Development and Validation of a Questionnaire-Based Deficit Accumulation Model for Identifying Multidomain Impairment Phenotypes in Childhood Cancer Survivors

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Background

Frailty is a complex condition characterized by reduced physiological reserve and increased vulnerability to adverse health outcomes (Kalladi et al., 2026). Traditional frailty assessment was first conceptualized by Fried et al., who proposed the physical frailty phenotype based on five clinical criteria, including unintentional weight loss, exhaustion, low energy expenditure, slowness, and weakness. This phenotype has been shown to predict important clinical outcomes, including disability, hospitalization, and mortality (Fried et al., 2001).

The deficit accumulation model was first proposed by Mitnitski, Mogilner, and Rockwood (2001), who introduced the Frailty Index (FI) as the proportion of accumulated health deficits. Building on this work, Rockwood and Mitnitski (2007) further developed the conceptual framework, describing frailty as the cumulative effect of deficits across multiple health domains rather than only physiologic features. The FI is typically constructed using at least 30 age-related deficits, with higher scores indicating greater biological vulnerability and increased risk of adverse outcomes.

The deficit accumulation approach allows flexibility in selecting health-related variables. Searle et al. proposed a standardized procedure for constructing a frailty index and demonstrated that different combinations of deficits can generate valid frailty indices when selected variables represent multiple health domains and meet established criteria, including being associated with health status, generally increasing in prevalence with age, not becoming nearly universal at relatively young ages, collectively representing a range of physiological and functional systems, and remaining consistent across repeated assessments when the same index is used longitudinally (Searle et al., 2008). This flexibility provides an opportunity to develop alternative approaches when traditional clinical assessments are unavailable while maintaining the underlying deficit accumulation framework and supporting comparisons across studies and populations.

Deficit accumulation measures can be developed using a variety of data sources, including self-reported questionnaires, clinical assessments, performance testing, laboratory measures, and/or medical-record data. Frailty indices derived entirely or largely from self-reported questionnaire data have also been applied in general aging populations and in older adults with cancer (Cohen et al., 2016; Blodgett et al., 2017; D. M. Williams et al., 2018; Giri et al., 2022); however, their application in long-term survivors of childhood cancer remains limited. Existing frailty measures in this population often incorporate clinical or performance-based information that may not be consistently available in large longitudinal cohorts or remote follow-up settings (A. M. Williams et al., 2023). Although questionnaire-based approaches similarly depend on the availability or collection of appropriate patient-reported data, they may be particularly valuable in cohorts such as the Childhood Cancer Survivor Study (CCSS), where extensive longitudinal self-reported data are available but the comprehensive clinical and performance-based measures are not routinely collected.

Beyond feasibility, existing frailty measures primarily summarize overall deficit burden (Cohen et al., 2016; Blodgett et al., 2017; D. M. Williams et al., 2018; Giri et al., 2022) and may not distinguish the domains contributing to impairment. Childhood cancer survivors may experience long-term impairments across cognitive, psychological, and physical domains because of cancer and its treatment. Therefore, this study aims to develop and evaluate a questionnaire-derived multidomain deficit accumulation index (DAI) using patient-reported items from the Brief Symptom Inventory (BSI), Neurocognitive Questionnaire (NCQ), and Childhood Cancer Survivor Study (CCSS) questionnaires.

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Following item selection and domain construction, this study will generate both a continuous questionnaire-based DAI summary score and latent impairment classes from the same questionnaire data. The DAI score will quantify the overall burden of accumulated health deficits, providing a continuous measure of impairment severity, whereas latent class analysis (LCA) will identify distinct patterns of health deficits, potentially distinguishing survivors with similar overall burden but different impairment profiles. Together, these complementary approaches will characterize both the severity and pattern of impairment and may support survivor characterization and risk stratification when comprehensive clinical frailty assessments are unavailable.

The reproducibility of the questionnaire-based DAI will be evaluated across repeated visits and independent cohorts. Clinical validity will be further assessed by examining whether the questionnaire-based DAI score is consistent with the existing clinical DAI (A. M. Williams et al., 2023), and whether both the continuous questionnaire-based DAI score and LCA-derived impairment classes are associated with clinically relevant outcomes, such as mortality and biological age acceleration.

