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Longitudinal Trajectory of Adaptive Skills in Phelan-McDermid Syndrome

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Abstract:	Phelan-McDermid syndrome (PMS), caused by SHANK3 haploinsufficiency, lacks natural history data. We report the trajectory of adaptive behavior from a prospective, longitudinal, natural history study. Individuals, age 3-21 years, with a PMS diagnosis were followed over 2 years. We analyzed longitudinal Vineland Adaptive Behavior Scales, Second Edition domain-level standard scores and subdomain-level growth scale values (GSVs) obtained at baseline, 12 months, and 24 months. We assessed within-subject time effects and cross-sectional age effects using linear mixed effects models. This sample included 99 participants (baseline age=8.83±4.58 years). Within-subject standard scores decreased/remained constant for all domains: Communication (slope of within-subject mean-centered age=-0.33 [95% CI -1.08,0.41]; p=0.38), Socialization (-1.25 [-1.95,-0.56]; p<0.001), and Daily Living Skills (-0.35 [-1.37,0.67]; p=0.50). However, subdomain GSVs showed within-subject growth across several categories. Receptive (5.26 [2.49,8.02]; p<0.001) and Written (2.79 [1.11,4.47]; p=0.001) Communication GSVs increased. Personal (1.84 [0.81,2.86]; p<0.001) and Domestic (2.31 [0.98,3.64]; p<0.001) Daily Living Skills GSVs increased. Socialization subdomain GSVs did not change. PMS is characterized by slow, small gains in communication and daily living but not socialization skills as measured by subdomain GSVs. Unlike standard scores, measuring performance compared to same-age peers, GSVs quantify an individual's progress, emphasizing GSVs in interpreting developmental changes in PMS.

ABSTRACT

Purpose: Phelan-McDermid syndrome (PMS), caused by *SHANK3* haploinsufficiency, lacks natural history data. We report the trajectory of adaptive behavior from a prospective, longitudinal, natural history study.

Methods: English-speaking individuals, age 3-21 years, with a PMS molecular diagnosis were followed over 2 years. We analyzed longitudinal Vineland Adaptive Behavior Scales, Second Edition domain-level standard scores and subdomain-level growth scale values (GSVs) obtained at baseline, 12 months, and 24 months. We assessed within-subject time effects and cross-sectional age effects using linear mixed effects models.

Results: This sample included 99 participants (baseline age=8.83±4.58 years). Within-subject standard scores decreased/remained constant for all domains: Communication (slope of within-subject mean-centered age=-0.33 [95% CI -1.08,0.41]; p=0.38), Socialization (-1.25 [-1.95,-0.56]; p<0.001), and Daily Living Skills (-0.35 [-1.37,0.67]; p=0.50). However, subdomain GSVs showed within-subject growth across several categories. Receptive (5.26 [2.49,8.02]; p<0.001) and Written (2.79 [1.11,4.47]; p=0.001) Communication GSVs increased. Personal (1.84 [0.81,2.86]; p<0.001) and Domestic (2.31 [0.98,3.64]; p<0.001) Daily Living Skills GSVs increased. Socialization subdomain GSVs did not change.

Conclusion: PMS is characterized by impaired adaptive behavior and slow, small gains in communication and daily living but not socialization skills as measured by subdomain GSVs. Unlike standard scores, measuring performance compared to same-age peers, GSVs quantify an *individual's* progress, emphasizing need for GSVs in interpreting developmental changes in PMS.

KEYWORDS

Phelan-McDermid syndrome, SHANK3, intellectual disability, 22q13 deletion, autism spectrum disorder, Vineland Adaptive Behavior Scales, growth scale values, developmental trajectories

INTRODUCTION

Phelan-McDermid syndrome (PMS) is a genetic condition caused by either a 22q13 deletion including *SHANK3* or a pathogenic intragenic variant in *SHANK3*. Affected individuals can present with a wide spectrum of systemic abnormalities and neurodevelopmental challenges. Systemic features include congenital heart defects, structural kidney defects, and lymphedema. Neurological and neurodevelopmental challenges encompass intellectual disability (ID; often in the severe-to-profound range), autism spectrum disorder (ASD), epilepsy, regression, and other psychiatric disorders [1].

Currently, there are no treatments approved for use by the United States (US) Food and Drug Administration (FDA) for PMS. However, over the past two decades, there have been several small interventional clinical trials for this condition. Trials have evaluated insulin-like growth factor-1 [2,3], recombinant human growth hormone [4,5], intranasal oxytocin [6], and intranasal insulin [7,8]. Clinical outcome measures have included metrics of social communication, repetitive behaviors, and other maladaptive behaviors. Given the continued emergence of possible therapeutics for PMS, there is a great need to understand the natural history of the disorder, especially pertaining to cognitive and developmental domains targeted by emerging targeted treatments. Adaptive behavior in particular is an important outcome for treatment of this condition, given that it provides a measure of general daily functioning, an area highlighted by the FDA [9]. It is also a criterion used to diagnose ID and designate its severity level. Therefore, it is important to document the degree of impairment and change over time in adaptive behavior in this population. While there is documentation of significantly impaired adaptive behavior in this population cross sectionally [10,11], the longitudinal trajectory is critical to elucidate, as it can serve as a reference for future clinical trials examining adaptive functioning over time.

Here, we report initial results of a prospective, longitudinal, multi-site, natural history study of PMS which included longitudinal assessments of adaptive functioning over a two-year period. We focused on adaptive skills as measured by the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) with both standard scores and growth scale values (GSVs). The latter provides a more granular assessment of change within an individual, as opposed to standard scores, which assess functioning relative to same age, typically developing peers.

METHODS

Study Participants

We analyzed data collected from a prospective, multi-site, observational study evaluating the phenotype and natural history of PMS (ClinicalTrials.gov NCT02461420), as part of the Developmental Synaptopathies Consortium (DSC) investigating PMS, tuberous sclerosis complex, and PTEN hamartoma tumor syndrome. Sources of participant referrals for the PMS natural history study included the PMS Foundation, clinicians providing care for patients with PMS, and research programs across the US. In order to be eligible for the study, participants had to (1) have a chromosomal 22q13 deletion including *SHANK3* or a pathogenic *SHANK3* sequence variant, (2) be 3-21 years old at the time of enrollment, (3) be in a household where the family spoke and understood English.

The DSC PMS natural history study encompasses two phases: Phase 1 and Phase 2 (Figure 1). Phase 1, which is complete, involved three visits over a two-year period and was the source of data for the analysis in this paper. Phase 2, which is ongoing, includes new participants not previously enrolled as well as participants who already completed Phase 1 and who are undergoing additional longitudinal evaluations.

Neurodevelopmental Assessments

We collected the following measures as part of a larger testing battery completed during yearly visits.

Best Estimate IQ

We generated a best estimate IQ using baseline data. The best estimate IQ is either the IQ based on an IQ measure standardized for chronologic age used or an approximation for IQ using a hierarchy of cognitive/developmental tests. This hierarchy is needed for individuals who are unable to complete the designated IQ assessment either due to their age being outside of the range of the assessment or an inability to achieve a basal score on the assessment [12]. We used the following hierarchy of tests: Stanford Binet Intelligence Scales, Fifth Edition (standardized for age 2 years and older) [13], the Differential Abilities Scales (standardized for age 2 years 6 months through 17 years, 11 months) [14], and the Mullen Scales of Early Learning (standardized for age 0 years through 5 years 8 months) [15]. The best estimate IQ represents a mixture between IQ scores, standard scores, and developmental quotients. Although the current diagnostic criteria for ID emphasize adaptive functioning for designating severity level, here we denoted no ID as having a best estimate IQ $\geq$ 70; mild impairment as having a best estimate IQ of 50-69; moderate impairment as having a best estimate IQ of 35-49; and severe-profound impairment as having a best estimate IQ < 35.

Developmental Regression

We determined if there was a history of developmental regression. We defined regression as the loss (at any age) of previously obtained and consolidated skills present for at least 3 months. We assessed regression using the Autism Diagnostic Interview Revised (ADI-R) [16] Regression Supplement and by caregiver report during the clinical exam.

Vineland Adaptive Behavior Scales, Second Edition (Vineland-II)

The Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) is a standardized assessment of adaptive skills pertaining to the domains of Communication, Socialization, Daily Living Skills, and Motor Skills [17]. We used the comprehensive interview form, which includes clinician administration and scoring based on a semi-structured interview with parents or caregivers. In our analysis, we used the Communication, Socialization, and Daily Living Skills domain standard scores;

Adaptive Behavior Composite standard score; subdomain V-scale scores (which are norm-referenced scores by subdomain that allow for more granular assessment of performance); and subdomain growth scale values (GSVs, which are person ability scores meant to assess change over time). We did not include scores from the Motor Skills domain, as the normative scores only apply to individuals 0-7 years of age. Subdomains are as follows: Receptive Communication, Expressive Communication, and Written Communication subdomains correspond to the Communication domain; Interpersonal Relationships, Play and Leisure Time, and Coping Skills subdomains correspond to the Socialization domain; and Personal Daily Living Skills, Domestic Daily Living Skills, and Community Daily Living Skills subdomains correspond to the Daily Living Skills domain.

Vineland-II domain-level standard scores range from 20 to 160, with a population mean of 100 and a standard deviation of 15. Subdomain level V-scale scores range from 1 to 24, with a population mean of 15 and a standard deviation of 3. For a given subdomain, the actual floor value of the V-scale for that subdomain may vary depending on the age of the participant at the time of evaluation. GSVs [18] were not included in the original Vineland-II manual, but the publisher has since made them available upon request [Pearson, personal communication, 17 March 2022]. Individuals underwent evaluation with the Vineland-II at baseline, 12-month, and 24-month visits. Individuals underwent a larger battery of assessments, but we chose the Vineland-II for this analysis given its suitability for the PMS population with a wide range of ages and developmental levels.

The source data was subdomain raw scores. From these values, we derived scores (standard scores, GSVs, V-scale values, and floor of subdomain V-scale for a given subdomain and age) via automated processing with lookup tables created and validated by one of the study sites (NIH).

Statistical Analysis

We generated linear mixed effects (LME) regression models to determine changes in continuous variables (Vineland-II scores) over time. In each multi-level model, the dependent variable was the

Vineland-II score. We separately modeled each Vineland-II standard score and subdomain GSV. Not every individual had visits at all timepoints, and not every individual had data for every subdomain at each timepoint (see Results below). Fixed effects included the following:

- *between-subjects grand-mean centered age* $_i$. This variable represents the average age of a participant (*i*) across all of that individual's study timepoints for which there was instrument data available. We grand-mean centered this value. This term reflects the between-subject (cross-sectional) effects of age, or the expected difference in outcome for each year difference between a person's average age and the group's average age.
- *within-subject mean-centered age* $_{ij}$. This variable represents the age of a participant (*i*) at a given timepoint (*j*) minus the value of *between-subjects mean age* $_i$ for that participant (i.e., the average age of a participant (*i*) across all of that individual's study timepoints for which there was instrument data available). This term reflects the within-subject effects of age (i.e., expected change for each year in the study).
- Interaction between *between-subjects grand-mean centered age* $_i$ and *within-subject mean-centered age* $_{ij}$. This term allows the within-person trajectory to depend on the cross-sectional effect of age, as might be observed when change is slower or faster for older participants than younger participants.
- Quadratic term of *between-subjects grand-mean centered age* $_i$. Given that in typical development children may progress quickly during younger ages and then more slowly in later ages, we expected the acquisition of developmental milestones to be nonlinear over time. This would require that the difference in performance associated with a 1-year age difference be smaller at older ages than at younger ages.

Random effects included the following:

- Subject-level intercept. This term quantifies variability across participants in their average value of the outcome.

- Subject-level slope of *within-subject mean-centered age* $_{ij}$ (the within-subject effects of age). This term quantifies variability across participants in within-subject change.
- Study site-level intercept. This term quantifies variability in mean outcome value across the six study sites.

We used R (version 4.3.0) to conduct the analysis. For LME modeling, we used the `lmer` function in the `lme4` package (version 1.1.33). In each model, we were interested in the estimated slope of the terms representing the between-subjects effects of age and the within-subject effects of time in study. For the former, the coefficient represented the expected difference in the assessment score for every one year of age difference between two people; for the latter, the coefficient represented the expected change in an individual's assessment score for every one year of study participation. We determined 95% confidence intervals alongside exact uncorrected p-values, as opposed to setting a threshold for statistical significance, as suggested in [19]. We used the `modelsummary` [20] package (version 1.4.1) to generate 95% confidence intervals and p-values for these parameter estimates. To generate 95% confidence intervals around model-predicted values, we used a bootstrap method with `lme4`'s `bootMer` function, specifying 1000 simulations.

For categorical variable descriptives, we presented frequencies, and for continuous variables, we presented means followed by standard deviations after the plus minus symbol (±).

RESULTS

Overview of Cohort, Participant Retention, Missing Data

Out of the 100 participants enrolled in Phase 1 of the DSC, we analyzed data from 99 participants, after excluding one participant who had no Vineland-II data at any timepoint.

There were 79/99 (79.8%) participants who received the Vineland-II at all three timepoints, 16/99 (16.2%) participants who received the Vineland-II at two timepoints, and 4/99 (4.0%) participants who

received the Vineland-II at one timepoint. For n=94 participants, at any given timepoint, if the participant received the Vineland-II, there was data available for *all* the Vineland-II domain standard scores and all the subdomain GSVs. The remaining five participants had missing data at some timepoints with respect to the Written Communication GSV (n=4 with missing data for that subdomain at one timepoint, n=1 with missing data at two timepoints).

There were two participants with a baseline best estimate IQ that could not be computed. One participant completed some subtests of the Differential Abilities Scales but not enough to receive an IQ score. The other participant withdrew from the study and did not have a best estimate IQ generated; we included other available data for this participant in the analysis.

Demographics, Intellectual Disability, History of Developmental Regression

The cohort was 46.5% female (n=46) (Table 1). The average age at enrollment was 8.83 ± 4.58 years (n = 99). The baseline mean best estimate IQ of the cohort was 26.11 ± 17.93 (range: 3.4 – 88) (n = 97), with n = 2 with no ID, n = 7 with mild impairment, n = 22 with moderate impairment, and n = 66 with severe-profound impairment. Forty-three percent (n = 42) had a history of developmental regression,

Adaptive Functioning

Baseline adaptive characteristics of the cohort showed overall moderate impairments in adaptive abilities as assessed by Vineland-II standard scores (Table 1). The mean Vineland-II Adaptive Behavior Composite standard score was 51.11 ± 13.74 [range 25-86] (n = 99). Among the baseline scores pertaining to the Vineland-II non-motor subdomains, the Communication standard score was the lowest (50.17 ± 15.24 [range 26-91]), while the Socialization standard score was the highest (56.87 ± 13.91 [range 34-101]). Vineland-II Adaptive Behavior Composite standard score and non-motor domain standard scores correlated strongly with baseline best estimate IQ (Spearman rank correlation; rho = 0.82-0.87, all $p < 0.001$).

Characteristics of Vineland-II subdomain V-scale scores are shown in Supplementary Materials S1 and Supplementary Materials S2. At baseline, the percentage of individuals with a Vineland-II subdomain V-scale score at the floor of the subdomain for age was as high as 58.2% (n=57/98) (Written Communication) within the Communication domain; 26.3% (n=26/99) (Coping Skills) within the Socialization domain; and 38.4% (n=38/99) (Domestic Daily Living Skills) within the Daily Living Skills domain. The percentage of participants with a V-scale score at the floor across all timepoints (excluding those participants who had data for only one timepoint) was similarly high for Written Communication (50.0%, n=47/94) and Domestic Daily Living Skills (23.2%, n=22/95). Among those participants with baseline Vineland-II V-scale scores at the floor, all had best estimate IQs in the severe-profound impairment range, except for four participants with moderate best estimate IQ impairment. Of these four participants, one had an Expressive Communication V-scale score at the floor at baseline (and all timepoints); two participants had a Written Communication V-scale score at the floor at baseline (and one additional timepoint, out of one for which the Written raw score was available); and one participant had a Written Communication V-scale score at the floor at baseline (and one out of two additional timepoints).

With respect to each subdomain GSV, the percentage of participants with only one unique (i.e., non-changing) value across timepoints (excluding those who had only one timepoint of data for that value) was as high as 40.4% (n=38/94) for the Written Communication subdomain, 22.1% (n=21/95) for the Domestic Daily Living Skills subdomain, and 16.8% (n=16/95) for the Community Daily Living Skills subdomain (Supplementary Materials S3).

