For example, in families experiencing 280 poverty, parental substance use disorders, chronic illness or divorce, family routines predict child resilience³⁹⁻⁴¹. In addition, predictability protected child mental health in the context of societal-281 level disruptions such as the COVID-19 pandemic^{42,43}. (3) Community perspectives obtained 282 283 from pediatricians, allied health care providers and parents indicate that screening in pediatric primary care with the QUIC-5 may be more acceptable than screening with the PEARLS⁴⁴. (4)284 285 Finally, interventions seeking to promote predictability should and can incorporate culturally-286 responsive, person-centered, and community inclusive approaches with the acknowledgment that 287 the promotion of predictability requires consideration of the unique needs of each child and 288 family.

289

290 *Conclusion*

In sum, we demonstrate that large-scale systematic screening for ACES and early-life unpredictability is feasible in primary care clinics serving diverse communities. Exposures to these types of adversity are prevalent even among the youngest children, and both predict health

294	outcomes. The unpredictability screen (QUIC-5) portends child outcomes at least as well, and in					
295	some cases better, than current ACEs screening (PEARLS-tool) and for some health problems,					
296	the QUIC-5 identifies risk for mental and physical health problems that are not captured by the					
297	ACEs	screen These findings suggest that consideration of unpredictability will (1) identify				
298	childre	n at risk for health problems that will be otherwise missed and (2) may provide a tractable				
299	target	for prevention and intervention in the pediatric primary care setting with the potential to				
300	make r	neaningful positive impacts on child and life-span health.				
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Table 1. Participant Characteristics (N = 29,305).

	n	%			
Child Age					
0-4	5,833	19.9			
5-9	7,909	30.0			
10-14	9,278	31.7			
15-17	6,285	21.4			
Child Race					
Asian	2,892	9.9			
Black	506	1.7			
Native American or Alaskan	114	0.4			
Native Hawaiian	22	0.1			
White	7,400	25.3			
More than one race or other	9,219	30.4			
Unknown	9,152	31.2			
Child Ethnicity					
Hispanic/Latino/a	17,472	58.5			
Not Hispanic/Latino/a	8,903	29.8			
Unknown	3,486	11.7			
Preferred Language					
English	24,263	82.8			
Spanish	5,042	17.2			
Child Gender					
Female	14,169	48.4			
Male	15,136	51.6			
Insurance					
Public	20,112	68.7			
Private	9,041	30.9			
Self or Other	152	0.5			
health records. Race, ethnicity, and gender were collected from the caregiver at initial registration. Preferred language					

from the caregiver at initial registration. Preferred language indicates the language in which the screens were administered. Insurance status was determined from the visit concurrent with screening.



Figure 1. Distribution of ACEs (PEARLS) and unpredictability (QUIC-5) by child age.



Figure 2. Distribution of ACEs (PEARLS; Panel A) and unpredictability (QUIC-5; Panel B) by caregiver report and youth self-report.

Figure 3. ACEs (PEARLS) and unpredictability (QUIC-5) screens predict child mental health outcomes. Odds ratios and 95% confidence intervals. Panels A-B show associations for caregiver reports. Youth self-report in panels C-D.



Figure 4. ACEs (PEARLS) and unpredictability (QUIC-5) screens predict child physical health outcomes. Odds ratios and 95% confidence intervals. Panels A-B show associations for caregiver reports. Youth self-report in panels C-D.



Figure 5. ACEs (PEARLS) and unpredictability (QUIC-5) screens independently predict child mental and physical health outcomes. Odds ratios and 95% confidence intervals. Panels A-B show associations for caregiver reports. Youth self-report in panels C-D.



Figure 6. Evaluation of the independent and combined predictive power of ACEs (PEARLS) and unpredictability (QUIC) screens. Examples shown here are for youth self-report. Results for both youth and caregiver reports for all diagnoses can be found in Table S11.

Depression						
	4+	11.8 (5.1-27.2)	3.6 (.83-15.9)	5.2 (1.7-15.5)	5.9 (1.7-20.6)	13.0 (7.8-21.7)
RE	3	1.1 (.34-3.6)	1.3 (.32-5.6)	3.3 (1.2-9.6)	14.0 (7.0-28.0)	8.4 (5.0-14.1)
SCC	2	2.0 (1.2-3.4)	2.3 (1.0-5.2)	2.9 (1.1-7.6)	4.3 (1.6-11.3)	6.4 (2.7-15.0)
QUIC 8	1	1.3 (.84-2.0)	4.4 (2.6-7.4)	3.0 (1.2-7.1)	2.7 (.82-9.2)	9.5 (4.0-23.0)
	0	Ref	3.2 (1.9-5.3)	3.3 (1.4-8.0)	7.8 (2.5-23.9)	7.9 (2.1-28.7)
		0	1	2	3	4+
PEARLS SCORE						

OR
LE 1.0
1.1-1.9
2.0-2.9
3.0-3.9
GE 4.0

Sleep Disorders						
	4+	2.5 (.89-7.1)	5.1 (2.1-12.4)	3.2 (1.1-9.3)	4.8 (1.6-14.1)	5.4 (3.2-9.2)
RE	3	4.0 (2.4-6.4)	2.4 (1.0-5.7)	1.8 (.65-5.1)	5.7 (2.8-11.6)	4.1 (2.4-6.9)
QUIC SCO	2	2.2 (1.5-3.2)	2.0 (1.1-3.8)	2.0 (.84-4.6)	4.4 (2.0-9.4)	2.1 (.74-5.9)
	1	1.3 (.93-1.8)	2.6 (1.6-4.1)	2.7 (1.3-5.6)	1.8 (.54-5.7)	1.3 (.31-5.4)
	0	Ref	1.6 (.98-2.7)	1.7 (.68-4.3)	1.8 (.43-7.7)	0.0 (0.0)
		0	1	2	3	4+
PEARLS SCORE						

Obesity							
	4+	2.6 (1.5-4.6)	1.6 (.87-3.1)	2.6 (1.4-4.8)	1.8 (.85-3.8)	2.0 (1.4-2.9)	
RE	3	1.7 (1.3-2.3)	1.5 (.97-2.4)	1.3 (.82-2.2)	1.4 (.86-2.4)	1.5 (1.1-2.1)	
SCC	2	1.5 (1.3-1.8)	1.6 (1.2-2.2)	1.3 (.83-1.9)	1.2 (.69-2.0)	1.9 (1.2-3.2)	
	1	1.3 (1.1-1.5)	1.2 (.91-1.5)	1.2 (.78-1.8)	2.2 (1.3-3.7)	1.1 (.59-2.0)	
g	0	Ref	1.0 (.82-1.3)	1.5 (.95-2.2)	1.8 (.92-3.6)	.90 (.35-2.4)	
		0	1	2	3	4+	
PEARLS SCORE							