Objectives

Aim 1: To develop a questionnaire-based DAI using self-reported items from the NCQ, BSI, and CCSS questionnaires and to identify multidomain impairment phenotypes using latent class analysis, based on data from the most recent St. Jude LIFE visit.

> **Model 1**: screening (select candidate items from NCQ, BSI and CCSS questionnaires) → correlation test to identify and remove redundant questionnaire items → factor analysis to identify the underlying factor structure and group related items into clinically meaningful domains → domain construction and selection of retained items → latent class analysis using the retained items to identify multidomain impairment phenotypes → using the same retained items to calculate the questionnaire-based DAI summary score
> **Hypothesis:** We hypothesize that questionnaire-based DAI can quantify overall deficit burden and identify multidomain impairment phenotypes.

Aim 2: To evaluate the reproducibility and generalizability of the questionnaire-based DAI model across repeated St. Jude Lifetime Cohort (St. Jude Life) (1st visit-4th visit) and Childhood Cancer Survivor Study (CCSS) (follow-up 7 and follow-up 5).

> **Model 1**: The same selected variables, domain structure, scoring algorithm, impairment cutoffs, and number of classes derived from the development dataset will be applied to each validation dataset to assess the reproducibility of the DAI score distribution and impairment profiles across repeated St. Jude Life visits and the independent CCSS population. Reproducibility of the latent class solution will be further evaluated by comparing posterior class-membership probabilities and entropy across datasets.
> **Hypothesis:** The questionnaire-based DAI will reproduce consistent impairment patterns across repeated St. Jude Life visits and CCSS population, with comparable latent class separation and classification certainty.

Aim 3: To evaluate the concurrent, prognostic, and biological validity of the questionnaire-based DAI model:

> **Model 1:** The questionnaire-based DAI score will be compared with the existing 44-item clinical DAI (Williams et al., 2023) among participants with available data. The

association between the two measures will be assessed using Spearman rank correlation coefficients because DAI scores may not be normally distributed.
Hypothesis: Higher questionnaire-based DAI scores will be associated with higher clinical DAI scores.

Model 2: Mortality risk will be examined using Cox proportional hazards models. Survival time will be calculated from the baseline visit date to the date of death or last available follow-up. The model will be adjusted for age at visit, sex, race/ethnicity, and year of diagnosis. Among participants with both the questionnaire-based DAI and the 44-item clinical DAI available at the first visit, the predictive performance of the two measures will be compared. Discrimination will be evaluated using the C-index and time-dependent AUCs for 5- and 10-year mortality, with calibration also assessed as appropriate.
Hypothesis: Higher questionnaire-based DAI scores will be associated with higher mortality risk. The questionnaire-based and clinical DAI will show comparable ability to predict mortality.

Model 3: Latent class membership will be examined as a categorical predictor, with the non-impaired class as the reference group, to determine whether distinct impairment patterns are associated with different mortality risks. Cox proportional hazards models will be used for mortality outcomes. The model will be adjusted for age at visit, sex, race/ethnicity, and year of diagnosis. Hazard ratios and 95% confidence intervals will be reported for each latent class. Pseudo-R^2 will also be reported as an additional measure of overall model fit.
Hypothesis: Compared with the non-impaired class, participants in impaired classes are expected to have higher mortality risk.

Model 4: Examine whether questionnaire-based DAI is associated with biological age acceleration. The questionnaire-based DAI will be analyzed as both a continuous and a categorical variable (robust, prefrail, and frail), with the robust category serving as the reference group. For DNA methylation–based age clocks, including Horvath, Hannum, PhenoAge, GrimAge, AdaptAge, DamAge, CausAge, DNAmFitAge, and SystemsAge (overall and organ-specific), age-acceleration measures will be used rather than raw DNAm-predicted age. DunedinPACE and PCDNAmTL will be analyzed according to their established definitions. The questionnaire-based DAI assessment closest to the methylation sample collection date will be used. Multivariable linear regression models will be adjusted for sex, time since cancer diagnosis, year of diagnosis, chronic health conditions, and relevant treatment exposures.
Hypothesis: Higher questionnaire-based DAI scores are expected to be associated with greater biological age acceleration. Compared with participants in the robust category, those in the prefrail and frail categories are expected to have greater biological age acceleration.