Coefficients from the longitudinal LME models using both standard scores and GSVs are shown in Table 2. Visual depictions of Vineland-II standard scores and associated modeling are shown in Figure 2 and Supplementary Materials S4 (A-D), respectively; visual depictions of Vineland-II GSVs and associated modeling are shown in Figure 3 and Supplementary Materials S4 (E-M), respectively.

In the domain of Communication, there were within-subject increases over the course of the study in Receptive Communication GSVs (slope of within-subject mean-centered age = 5.26 [95% CI: 2.49,

8.02], p < 0.001) and Written Communication GSVs (slope of within-subject mean-centered age = 2.79 [95% CI: 1.11, 4.47], p = 0.001). Expressive Communication GSVs did not change appreciably. These increases in Receptive and Written GSVs were insufficient to increase the Communication standard score (slope of within-subject mean-centered age = -0.33 [95% CI: -1.08, 0.41], p = 0.38).

In the domain of Socialization, within-subject subdomain GSV scores (Interpersonal Relationships, Play and Leisure Time, Coping Skills) did not change over the course of the study (i.e., the 95% CIs of slope of within-subject mean-centered age all included zero). As a result of lack of changes in Socialization subdomain GSVs, the within-person Socialization standard score decreased over the course of the study (slope of within-subject mean-centered age = -1.25 [95% CI: -1.95, -0.56], p < 0.001).

In the domain of Daily Living Skills, we observed increases in within-subject Personal Daily Living Skills (slope of within-subject mean-centered age = 1.84 [95% CI: 0.81, 2.86], p < 0.001) and Domestic Daily Living Skills (slope of within-subject mean-centered age = 2.31 [95% CI: 0.98, 3.64], p < 0.001) subdomain GSVs over the course of the study. However, these increases were not enough to increase the Daily Living Skills standard score: over the study time, the within-subject Daily Living Skills standard score did not change (slope of within-subject mean-centered age = -0.35 [95% CI: -1.37, 0.67], p = 0.50).

With respect to between-subjects effects of age, there was a minor age-related decline in the Vineland-II Socialization standard score (slope of between-subject grand mean centered age = -0.73 [95% CI: -1.45, -0.01]; p = 0.044). There were no changes in Vineland-II Adaptive Behavior Composite standard score (slope of between-subject grand mean centered age = -0.58 [95% CI: -1.30, 0.14]; p = 0.11) or other Vineland-II standard scores cross-sectionally across ages: Communication standard score (slope of between-subject grand mean centered age = -0.30 [95% CI: -1.10, 0.49]; p = 0.45) and Daily Living Skills standard score (slope of between-subject grand mean centered age = -0.62 [95% CI, -1.36, 0.11]; p = 0.10).

We compared the between-subjects and within-subject effects in the models. For each of the models, the coefficient of the interaction between these two terms was small, and the 95% CI for the coefficient included 0 except for Vineland-II Socialization standard score (Table 2). For each model, we plotted predicted output values of the model based on the fixed effects of the model (with no random effects included) for each participant (black lines in each subplot in Figure S4), as well as predicted output values of the model based on the data used for the fit (with no random effects included) vs. between-subjects mean age (red line in each subplot in Figure S4). For each of the Vineland-II subdomain GSVs, when visually comparing the slope of the between-subjects effect at different ages (red line) to the slopes of the within-subject effects at different ages (black lines), we noted differences in the between-subjects effects and within-subject effects; these differences were also apparent when comparing the slopes of the between-subjects and within-subject effects in Table 2.

DISCUSSION

Overview of the Cohort

In this large, prospective, longitudinal cohort of individuals with PMS, we have shown that impairment in adaptive behavior is significant and pervasive across the domains/subdomains assessed. For example, the percentage of individuals in the cohort who had V-scale scores at the floor for age/subdomain at baseline was >15% for six of the nine subdomains, reaching as high as 58.2% for the Written Communication subdomain. Moreover, the percentage of individuals in the cohort who had V-scale scores at the floor across timepoints was similarly high (i.e., > 15%) for five out of these six subdomains.

At baseline, mean Vineland-II domain standard scores ranged from 50.17-56.87 (as shown in Table 1), and the mean Vineland-II Adaptive Behavior Composite standard score was 51.11, suggesting an overall significant impairment, more than 2 standard deviations below the mean. The average baseline Adaptive Behavior Composite standard score in our cohort fell between that for a moderate ID group

(61.1 ± 11.1, 6-17 years) and a severe-profound ID group (41.5 ± 10.1, 6-18 years), as published in the Vineland-II manual [17]. It is important to note that the Vineland-II standard scores in our cohort were potentially higher than what the current version of the Vineland (Vineland-3) may produce. Specifically, the Vineland-II can produce higher standard scores for individuals with moderate to profound impairments compared to Vineland-3 standard scores on the same sample [21]. In other words, standard scores on the Vineland-II may be less sensitive to capturing the level of impaired adaptive behavior in individuals with severe-profound ID. Hence, the values of the standard scores reported in this analysis must be interpreted with caution compared to other analyses using the recently updated Vineland version.

Cross-Sectional Effects of Age

We examined cross-sectional effects of age and showed that there was a decrease in Vineland-II Socialization standard scores with increasing age. These values indicate that individuals with PMS are developing socialization skills much more slowly than their typically developing peers, and that the difference in socialization skills between these groups (PMS vs. typically developing peers) increases with age. With respect to the other Vineland-II domain standard scores and the Adaptive Behavior Composite standard score, there was also increasing levels of impairment with increasing age, but the 95% confidence intervals of the slopes of these terms in the models included zero.

These findings are aligned with data from other studies in neurodevelopmental disorders and in PMS specifically. There is data supporting an inverse relationship between age and Adaptive Behavior Composite standard scores in children with ASD who are verbal (n=1089; ages 4-17 years; adaptive function measured with the Vineland-II) [22], as well as in boys with ASD and a verbal IQ > 70 (n=187; ages 7-18 years; adaptive function measured with the Vineland Adaptive Behavior Scales) [23]. In a study of 181 individuals with ID and one of 5 different genetic syndromes (Down syndrome n=109, Williams syndrome n=12, Angelman syndrome n=16, Prader-Willi syndrome n=18, and Fragile X syndrome n=26), there was an inverse relationship between age and adaptive sills as assessed by the Vineland Adaptive Behavior Scales for the Angelman syndrome group, but not for the other groups [24]. With respect to PMS

specifically, in one study of 60 individuals with PMS (ages 0.9 to 41 years; median: 8.5 years), there was a statistically significant inverse correlation between age and standard scores on Vineland-3 domains (Communication, Daily Living Skills, Socialization) as well as the Adaptive Behavior Composite standard score; however, this data was not longitudinal [25]. Our results expand on this relationship with respect to age, and they highlight that out of all the adaptive domains measured by the Vineland-II, the Socialization standard score specifically was associated with declines cross-sectionally with increasing age. We expect that this is not a cohort effect, as one would expect all developmental domains to be affected like this; rather, this result may reflect a greater impairment in the development of socialization skills associated with the underlying disease pathophysiology of PMS.

Longitudinal Effects of Time

The within-subject results were also broadly consistent with the between-subjects trends across ages, as shown in Table 2. Within a given individual, there were mild gains in adaptive communication skills and daily living skills — but no changes in adaptive socialization skills — over the 2-year period, as measured by Vineland-II GSVs. The small gains in Communication and Daily Living Skills subdomain GSVs were insufficient to increase the associated domain standard scores; moreover, the lack of gains in socialization GSVs were associated with decreases in the Socialization standard score over time.

Even with these trends, the participants exhibited broad variability in adaptive and cognitive skills. While most participants were in the severe-profound impairment range based on their best-estimate IQ, there were some individuals in the mild/moderate impairment range. These individuals were more likely to produce Vineland-II scores above the floor, allowing for measurable change over time. However, there were also subgroups of participants who demonstrated either no or minimal gains in adaptive skills, even measured by Vineland-II GSVs over the two years of this study. For example, the Vineland-II Written Communication, Domestic Daily Living Skills, and Community Daily Living Skills subdomains were each associated with > 15% of participants having non-changing GSVs across study timepoints. Moreover, with respect to some subdomains like Vineland-II Expressive Communication and Written

Communication, there seemed to be a divide between some participants who seemed to progress and those whose skills did not change measurably, as seen visually in Figure 3. These results point to the need for more sensitive measures that can capture the subtle developmental growth of this population.

It is important to note that our LME models (1) allow for each participant to have their own trajectory via a random slope and intercept, and (2) estimate an average trajectory for the outcome variable using fixed effects predictors. This approach allows us to account for variability within the population without removing it. In this analysis, we have examined the outcome variable (Vineland-II scores) in terms of age and time in the study. In each of the models, the between-subjects effects and within-subject effects differed, suggesting that the differences between older and younger were not due entirely to the developmental course and may have been due to cohort effects. Additional analyses of outcomes could include genotype information, medical or intervention history, and other factors that might explain variability in the individual intercept and slope.

Our data support prior findings in other genetic NDD populations where a lack of progress or only mild gains in adaptive subdomain skills are mirrored by declining or plateaued Vineland-II standard scores [26–28]. Unlike standard scores, which measure a child's ability compared to same age peers (and thus may plateau or even show declines in spite of a child making developmental progress), GSVs allow quantification of an individual's progress, especially if the individual is making gains that are small relative to developmental expectations or that are beneath the norm-referenced floor [29,30]. These results emphasize the need for GSVs in interpreting change over time in PMS – an important concept for clinical trial readiness. Theoretical and psychometric support for this approach is amassing, including from simulation [31], natural history studies of other genetic disorders (e.g., creatine transporter deficiency [32], mucopolysaccharidosis, and CNL3 Batten disease [33]), and re-analysis of clinical trial data [34].

LIMITATIONS

Our study had some notable limitations. First, since this study was initiated before the Vineland-3 was published, we were unable to use this later version, which includes additional items that better characterize individuals scoring far from the mean, such as those with severe/profound ID [21]. We observed floor effects in several of the Vineland-II subdomains, which may be less pronounced with use of the newer version. The Vineland-3 also publishes GSVs with the measure and includes reports that show whether change exceeds a confidence interval constructed using the standard error of measurement, which is required for clinical interpretation of GSVs. These changes are important to consider when generalizing findings from the Vineland-II to future results from this population with the new version [21]. In addition, the presence of floor effects indicates limitations with use of this measure in the context of a clinical trial, underscoring the need for continued improvements in measures specifically for a population enriched with severe/profound ID. Second, the overall study duration of the current analyses was only two years, and additional timepoints are needed to further assess the longitudinal neurobehavioral profile of PMS. Further longitudinal data will be especially important in the use of these findings for clinical trial applications, since therapeutic trials may need to last several years to illustrate the developmental gains of any disease modifying treatments. Third, this analysis only included adaptive behavior, as it was deemed the most appropriate measure of this population given the extensive associated cognitive impairment. Analyses with additional measures are ongoing. Fourth, the Vineland-II is based on parental report rather than direct observation of functional abilities. Other measures of adaptive ability in the research setting include the Adaptive Behavior Assessment System, Third Edition (ABAS-3), used for individuals with ASD [35] and other genetic neurodevelopmental disorders like Kleefstra Syndrome [36]. However, there are practical issues with use of the ABAS-3: although the instrument is meant for infants to adults, age-equivalents are not available for those with developmental ages < 5 years who receive the parent form for ages 5-21 years or adult form. Therefore, several versions of the instrument may be needed to fully encapsulate a wide range of adaptive abilities. In addition to adaptive skills, others domains important for assessment in PMS include repetitive behaviors (such as with the Repetitive Behavior Scales-Revised as investigated as part of baseline analysis of the current natural history study [37]); other maladaptive

behaviors (such as with the Aberrant Behavior Checklist as utilized in clinical trials for PMS [2,6]); and communication (such as with the Expressive Vocabulary Test Third Edition and Peabody Picture Vocabulary Test Fifth Edition).

Finally, we did not fully capture characteristics of developmental regression, such as age of onset and duration, in this present work, but these aspects are characterized in parallel work [38]. It is worthwhile to note that in our analysis we used GSVs which are responsive to skill losses, unlike standard scores for which a decrease could signify (a) skill loss (b) skill stability, or (c) slower-than-expected developmental growth. Thus, our models allow for "developmental regression" at the individual level and would be modeled if present.

CONCLUSIONS

This study has provided an initial characterization of the longitudinal trajectory of adaptive skills in PMS. We have shown that over a two-year follow-up period, individuals with PMS had mild gains in communication skills and daily living skills, as assessed by Vineland-II subdomain GSVs, but these gains were insufficient to increase the corresponding standard scores. Future clinical trials in PMS should not rely on standard scores alone, but rather incorporate use of GSVs or other (potentially new) measures that more sensitively capture the subtle developmental trajectory of this population.

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Table 1. Demographic characteristics and baseline Vineland-II standard scores. n = 99 for all variables except for baseline best estimate IQ (n = 97).

Variable	**Value**
	n / N (%) or mean ± SD
Sex	
female	46 / 99 (46%)
male	53 / 99 (54%)
Age at enrollment (years)	8.83 ± 4.58
Baseline best estimate IQ	26.11 ± 17.93
Vineland-II Adaptive Behavior Composite standard score	51.11 ± 13.74
Vineland-II Communication standard score	50.17 ± 15.24
Vineland-II Socialization standard score	56.87 ± 13.91
Vineland-II Daily Living Skills standard score	51.51 ± 14.67

Table 2. Linear mixed effects regression model results of the longitudinal Vineland-II subdomain GSVs and standard scores, showing coefficients, 95% confidence intervals (CIs), t-statistic, and p-values.

Vineland-II score	within-subject mean-centered age	within-subject mean-centered age * between-subjects grand-mean centered age	between-subjects grand-mean centered age	between-subjects grand-mean centered age ^ 2
Adaptive Behavior Composite standard score	-0.397 [-1.060, 0.267], t = -1.177, p = 0.240	0.034 [-0.108, 0.177], t = 0.472, p = 0.637	-0.581 [-1.300, 0.138], t = -1.591, p = 0.113	-0.090 [-0.213, 0.032], t = -1.457, p = 0.146
Communication standard score	-0.338 [-1.089, 0.412], t = -0.888, p = 0.376	0.075 [-0.086, 0.236], t = 0.913, p = 0.362	-0.308 [-1.105, 0.489], t = -0.761, p = 0.447	-0.098 [-0.234, 0.039], t = -1.411, p = 0.159
Receptive Communication GSV	5.255 [2.485, 8.024], t = 3.736, p = <0.001	0.008 [-0.587, 0.602], t = 0.025, p = 0.980	3.833 [1.441, 6.225], t = 3.155, p = 0.002	-0.228 [-0.636, 0.181], t = -1.098, p = 0.273
Expressive Communication GSV	0.190 [-2.566, 2.946], t = 0.136, p = 0.892	0.041 [-0.552, 0.633], t = 0.135, p = 0.893	5.227 [2.024, 8.429], t = 3.213, p = 0.001	-0.388 [-0.923, 0.146], t = -1.431, p = 0.154
Written Communication GSV	2.793 [1.112, 4.474], t = 3.272, p = 0.001	0.078 [-0.279, 0.436], t = 0.432, p = 0.666	5.412 [2.925, 7.900], t = 4.285, p = <0.001	-0.334 [-0.744, 0.077], t = -1.602, p = 0.110
Socialization standard score	-1.258 [-1.955, -0.561], t = -3.555, p = <0.001	0.193 [0.043, 0.342], t = 2.539, p = 0.012	-0.736 [-1.453, -0.018], t = -2.019, p = 0.044	-0.024 [-0.147, 0.098], t = -0.394, p = 0.694
Interpersonal Relationships GSV	1.597 [-0.352, 3.545], t = 1.614, p = 0.108	-0.010 [-0.428, 0.409], t = -0.046, p = 0.964	3.241 [1.210, 5.273], t = 3.142, p = 0.002	-0.284 [-0.624, 0.056], t = -1.643, p = 0.102
Play and Leisure Time GSV	0.339 [-2.276, 2.954], t = 0.255, p = 0.799	0.293 [-0.268, 0.854], t = 1.028, p = 0.305	2.976 [0.766, 5.187], t = 2.651, p = 0.009	-0.254 [-0.630, 0.123], t = -1.325, p = 0.186
Coping Skills GSV	0.992 [-0.333, 2.316], t = 1.474, p = 0.142	0.050 [-0.235, 0.334], t = 0.343, p = 0.732	1.966 [1.100, 2.831], t = 4.471, p = <0.001	-0.082 [-0.227, 0.062], t = -1.126, p = 0.261
Daily Living Skills standard score	-0.351 [-1.375, 0.672], t = -0.676, p = 0.500	0.015 [-0.204, 0.235], t = 0.138, p = 0.891	-0.627 [-1.368, 0.114], t = -1.665, p = 0.097	-0.104 [-0.231, 0.023], t = -1.615, p = 0.108
Personal Daily Living Skills GSV	1.837 [0.813, 2.861], t = 3.533, p = <0.001	-0.043 [-0.263, 0.177], t = -0.385, p = 0.701	3.446 [2.155, 4.736], t = 5.258, p = <0.001	-0.159 [-0.376, 0.058], t = -1.446, p = 0.149
Domestic Daily Living Skills GSV	2.308 [0.977, 3.638], t = 3.416, p = <0.001	0.030 [-0.255, 0.316], t = 0.210, p = 0.834	3.018 [1.897, 4.140], t = 5.298, p = <0.001	-0.185 [-0.376, 0.007], t = -1.901, p = 0.058
Community Daily Living Skills GSV	1.560 [-0.220, 3.341], t = 1.725, p = 0.086	0.011 [-0.372, 0.394], t = 0.056, p = 0.955	3.801 [2.138, 5.465], t = 4.499, p = <0.001	-0.267 [-0.536, 0.002], t = -1.951, p = 0.052

Figure 1. Flow chart of participant visits in the Developmental Synaptopathies Consortium natural history study of PMS. This paper analyzed data collected during Phase 1 of this study (Baseline – Year 2).