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Study Population

Adult survivors of childhood cancer enrolled in the St. Jude Lifetime Cohort (St. Jude LIFE) and the Childhood Cancer Survivor Study (CCSS) will be included in this study. The questionnaire-based DAI will be developed using data from the most recent St. Jude LIFE visit. Model performance will then be evaluated through internal temporal validation using earlier St. Jude LIFE visits (Visits 1–4) to assess reproducibility across repeated assessments, and through external validation using the independent CCSS Follow-up 5 and Follow-up 7 cohorts, excluding participants who are also enrolled in St. Jude LIFE, to assess generalizability across study populations.

Outcomes:

Aim 1

Primary outcome: 1) the questionnaire-based DAI score developed from self-reported questionnaire items; 2) latent impairment class membership derived from latent class analysis.

Aim 2

Primary outcomes: Class-specific trajectories of questionnaire-based DAI scores, mean DAI scores within each latent class, posterior probabilities of class membership, and entropy.

Aim 3

Model 1. The primary outcome is the 44-item clinical DAI score.
Model 2. The primary outcome is all-cause mortality.
Model 3. The primary outcome is all-cause mortality.
Model 4. DNAm age acceleration: Horvath, Hannum, PhenoAge, GrimAge, AdaptAge, DamAge, CausAge, DNAmFitAge, SystemsAge (overall and organ-specific); Other DNAm-based aging measures: DunedinPACE, PCDNAmTL

Statistical Approach

Descriptive statistics will be reported for participants involved in questionnaire-based DAI derivation.

Aim 1: Model development

Initial candidate items will be selected from the NCQ, BSI, and CCSS questionnaires according to the standard criteria for constructing a deficit accumulation index (Searle et al., 2008), their clinical relevance to the intended constructs, and the availability of questionnaire-based measures in St. Jude life. Specifically, selected items should represent health-related deficits, generally increase in prevalence with age, avoid early saturation, cover multiple health domains, remain consistent across study populations and time points, and provide sufficient coverage of overall health (Searle et al., 2008). Selected questionnaire items will first be evaluated using correlation analysis to identify highly correlated or potentially redundant items. Cronbach's alpha will also be examined within each domain to assess whether removal of individual items improves internal consistency as a supportive measure. Exploratory factor analysis (EFA) will then be used to examine the underlying factor structure and identify groups of related items. Final item selection will be based on factor loadings, redundancy, domain representation, and clinical relevance, rather than on a single statistical cutoff. The retained items will be grouped into impairment domains. Domain scores will be calculated by averaging the corresponding items. Because established cutoffs are not available for these newly constructed

domains, domain-level impairment will be defined using the 75th percentile as the primary cutoff. Sensitivity analyses using the 70th, 80th, and 90th percentiles will assess the robustness of the latent class solutions, including model fit, class stability, and class size. Latent class analysis will subsequently be performed using the domain impairment indicators to identify distinct impairment classes. We will fit models with different numbers of classes and compare their performance using several model fit indices (Sinha et al., 2021).

Once items are identified, the questionnaire-based DAI will be calculated using the same approach as the published 44-item clinical DAI (Mitnitski et al., 2001). Deficits will be summed up and divided by the total number of non-missing items, resulting in a score ranging from 0 to 1. Participants with more than 10% missing questionnaire items will be excluded from DAI calculation. DAI scores will be categorized using previously established frailty index thresholds as robust (<0.20), pre-frail (0.20 to <0.35), and frail (≥0.35) (Kulminski et al., 2008; Cohen et al., 2016; Williams et al., 2023).

The Fried frailty phenotype will be calculated according to the established criteria described by Ness et al. (2013), in which the original clinical criteria were adapted for childhood cancer survivors. Participants will be classified as robust (0 criteria), pre-frail (1–2 criteria), or frail (≥3 criteria).