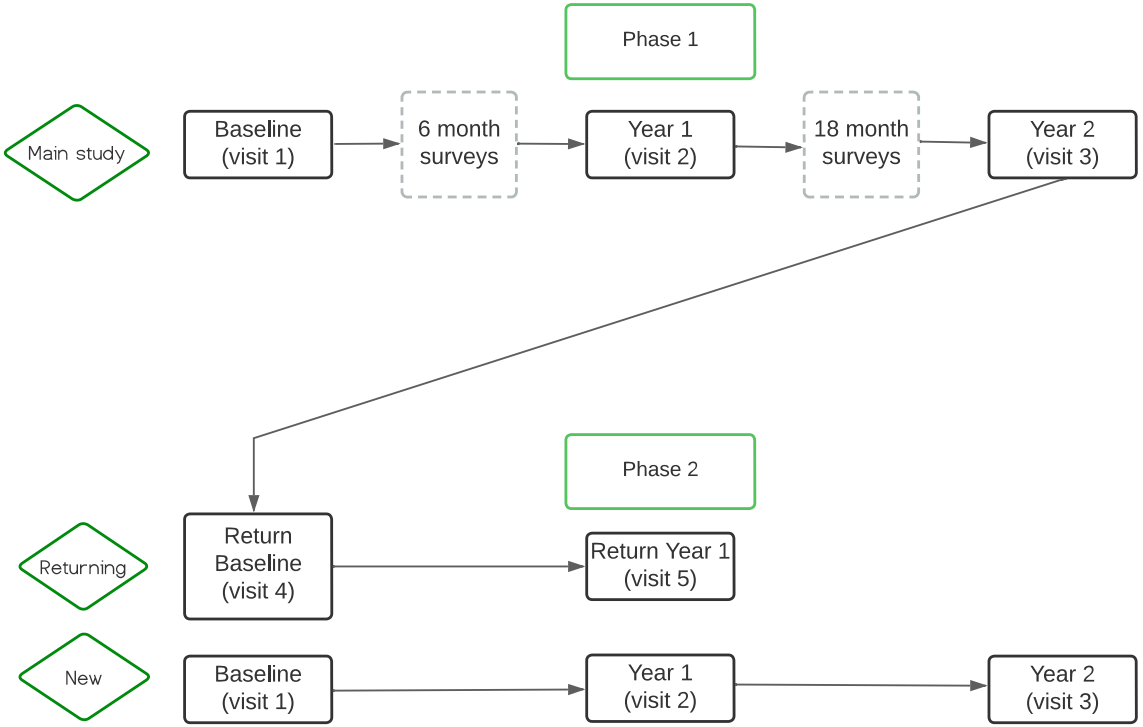


Figure 2. Spaghetti plot of longitudinal Vineland-II standard scores. Vineland-II standard scores have a population mean of 100 and standard deviation of 15.

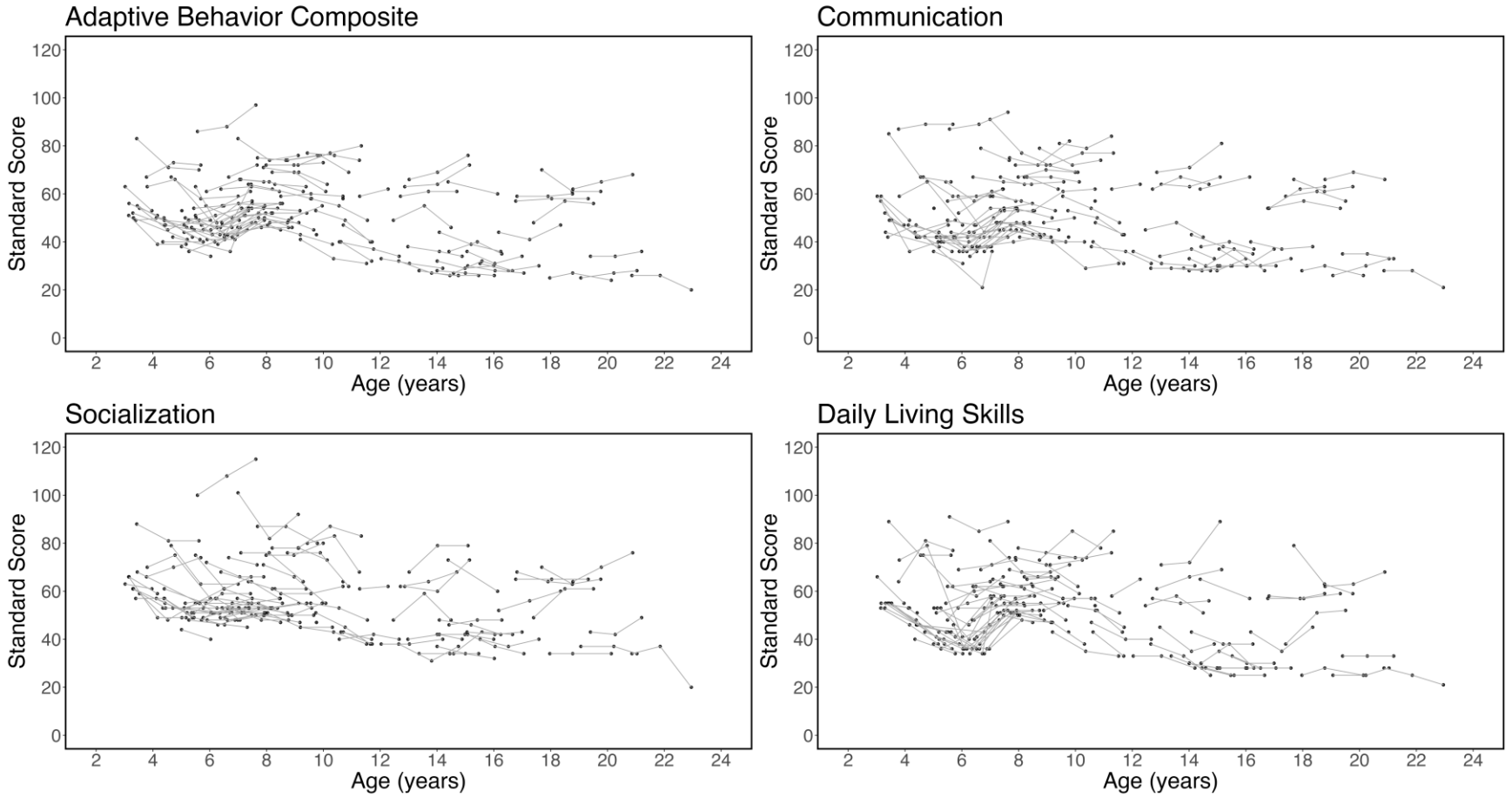
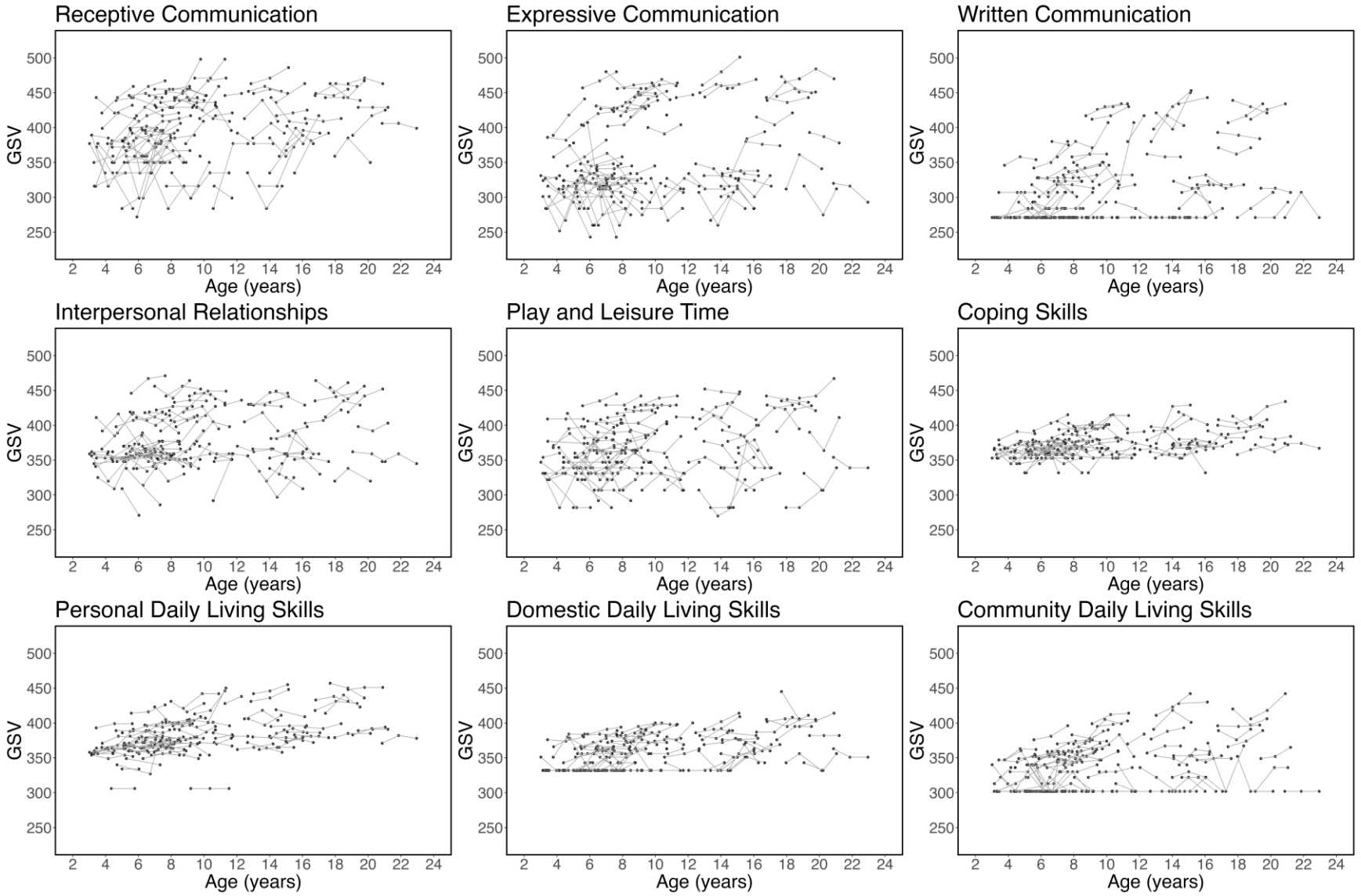


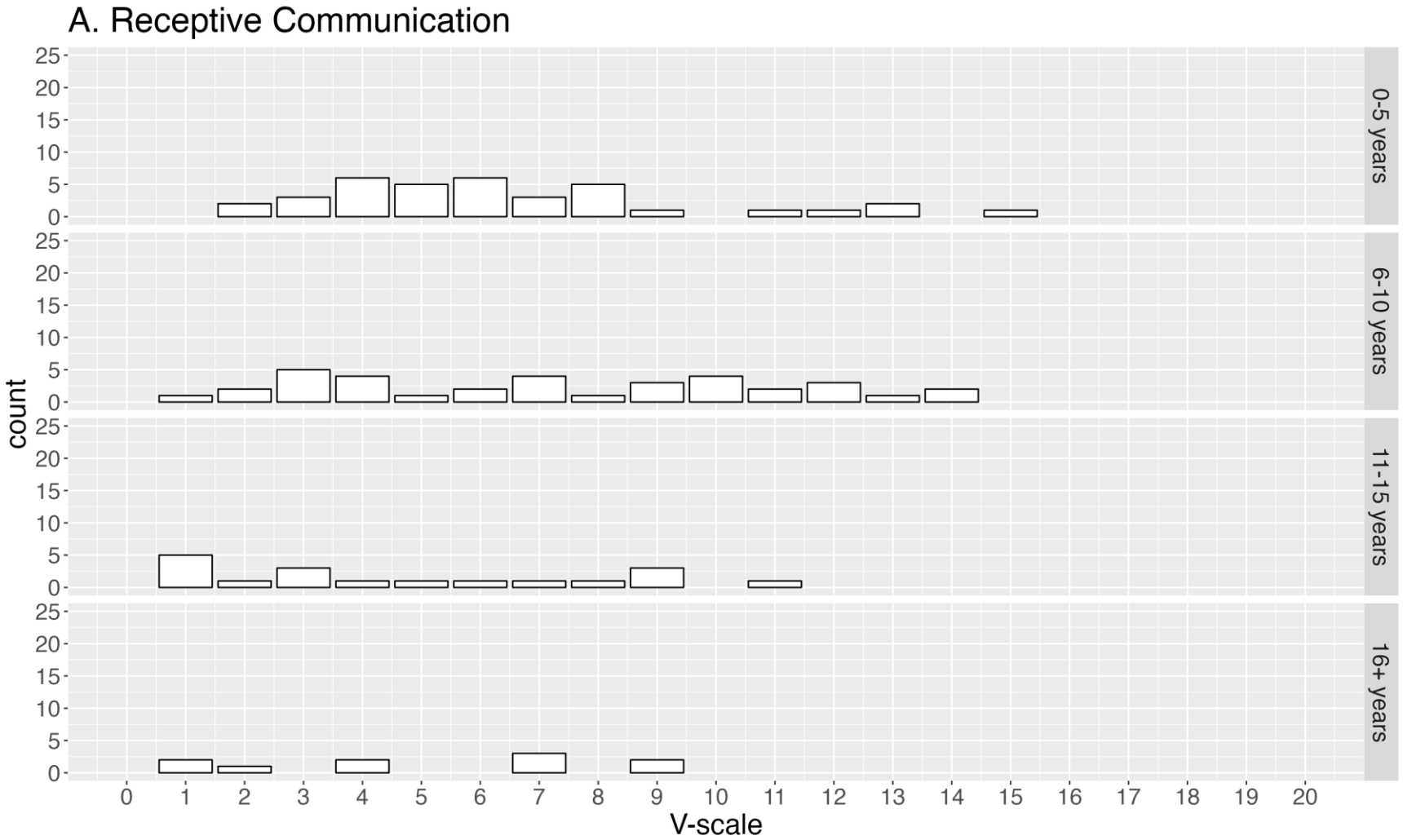
Figure 3. Spaghetti plot of longitudinal Vineland-II GSVs. The ranges and distributions of GSVs are specific to each subdomain; scores are comparable within each graph but not across subdomains.

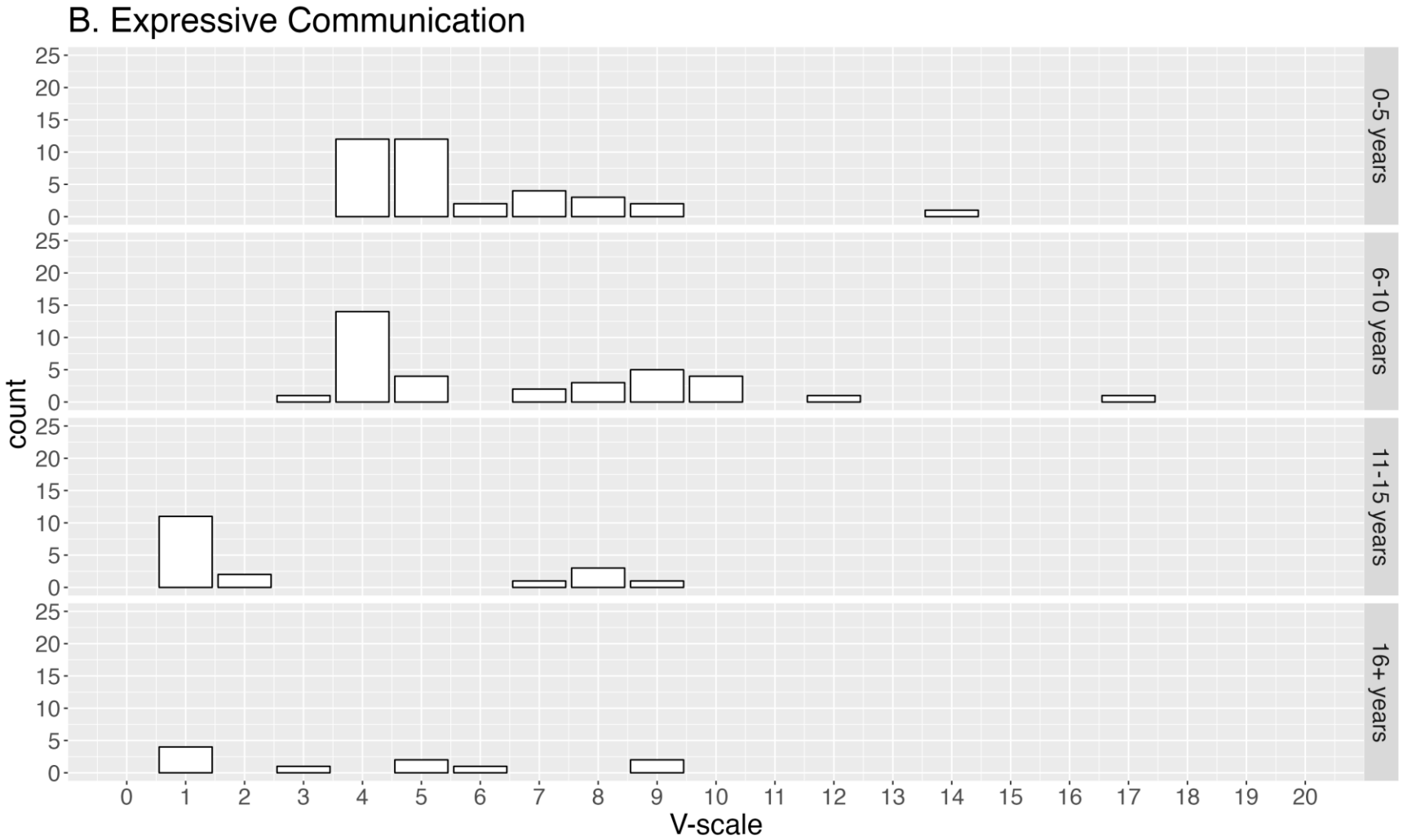

Receptive Communication
Expressive Communication
Written Communication
Interpersonal Relationships
Play and Leisure Time
Coping Skills
Personal Daily Living Skills
Domestic Daily Living Skills
Community Daily Living Skills
GSV
Age (years)

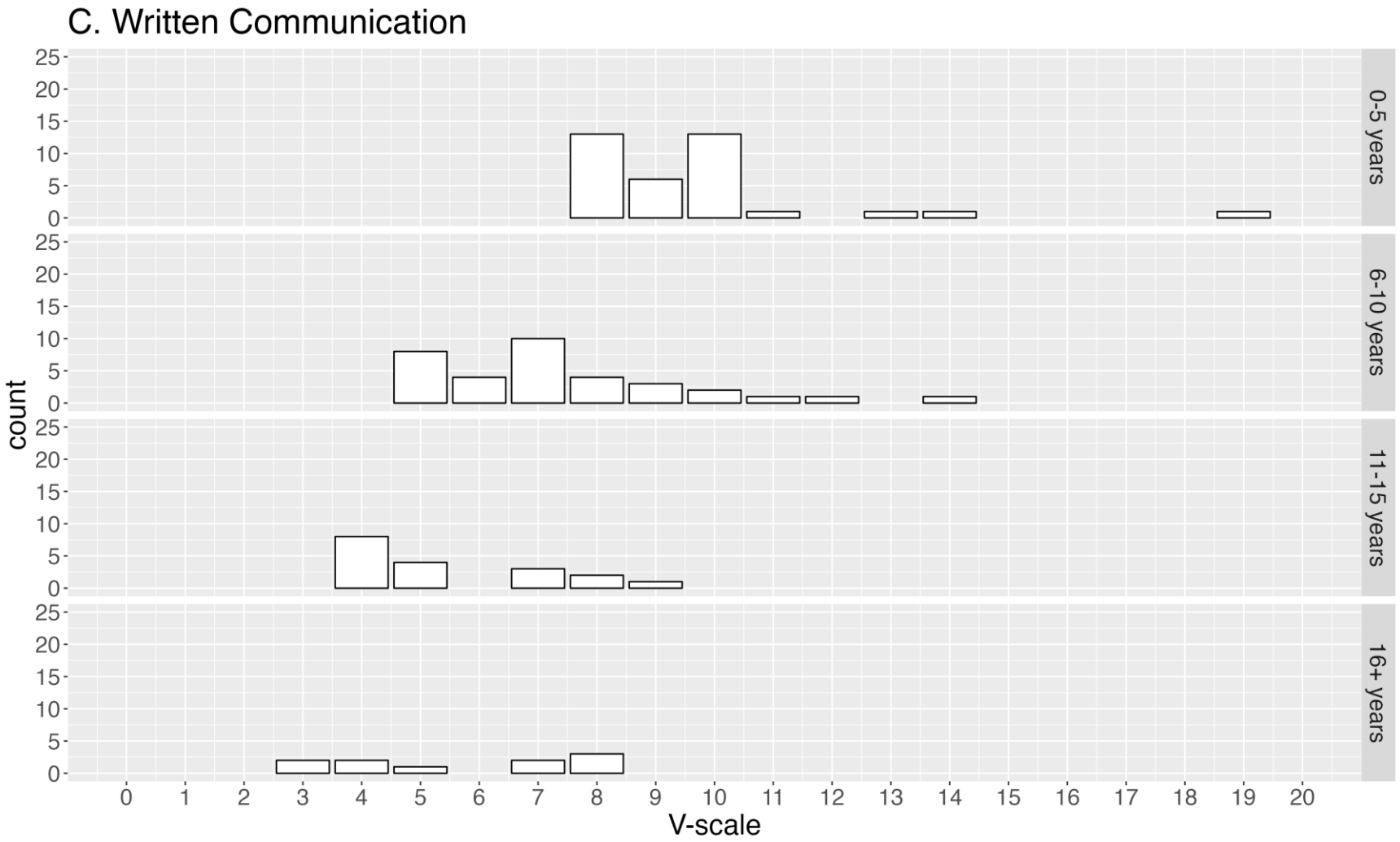
Supplementary Materials S1. Characteristics of Vineland-II subdomain V-scale scores. Vineland-II V-scale scores have a population mean of 15 and standard deviation of 3. While the range of possible V-scale scores is 1 to 24, the actual basal value or "floor" V-scale score for each subdomain is age dependent. The floor values presented here represent the lowest possible V-scale score that individual could obtain. The percentage of individuals with a Vineland-II subdomain V-scale score at floor across all timepoints excludes those with data available only for one visit.

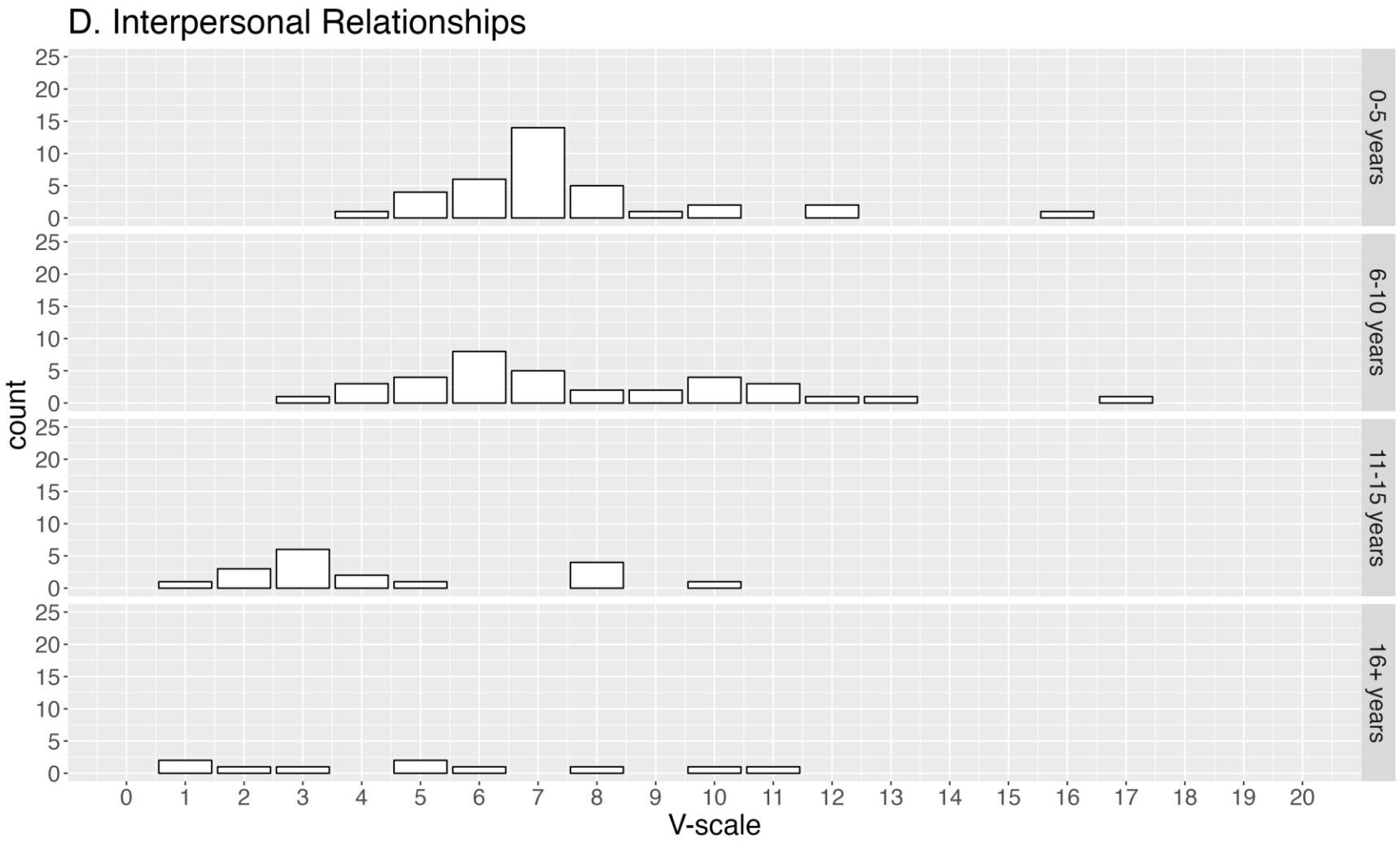
subdomain	Percentage of participants with baseline V-scale values at floor	Percentage of participants with V-scale values at floor across timepoints	Percentage of total number of V-scale datapoints/observations that are at the floor
Receptive Communication	10 / 99 (10.1%)	1/95 (1.1%)	23/273 (8.4%)
Expressive Communication	15 / 99 (15.2%)	15/95 (15.8%)	50/273 (18.3%)
Written Communication	57 / 98 (58.2%)	47/94 (50%)	148/267 (55.4%)
Interpersonal Socialization	3 / 99 (3.0%)	1/95 (1.1%)	14/273 (5.1%)
Play Socialization	11 / 99 (11.1%)	8/95 (8.4%)	42/273 (15.4%)
Coping Socialization	26 / 99 (26.3%)	5/95 (5.3%)	52/273 (19%)
Personal Daily Living Skills	16 / 99 (16.2%)	15/95 (15.8%)	50/273 (18.3%)
Domestic Daily Living Skills	38 / 99 (38.4%)	22/95 (23.2%)	99/273 (36.3%)
Community Daily Living Skills	31 / 99 (31.3%)	21/95 (22.1%)	96/273 (35.2%)

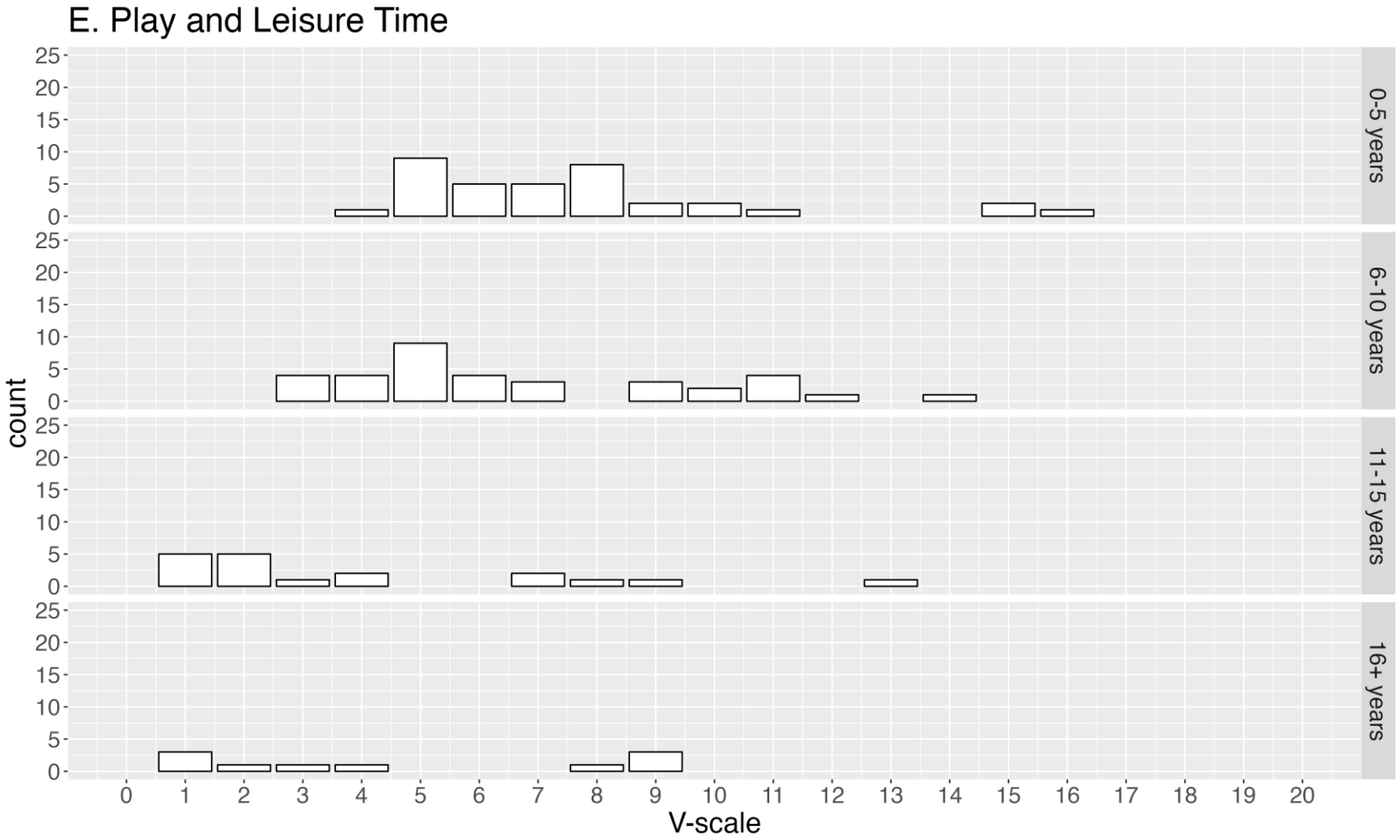
Supplementary Materials S2. Histogram of baseline Vineland-II V-scale scores, stratified by age group, for each of the subdomains (A-I). Age groupings are for illustrative purposes only and were not used in analysis. Vineland-II V-scale scores have a population mean of 15 and standard deviation of 3. The lowest possible V-scale score for each subdomain is age dependent.