Aim 2: Evaluate the reproducibility and generalizability

The final questionnaire-based DAI model, including the selected items, domain structure, scoring algorithm, impairment cutoffs, and number of classes, will be applied to repeated SJLIFE assessments and the independent CCSS cohort. Model reproducibility will be evaluated by comparing the DAI scores distributions, trajectories, latent impairment class assignments, and entropy across validation datasets. In addition, longitudinal measurement invariance analyses, such as longitudinal EFA/CFA and latent class approaches, may be considered to evaluate whether the underlying measurement structure, domain- and item-level parameters, and item-level measurement errors remain consistent over time.

Aim 3: Evaluate the concurrent, prognostic, and biological validity

The questionnaire-based DAI will be compared with the existing 44-item clinical DAI, calculated according to the method described by Williams et al. (2023). Associations between the two measures will be assessed using Spearman rank correlation coefficients. Cox proportional hazards regression will be used to evaluate associations of the questionnaire-based DAI with mortality. Survival time will be calculated from the baseline visit date to the date of death or max (last available follow-up, NDI search date). The questionnaire-based DAI will be analyzed both as a continuous score and by latent class membership (the non-impaired class will serve as the reference group). Models will be adjusted for age at visit, sex, race/ethnicity, and year of diagnosis. Among participants with both the questionnaire-based DAI and the 44-item clinical DAI available at the first visit, the predictive performance of the two measures will be compared. Discrimination will be evaluated using the C-index and time-dependent AUCs for 5- and 10-year mortality, with calibration also assessed as appropriate.

Biological validity will be evaluated by examining associations between questionnaire-based DAI and biological age acceleration. PC-based versions of the available epigenetic clocks will be used, including Horvath, Hannum, PhenoAge, GrimAge, AdaptAge, DamAge, CausAge, DNAmFitAge, and SystemsAge measures. Epigenetic age acceleration (EAA) will be calculated by regressing each DNAm-predicted age on chronological age at sample collection and using the residual as the outcome. DunedinPACE and PCDNAmTL will be analyzed according to their established definitions. The questionnaire-based DAI assessment closest to the methylation

sample collection date will be used. Multivariable linear regression models will be adjusted for sex, time since cancer diagnosis, and year of diagnosis. Chronic health conditions and treatment exposures will be considered in sensitivity analyses.

Missing data handling

Missing BSI items were first handled at the subscale level. For each six-item BSI subscale, when no more than two items were missing, missing responses were imputed using the participant-specific mean of the observed items within that subscale. After excluding participants with more than 10% missing data across all questionnaire items used to construct the DAI, item-level missingness was below 3% for all items across study visits. In the CCSS validation cohort, the same BSI subscale-level imputation procedure was applied. The maximum item-level missingness across the three questionnaires was 8.2% before application of the exclusion criterion and 3.9% among participants retained for the questionnaire-based DAI calculation. Any remaining missing values on the latent class indicators were accommodated in the latent class analysis using maximum-likelihood estimation based on all available indicator responses.

Potential Sensitivity Analyses

1. The number of latent classes will be re-evaluated independently in each validation dataset rather than fixing the four-class solution identified in the development sample. Three-, four-, and five-class models will be fitted using the same items and model-selection criteria to assess whether a similar four-class structure emerges across repeated St. Jude Life visits and the CCSS population. Consistent selection of a four-class solution would provide additional evidence for the reproducibility and generalizability of the latent class structure.
2. An alternative domain-weighted scoring approach will be considered to examine whether the findings are influenced by differences in the number of items across domains. The primary questionnaire-based DAI will be calculated using the traditional deficit accumulation approach:

$$qDAI = \frac{\text{Number of deficits present}}{\text{Number of deficits measured}}$$

   For the alternative domain-weighted approach, domain-specific DAI scores will first be calculated within the cognitive, emotional, and physical domains. These scores will then be averaged so that each domain contributes equally to the overall DAI:

$$DAI_{\text{weighted}} = \frac{\text{Cognitive DAI score} + \text{Emotional DAI score} + \text{Physical DAI score}}{3}$$

   Findings from the domain-weighted approach will be compared with those obtained using the primary traditional deficit accumulation scoring method.
3. Questionnaire-based DAI impairment cut points will also be evaluated rather than assuming that thresholds established for the clinical DAI have the same interpretation for this instrument. Alternative instrument-specific cut points will be explored and validated based on their ability to distinguish clinically relevant outcomes, and their performance will be compared with that of the established DAI cut points.