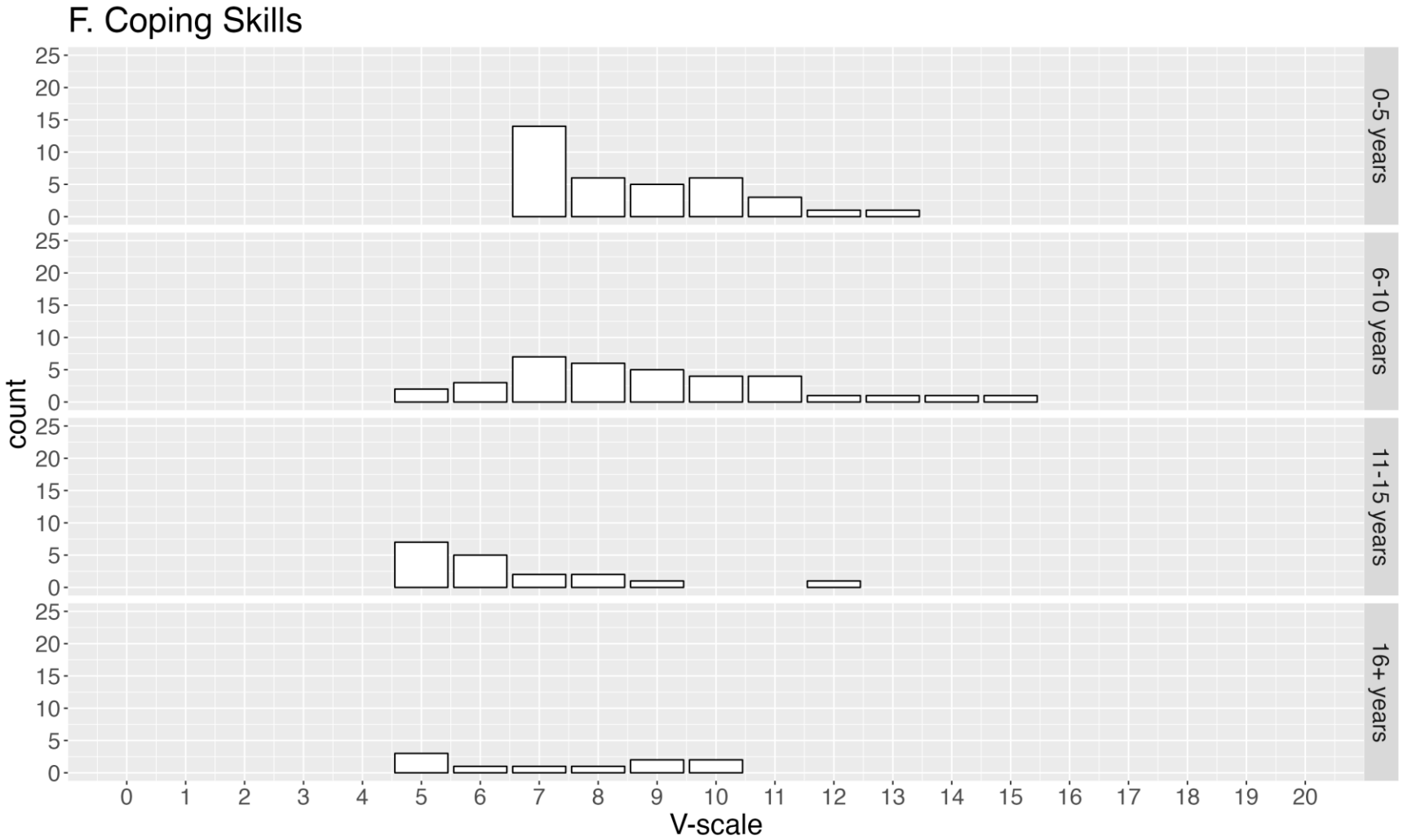

A. Receptive Communication
count
V-scale
0-5 years
6-10 years
11-15 years
16+ years
0
5
10
15
20
25
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

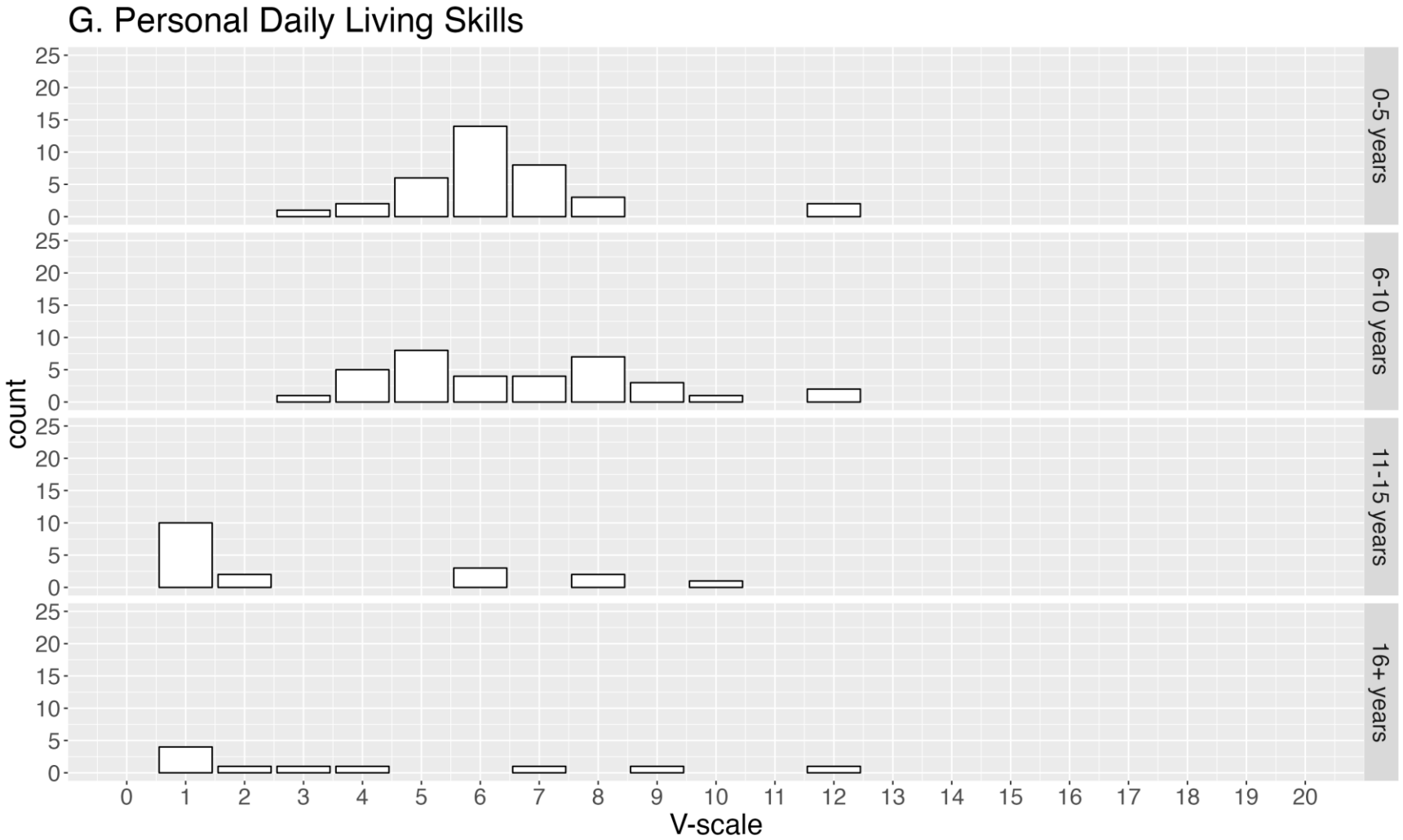

B. Expressive Communication
count
V-scale
0-5 years
6-10 years
11-15 years
16+ years
0
5
10
15
20
25
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

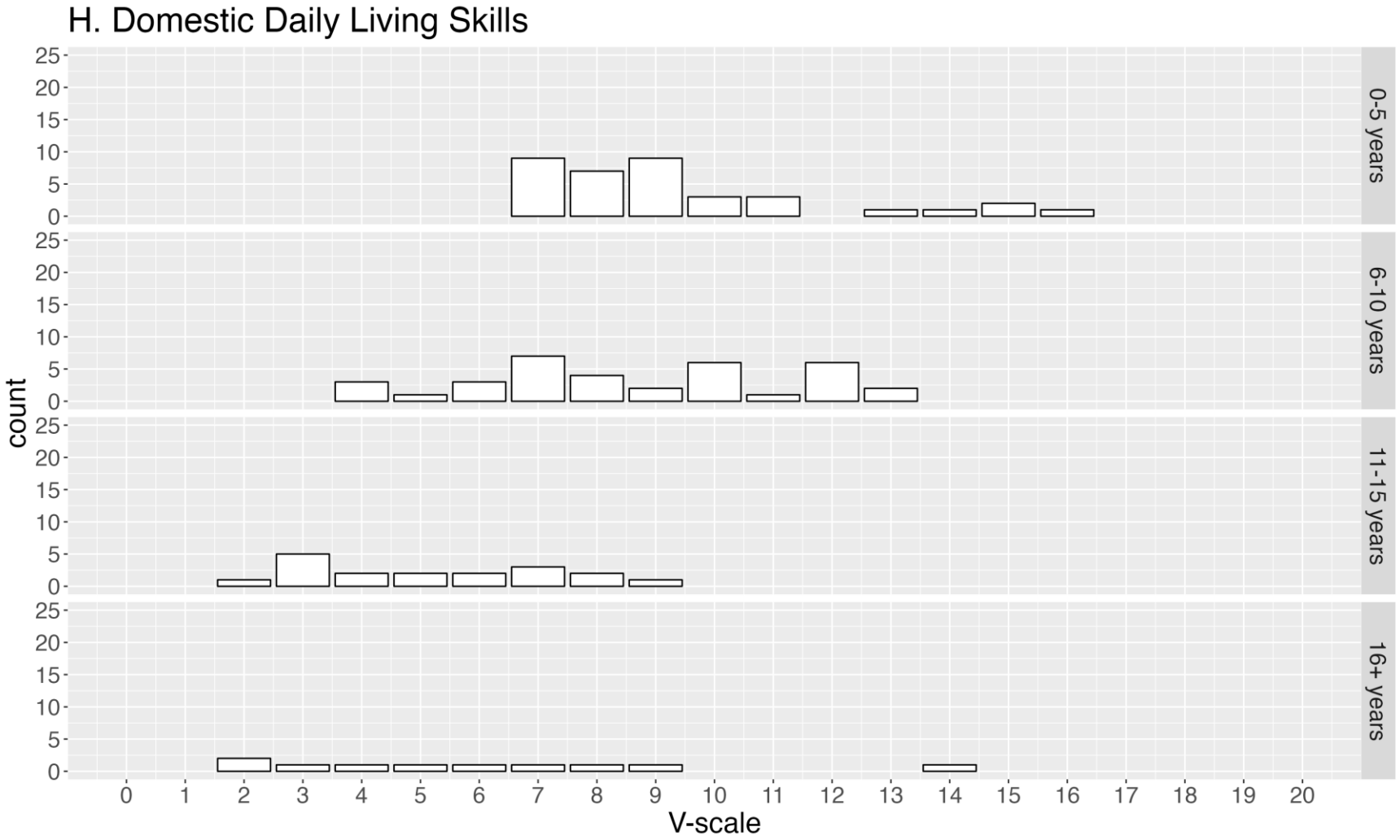

C. Written Communication
count
V-scale
0-5 years
6-10 years
11-15 years
16+ years
0
5
10
15
20
25
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

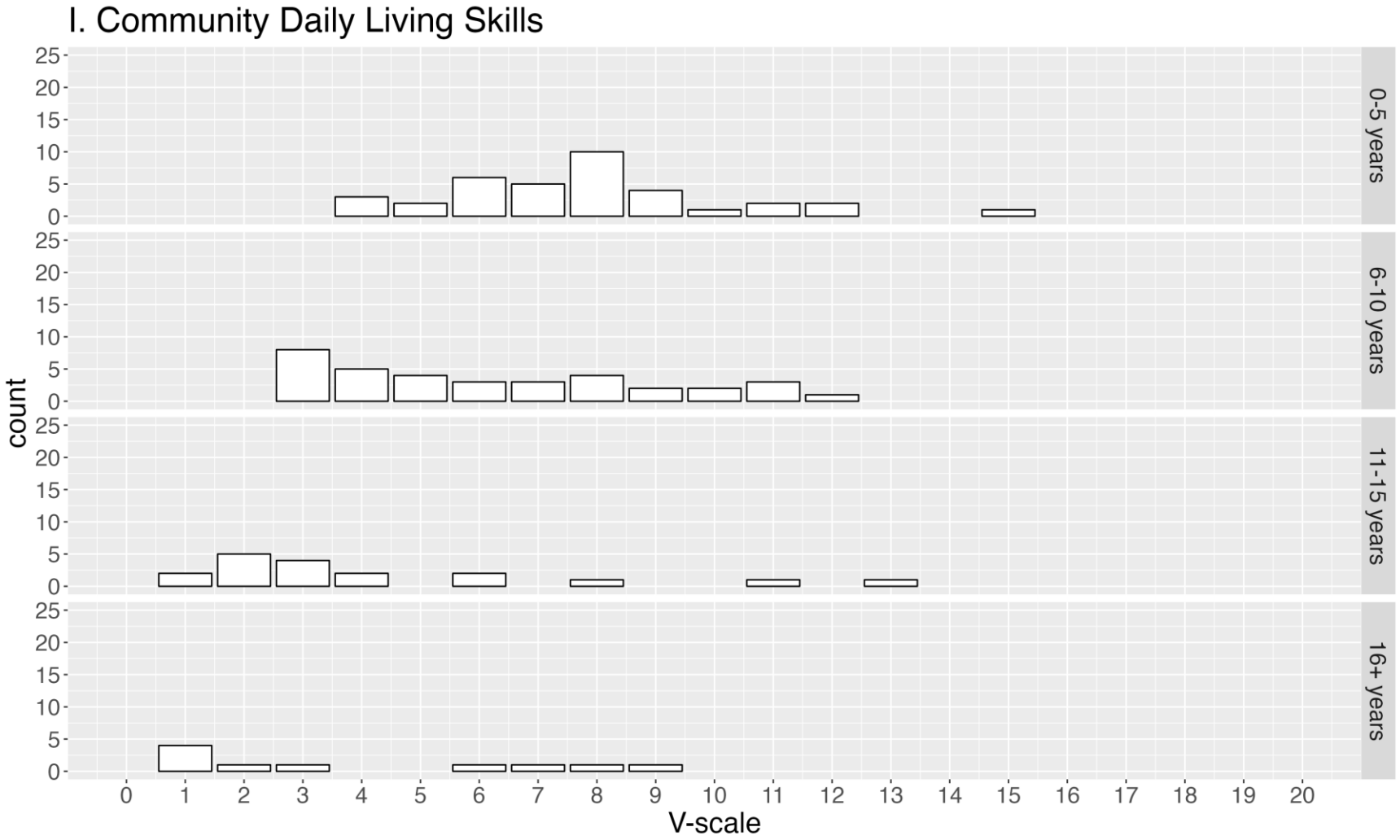

D. Interpersonal Relationships
count
V-scale
0-5 years
6-10 years
11-15 years
16+ years
0
5
10
15
20
25
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20


E. Play and Leisure Time
count
0-5 years
6-10 years
11-15 years
16+ years
0 5 10 15 20 25
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
V-scale


F. Coping Skills
count
V-scale
0-5 years
6-10 years
11-15 years
16+ years
0
5
10
15
20
25
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20