All statistical analyses will be performed using SAS. Two-sided *P* values <0.05 will be considered statistically significant.

Preliminary Results

The initial item pool included approximately 47 questionnaire items (**Appendix eTable 1**), including 18 items from the Brief Symptom Inventory (BSI), 19 items from the

Neurocognitive Questionnaire (NCQ), and 10 items from the CCSS questionnaires assessing physical activity and functional limitations. Following correlation and factor analyses, 40 items were retained for the final questionnaire-based DAI (**Appendix eTable 2**).

Factor analysis identified nine impairment domains: task efficiency, emotional regulation, organization, memory, depression, somatization, anxiety, activities of daily living (ADL) limitations, and instrumental activities of daily living (IADL) limitations.

Latent class models with three, four, and five classes were evaluated using multiple model-fit indices. The four-class solution was selected as the best-fitting and most interpretable model. The four latent classes were labeled according to their domain-specific impairment probability profiles (**Figure 1**). The multidomain impairment class showed the highest probabilities of impairment across nearly all domains, whereas the low impairment class showed consistently low probabilities of impairment across domains. The cognitive impairment class was characterized primarily by elevated probabilities of impairment in the cognitive domains, including task efficiency, emotional regulation, organization, and memory. The emotional impairment class showed greater probabilities of impairment in the mental health domains, including depression, somatization, anxiety, and emotional regulation. These findings identified four distinct multidomain impairment profiles among survivors. Similar latent class patterns were observed across internal validation cohorts and external validation cohorts (**Figure 1**).

Mean questionnaire-based DAI scores showed similar distributions across the development (St. Jude Life latest visit) and validation datasets (repeated St. Jude Life visits and CCSS follow-up assessments). Across all cohorts, the multidomain impairment group had the highest mean questionnaire-based DAI scores (0.56–0.64), followed by the cognitive impairment (0.36–0.40), emotional impairment (0.29–0.37), and low impairment (0.10–0.16) groups. Among participants with both measures available, the mean traditional 44-item clinical DAI score was 0.17 (SD, 0.11), with mean scores of 0.30 (SD, 0.13), 0.12 (SD, 0.07), 0.39 (SD, 0.09), and 0.20 (SD, 0.11) in multidomain impairment, low impairment, cognitive impairment, and emotional impairment groups, respectively **(Table 1).**

Mean Fried frailty scores were highest in multidomain impairment group (1.44–1.96), followed by the cognitive impairment group (0.91–1.17), the emotional impairment group (0.92–1.06), and the low impairment group (0.47–0.61) across both the SJLIFE and CCSS cohorts. Overall mean Fried frailty scores ranged from 0.72 to 0.90 across study cohorts. Mean scores in all cohorts were <2, corresponding to the robust to pre-frail range **(Table 1).**

Average posterior class-assignment probabilities were consistently high across SJLIFE visits, ranging from 0.75 to 0.94, and were similarly high in CCSS (0.78–0.93). All values exceeded 0.70, indicating adequate to strong classification certainty. The comparable probabilities across visits and cohorts further support the stability and reproducibility of the four latent classes **(Table 1).**

Adjusted mean questionnaire-based DAI increased with age after accounting for sex and race/ethnicity (**Figure 2**). The questionnaire-based DAI showed a moderate to strong correlation (0.64) with the 44-item clinical DAI **(Figure 3).** Adjusted cox regression was used to evaluate the prognostic validity of the questionnaire-based DAI for mortality. A higher questionnaire-based DAI score was significantly associated with an increased risk of mortality (HR=1.22, 97% CI: 1.13-1.32, p<0.001) **(Figure 4).** No violations of the proportional hazards or linearity assumptions were observed.