G. Personal Daily Living Skills
count
V-scale
0-5 years
6-10 years
11-15 years
16+ years
0
5
10
15
20
25
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

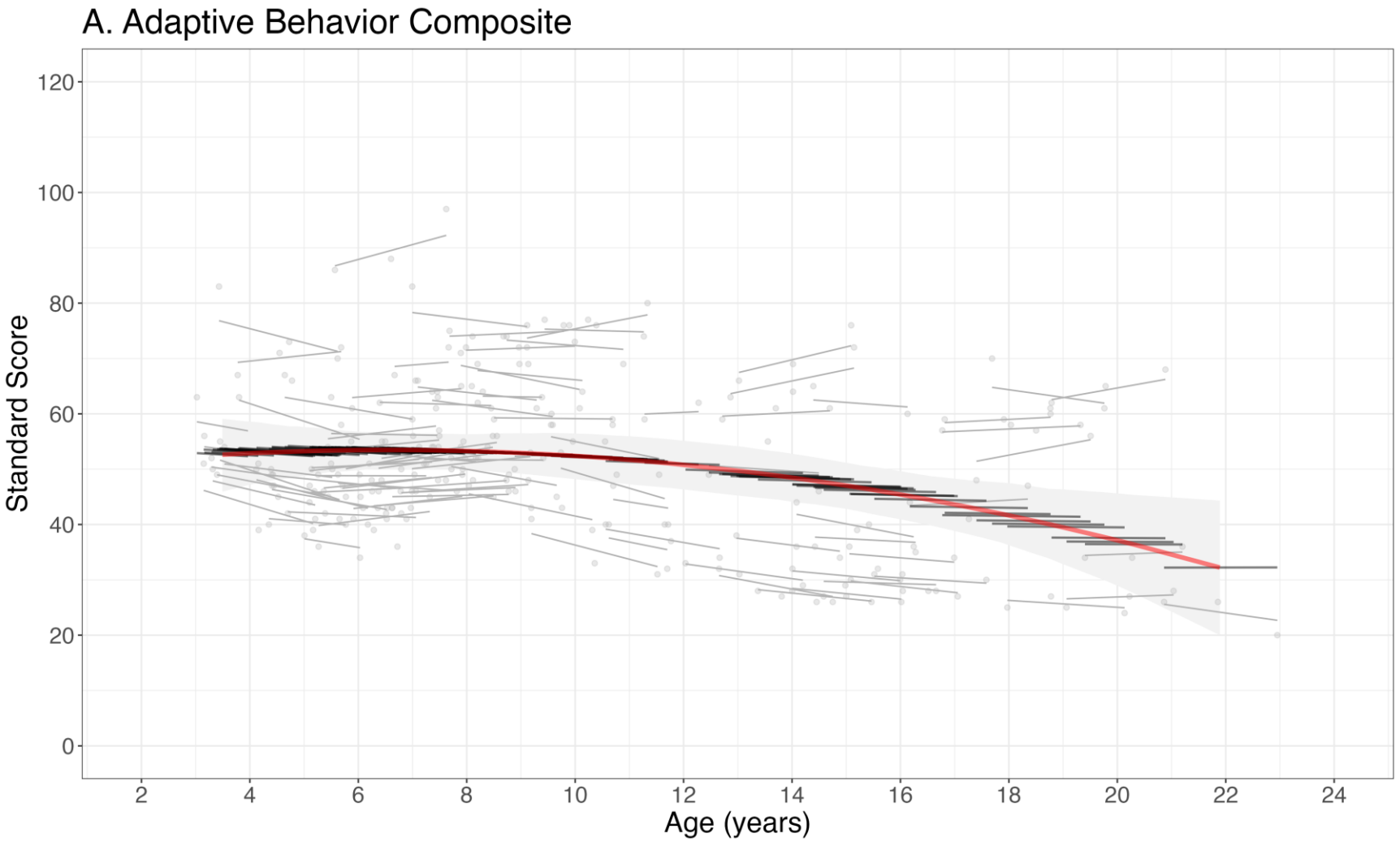

H. Domestic Daily Living Skills
count
V-scale
0-5 years
6-10 years
11-15 years
16+ years
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
0 5 10 15 20 25

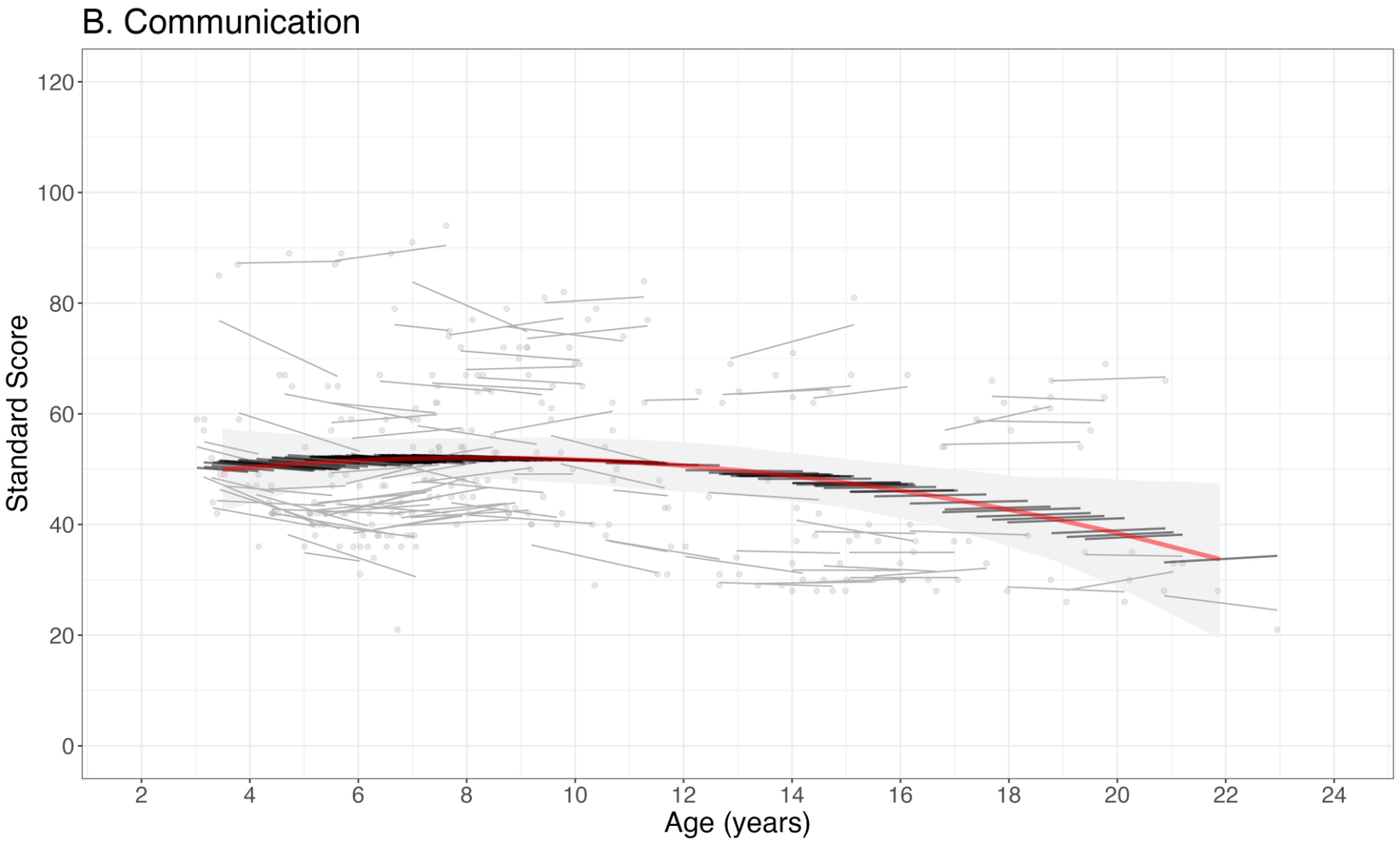

I. Community Daily Living Skills
count
V-scale
0-5 years
6-10 years
11-15 years
16+ years
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
0 5 10 15 20 25

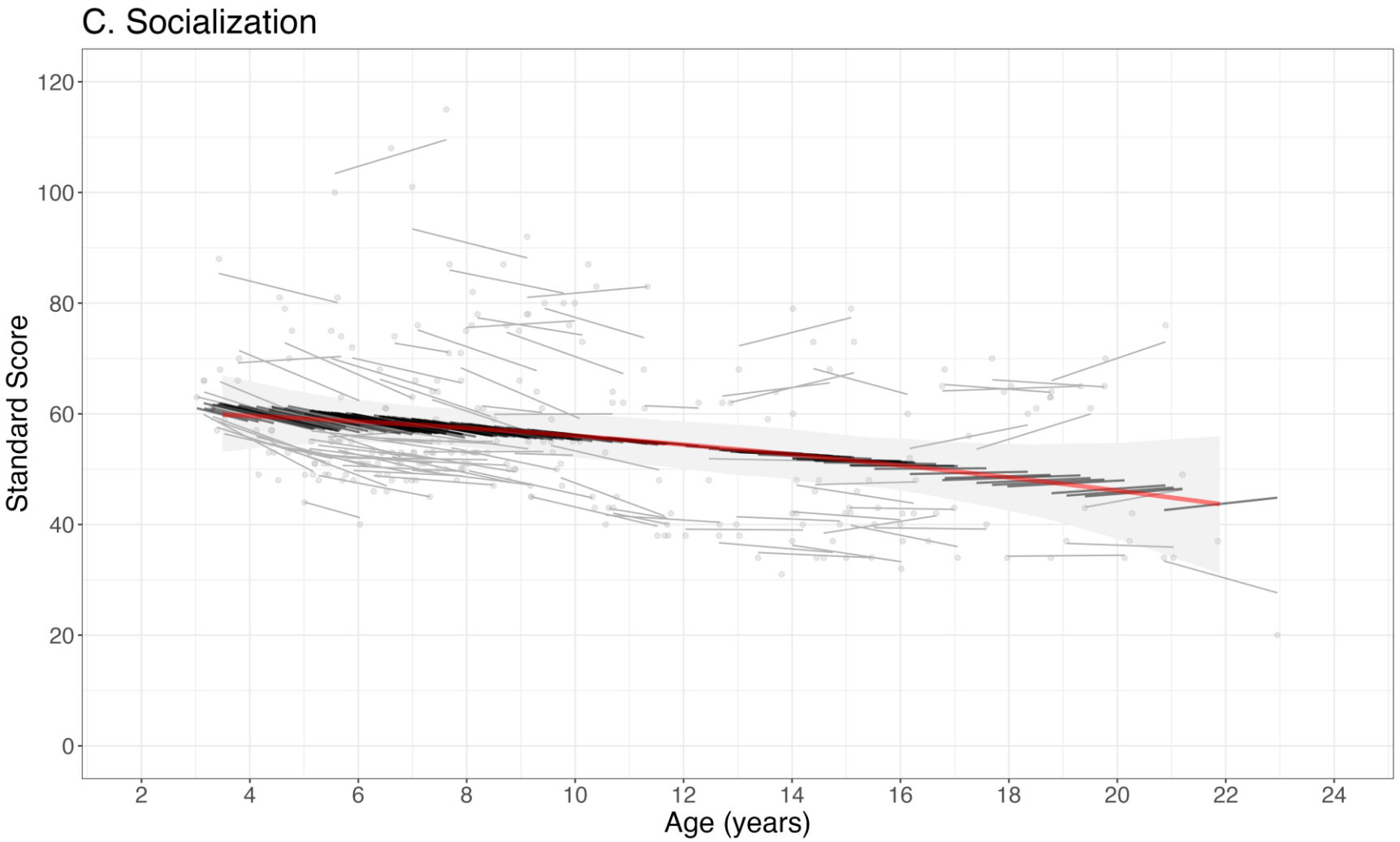
Supplementary Materials S3. The percentage of individuals with only one unique Vineland-II GSV across all timepoints (excluding those with data available only for one visit).

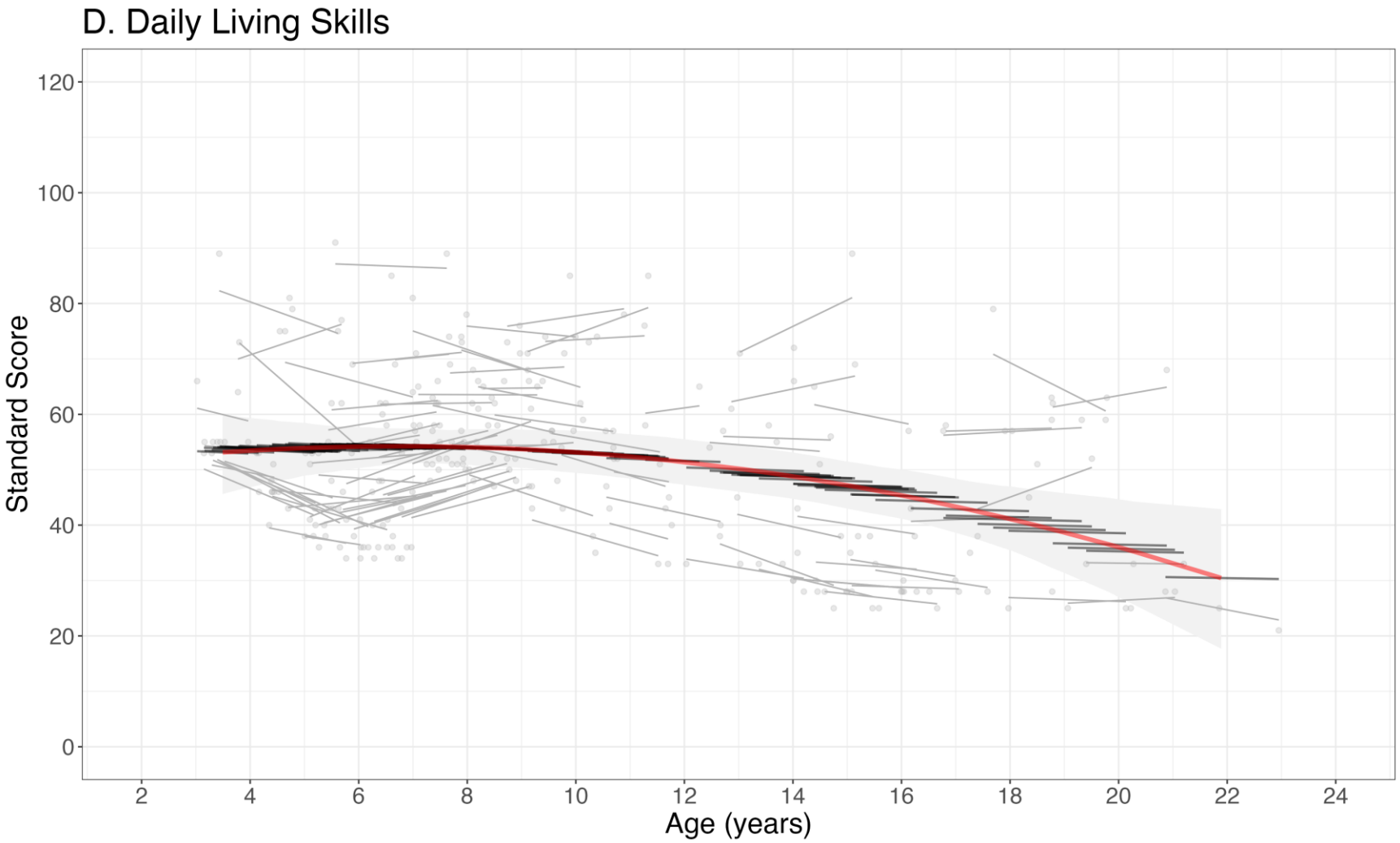
	Percentage of participants with one unique GSV across all timepoints
Receptive Communication	3/95 (3.2%)
Expressive Communication	3/95 (3.2%)
Written Communication	38/94 (40.4%)
Interpersonal Relationships	2/95 (2.1%)
Play and Leisure Time	6/95 (6.3%)
Coping Skills	3/95 (3.2%)
Personal Daily Living Skills	4/95 (4.2%)
Domestic Daily Living Skills	21/95 (22.1%)
Community Daily Living Skills	16/95 (16.8%)

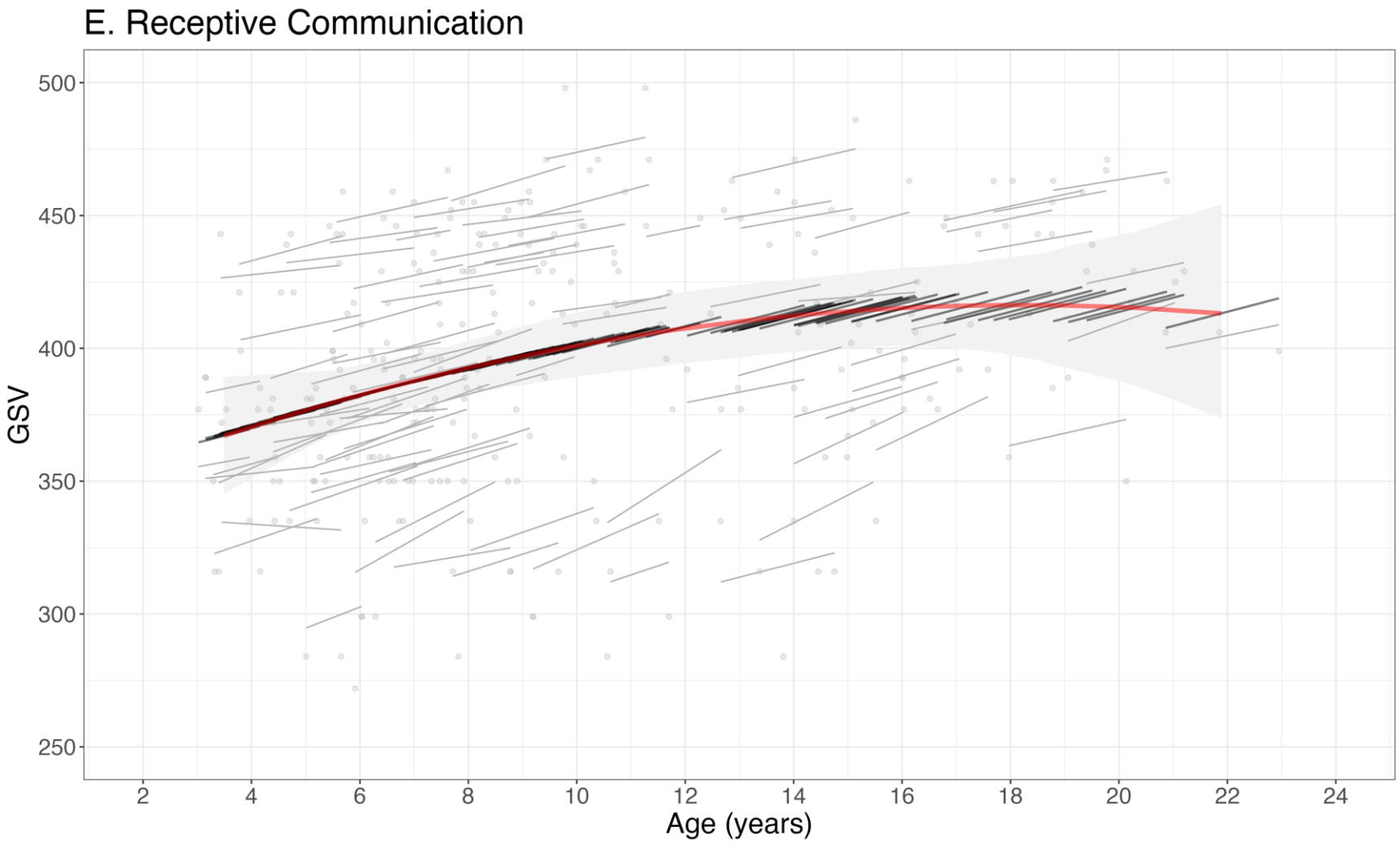
Supplementary Materials S4. Visual depiction of LME modeling pertaining to longitudinal Vineland-II standard scores (A-D) and GSVs (E-M). The x-axis represents age in years. The y-axis represents the score of the instrument (either standard score or GSV). Vineland-II standard scores have a population mean of 100, a standard deviation of 15, and possible range of 20-160. Like raw scores, GSVs have no defined population distribution and are not comparable across subdomains. The gray dots are the actual scores of the participants. Each gray line corresponds to an individual and is a plot of predicted output values of the model based on the data used for the fit vs. age in years for that participant. Each black line corresponds to an individual and is a plot of predicted output values of the model based on the fixed effects of the model (with no random effects included) for that participant. The red trend line corresponds to the sample as a whole and is a plot of predicted output values of the model based on the data used for the fit (with no random effects included) vs. between-subjects mean age (average age of a participant across all of that individual's study timepoints). The gray ribbon represents the 95% confidence intervals around the red trend line as generated using a bootstrap method (`bootMer` in R) with a bootstrap sample size of 1000. Note that the red line includes a quadratic term with respect to age (i.e., age^2), which forces a nonlinear fit to the data. While we expect the developmental trajectories to be nonlinear, with potential plateaus or even decreases in developmental progressions at older ages, the downsloping trend observed for older individuals in the graphs below may be accentuated by this quadratic fit and the smaller number of participants at these ages. The greater uncertainty of this fit is shown through a larger confidence interval as well.

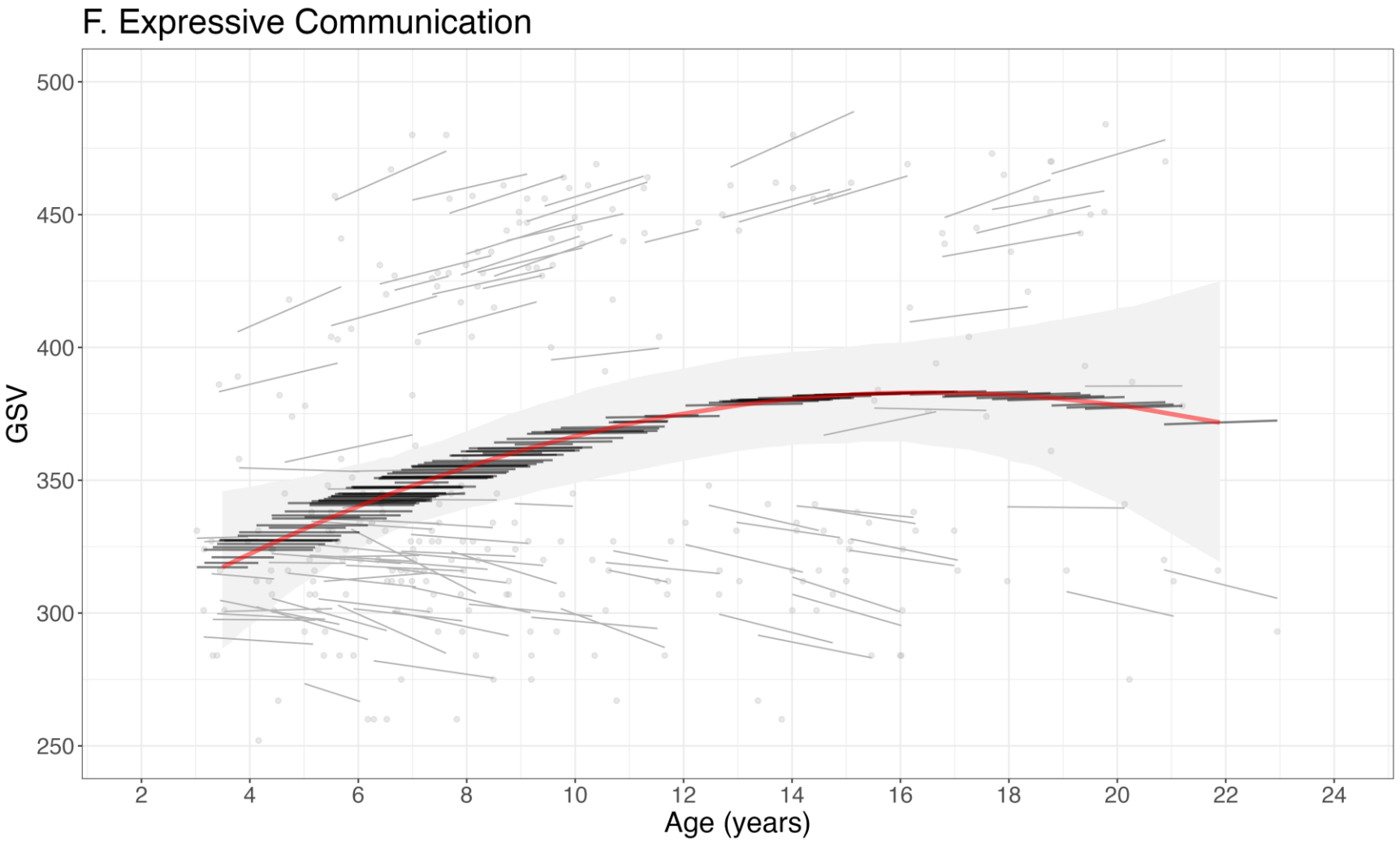

A. Adaptive Behavior Composite
Standard Score
120
100
80
60
40
20
0
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)