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Results

Table 1

Questionnaire-based DAI score table: mean (SD)

St. Jude Life	Multidomain impairment	Low impairment	Cognitive impairment	Emotional impairment	Overall
Last visit N=4182	0.61 (0.13)	0.14 (0.10)	0.39 (0.09)	0.33 (0.12)	0.27 (0.20)
1st visit N=3050	0.60 (0.13)	0.16 (0.10)	0.39 (0.09)	0.36 (0.12)	0.28 (0.18)
2nd visit N=1953	0.64 (0.14)	0.16 (0.10)	0.40 (0.09)	0.37 (0.13)	0.29 (0.20)
3rd visit N=1060	0.61 (0.14)	0.13 (0.09)	0.36 (0.10)	0.33 (0.13)	0.28 (0.20)
4th visit N=360	0.61 (0.11)	0.15 (0.11)	0.40 (0.07)	0.34 (0.13)	0.30 (0.20)
CCSS					
Fu7 N=8997	0.58 (0.13)	0.11 (0.09)	0.39 (0.1)	0.30 (0.12)	0.22 (0.18)
Fu5 N=8487	0.56 (0.13)	0.10 (0.09)	0.36 (0.1)	0.29 (0.11)	0.21 (0.18)

44-item Clinical DAI score table: mean (SD)

St. Jude Life	Multidomain impairment	Low impairment	Cognitive impairment	Emotional impairment	Overall
1st visit	0.30 (0.13)	0.12 (0.07)	0.39 (0.09)	0.20 (0.11)	0.17 (0.11)
Waiting for the release of the 2023 ocular data to continue the follow-up analysis.					

Fried frailty score table: mean (SD)

St. Jude Life	Multidomain impairment	Low impairment	Cognitive impairment	Emotional impairment	Overall
Last visit N=4182	1.52 (0.96)	0.57 (0.75)	1.11 (1.01)	0.98 (0.89)	0.85 (0.91)
1st visit N=3050	1.44 (0.93)	0.55 (0.73)	0.98 (0.95)	0.92 (0.88)	0.79 (0.87)
2nd visit N=1953	1.47 (0.91)	0.55 (0.71)	1.05 (0.90)	1.00 (0.86)	0.80 (0.85)
3rd visit N=1060	1.50 (0.95)	0.52 (0.70)	0.91 (0.93)	1.06 (0.93)	0.83 (0.90)
4th visit N=360	1.58 (0.93)	0.61 (0.74)	0.98 (0.92)	1.02 (0.85)	0.90 (0.89)
CCSS					
Fu7 N=8997	1.96 (1.15)	0.5 (0.7)	1.17 (1.06)	1.06 (1)	0.80 (0.96)
Fu5 N=8487	1.80 (1.21)	0.47 (0.68)	1.04 (1)	0.92 (0.96)	0.72 (0.91)

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Fried frailty score >=3 (%) table: n (%)

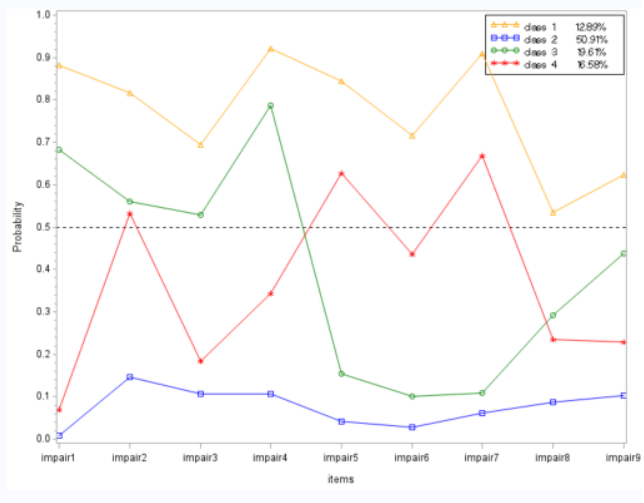
St. Jude Life	Multidomain impairment	Low impairment	Cognitive impairment	Emotional impairment	Overall
Last visit N=4182	69 (13.27)	36 (1.6)	77 (10.34)	32 (4.79)	214 (5.12)
1st visit N=3050	37 (10.79)	19 (1.16)	43 (7.15)	24 (5.06)	123 (4.03)
2nd visit N=1953	25 (11.16)	12 (1.07)	18 (5.73)	14 (4.84)	69 (3.53)
3rd visit N=1060	20 (12.50)	5 (0.97)	14 (6.93)	12 (6.63)	51 (4.81)
4th visit N=360	8 (13.56)	3 (1.64)	3 (4.84)	1 (1.79)	15 (4.17)
CCSS					
Fu7 N=8997	228 (29.96)	82 (1.47)	144 (11.49)	119 (8.52)	573 (6.37)
Fu5 N=8487	178 (26.85)	68 (1.28)	115 (8.69)	77 (6.56)	438 (5.16)