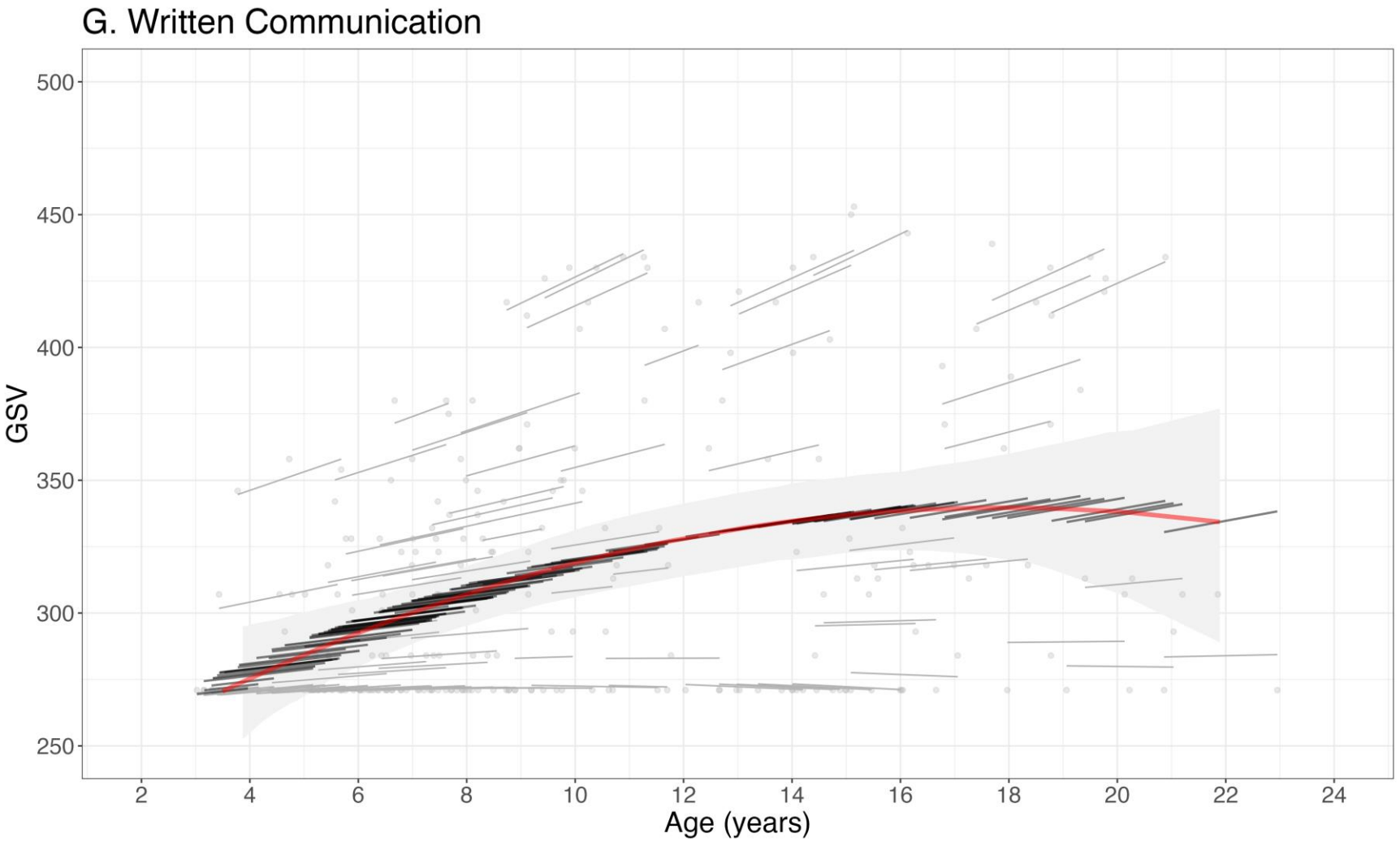

B. Communication
Standard Score
120
100
80
60
40
20
0
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)

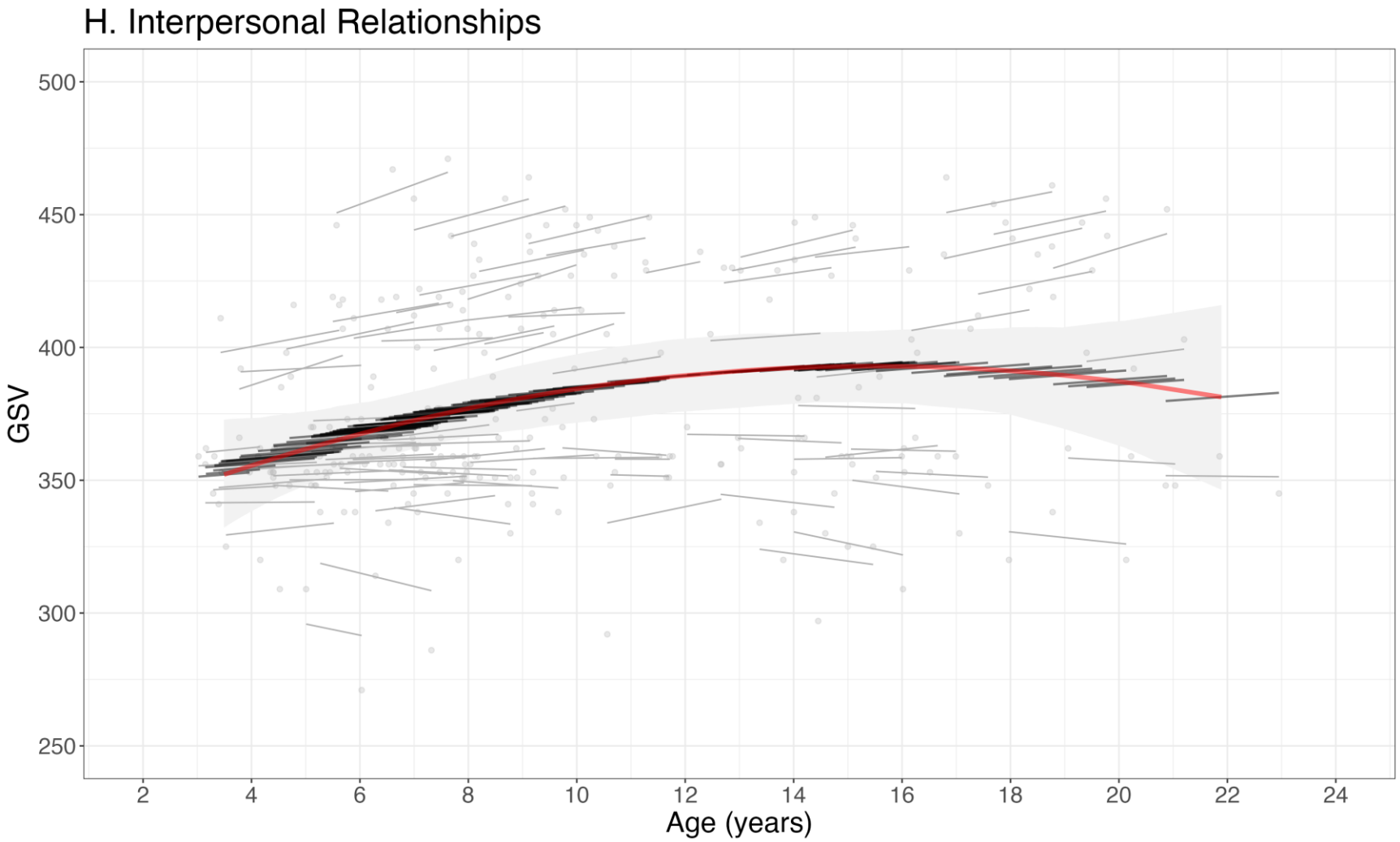

C. Socialization
Standard Score
120
100
80
60
40
20
0
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)


D. Daily Living Skills
Standard Score
120
100
80
60
40
20
0
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)

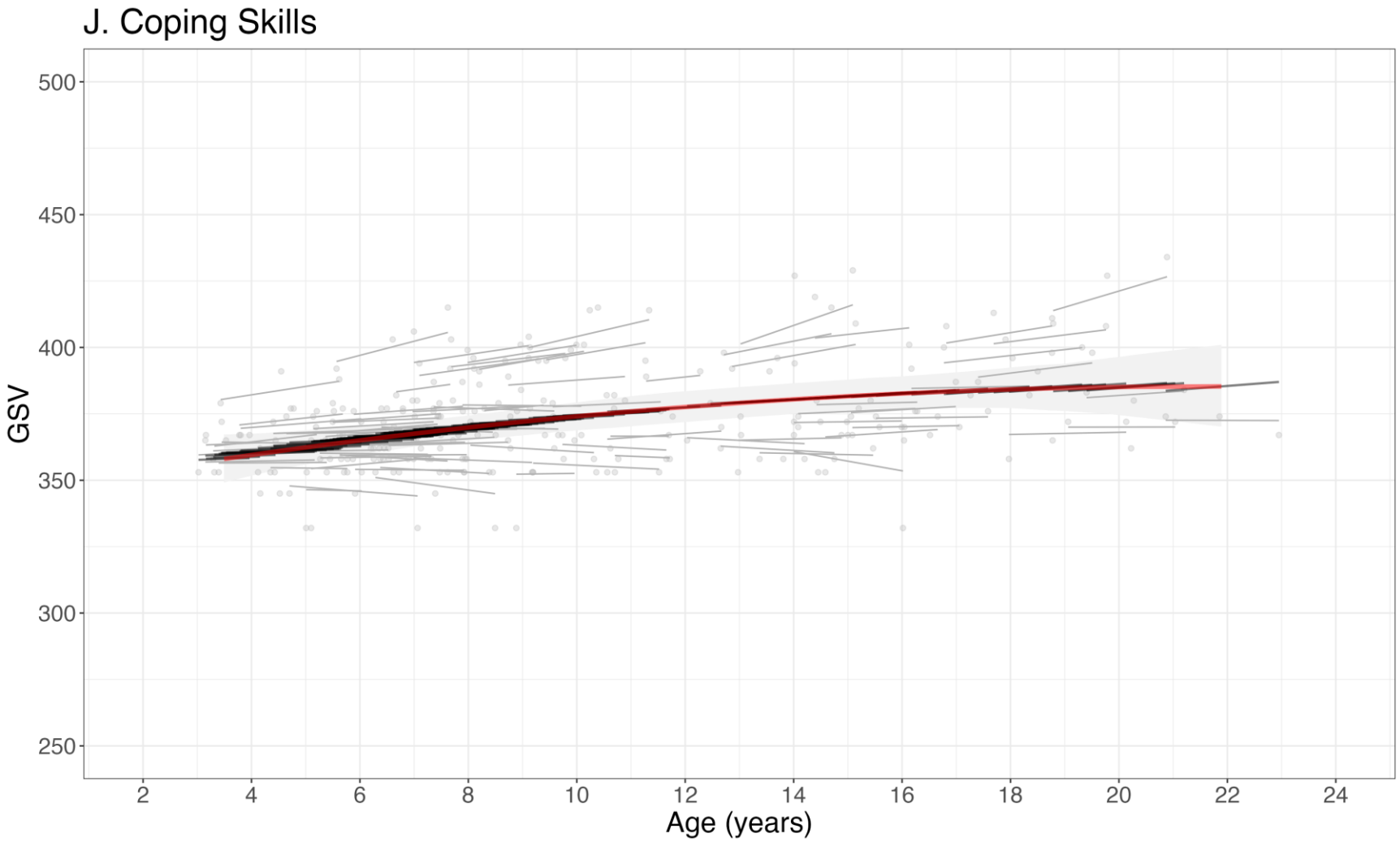

E. Receptive Communication
GSV
500
450
400
350
300
250
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)

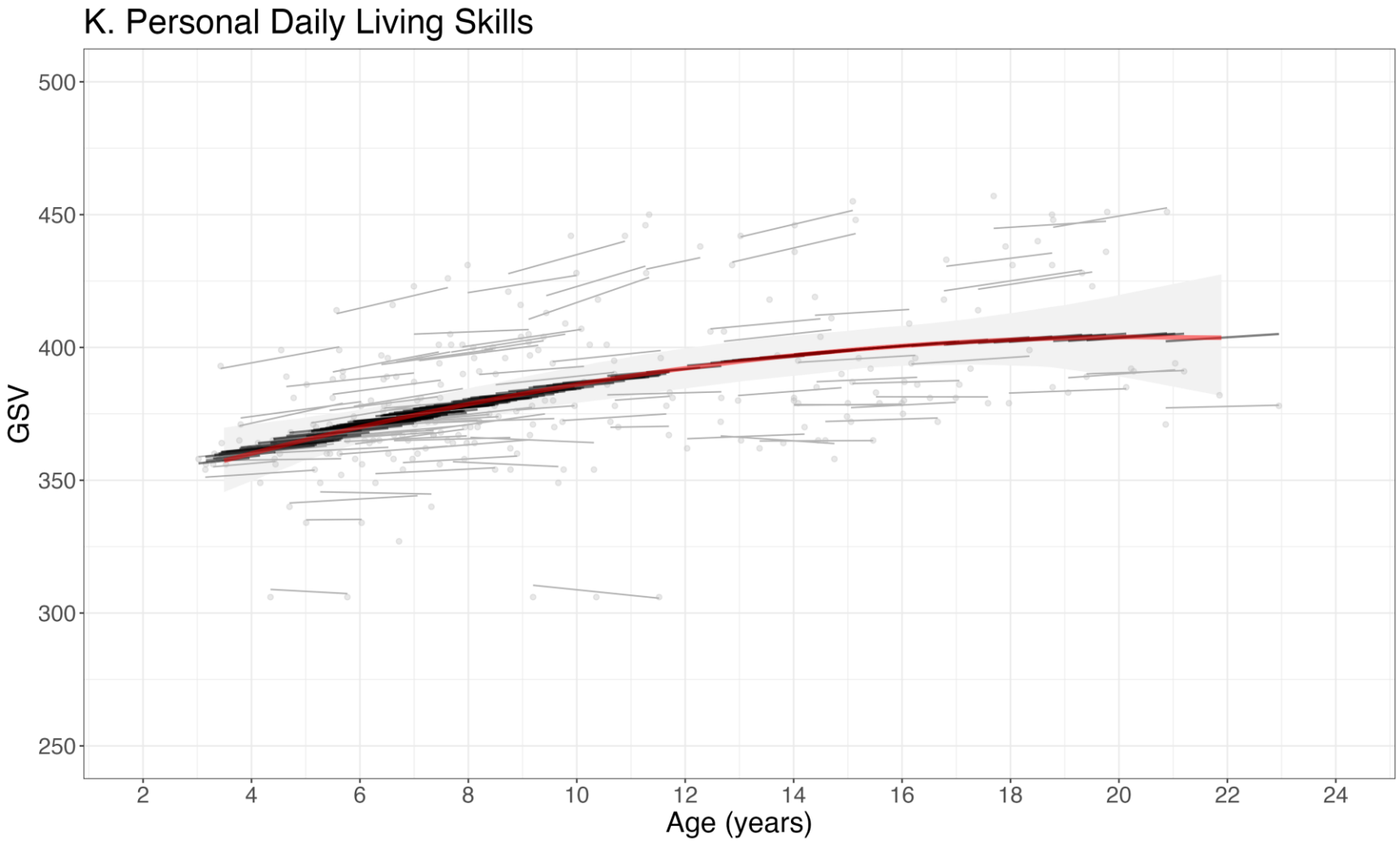

F. Expressive Communication
GSV
500
450
400
350
300
250
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)

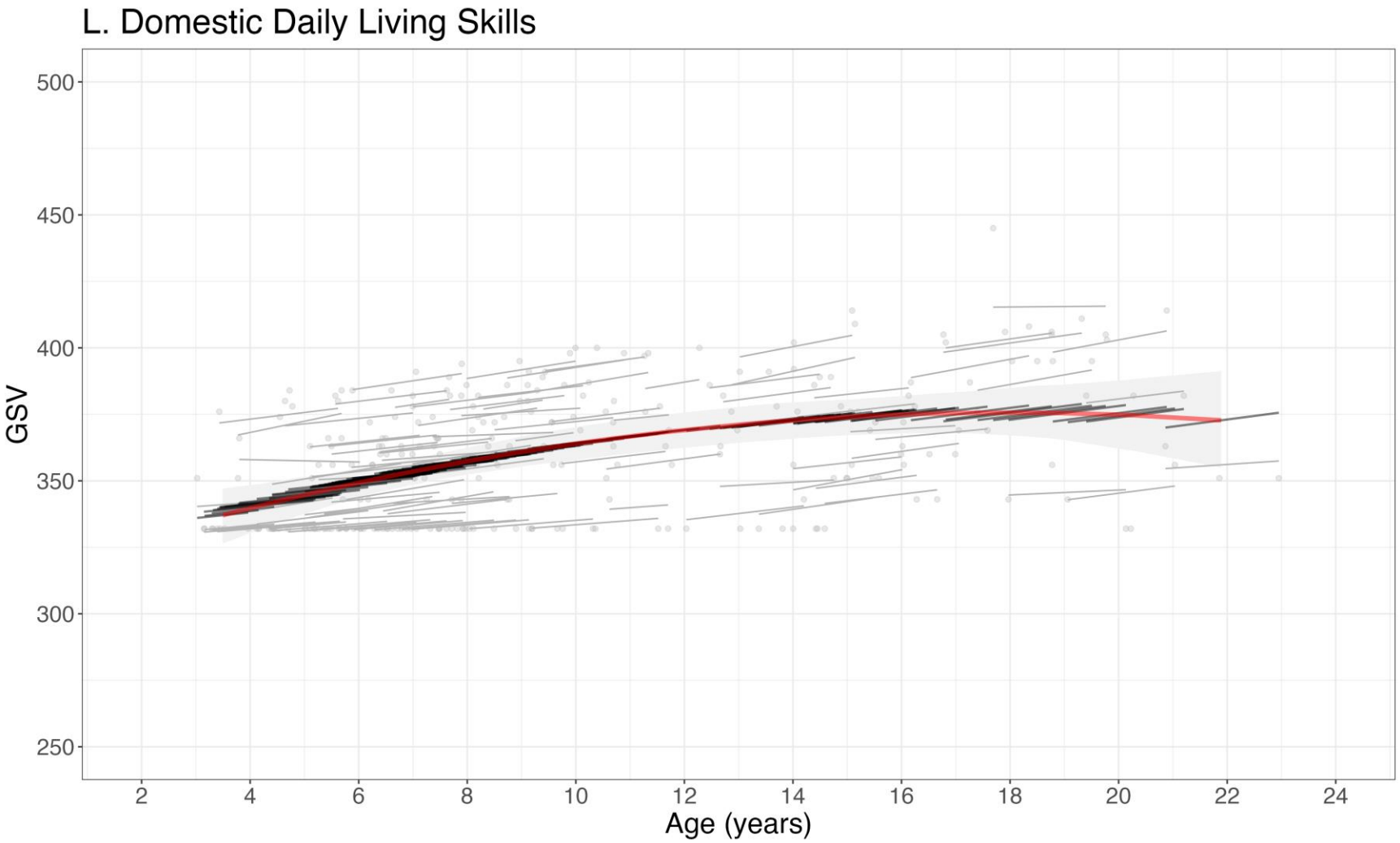

G. Written Communication
GSV
500
450
400
350
300
250
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)

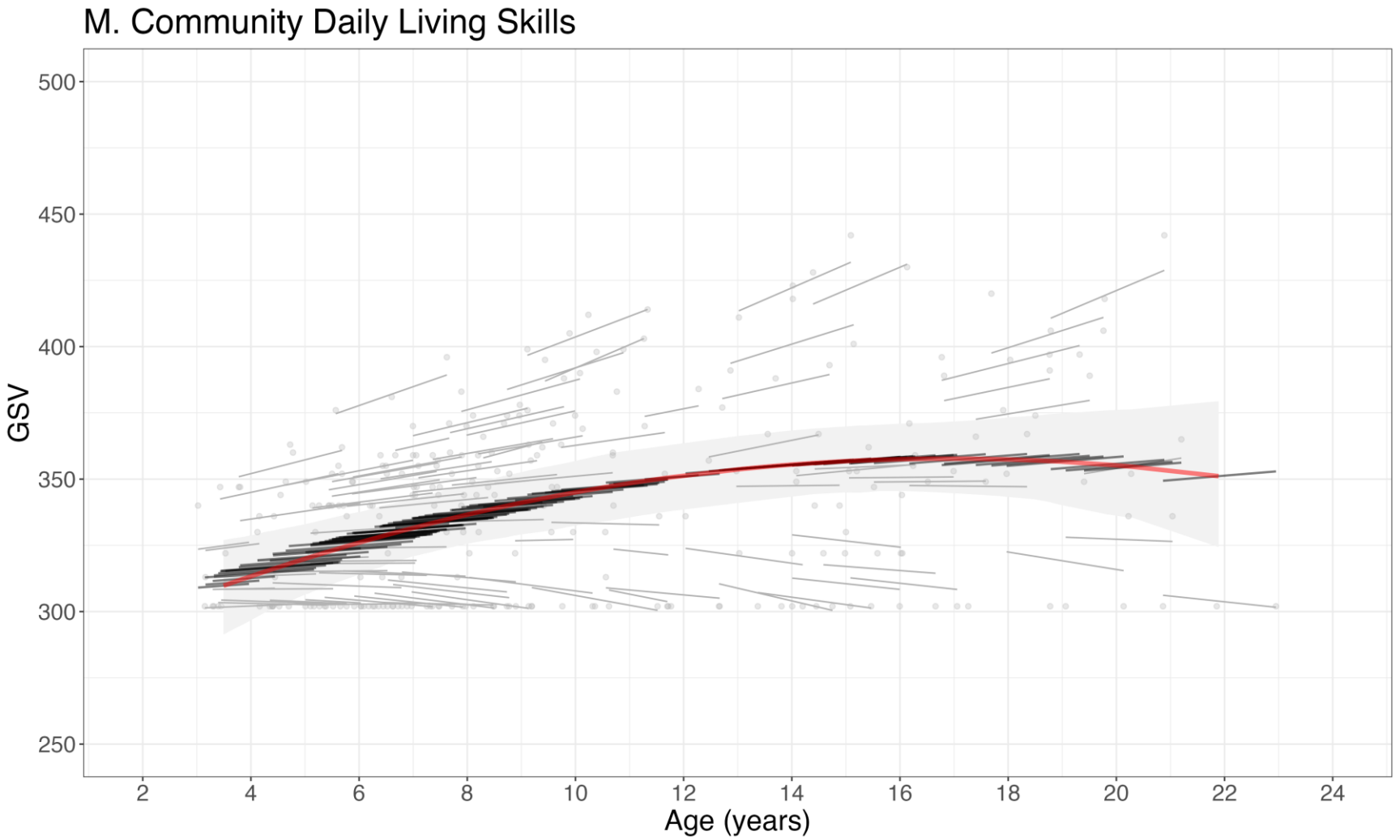

H. Interpersonal Relationships
GSV
500
450
400
350
300
250
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)


I. Play and Leisure Time
GSV
500
450
400
350
300
250
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)


J. Coping Skills
GSV
500
450
400
350
300
250
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)


K. Personal Daily Living Skills
GSV
500
450
400
350
300
250
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)


L. Domestic Daily Living Skills
GSV
500
450
400
350
300
250
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)


M. Community Daily Living Skills
GSV
500
450
400
350
300
250
2
4
6
8
10
12
14
16
18
20
22
24
Age (years)