Class assignments probabilities table: mean (SD)

St. Jude Life	Multidomain impairment	Low impairment	Cognitive impairment	Emotional impairment
Last visit N=4182	0.90 (0.14)	0.90 (0.14)	0.85 (0.15)	0.78 (0.18)
1st visit N=3050	0.85 (0.17)	0.91 (0.13)	0.84 (0.16)	0.78 (0.17)
2nd visit N=1953	0.88 (0.15)	0.92 (0.13)	0.83 (0.17)	0.79 (0.16)
3rd visit N=1060	0.90 (0.13)	0.90 (0.13)	0.75 (0.20)	0.80 (0.16)
4th visit N=360	0.94 (0.13)	0.91 (0.13)	0.83 (0.17)	0.84 (0.18)
CCSS				
Fu7 N=8997	0.87 (0.15)	0.93 (0.12)	0.82 (0.17)	0.81 (0.16)
Fu5 N=8487	0.87 (0.15)	0.93 (0.11)	0.78 (0.18)	0.79 (0.16)

Figure 1.
Latent classes analysis for St. Jude Life patients

a) Last visit



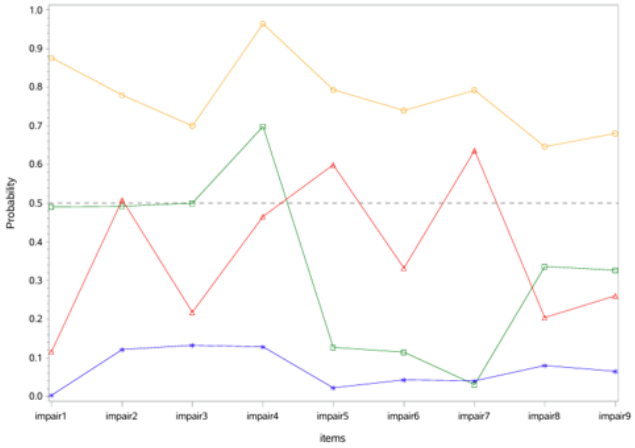
b) Baseline visit



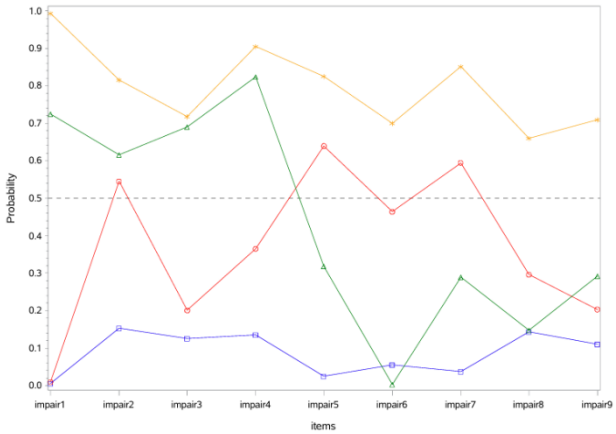
c) 2nd visit



d) 3rd visit



e) 4th visit



y axis: the probability of impairment for each domain.

x axis: impair1=task efficiency
impair2=emotional regulation
impair3=organization
impair4=memory
impair5=depression
impair6=somatization
impair7=anxiety
impair8=adl limitations
impair9=iadl limitations

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Latent classes analysis for CCSS patients

f) Follow-up 7



j) Follow-up 5



Figure 2. Questionnaire-based DAI by age

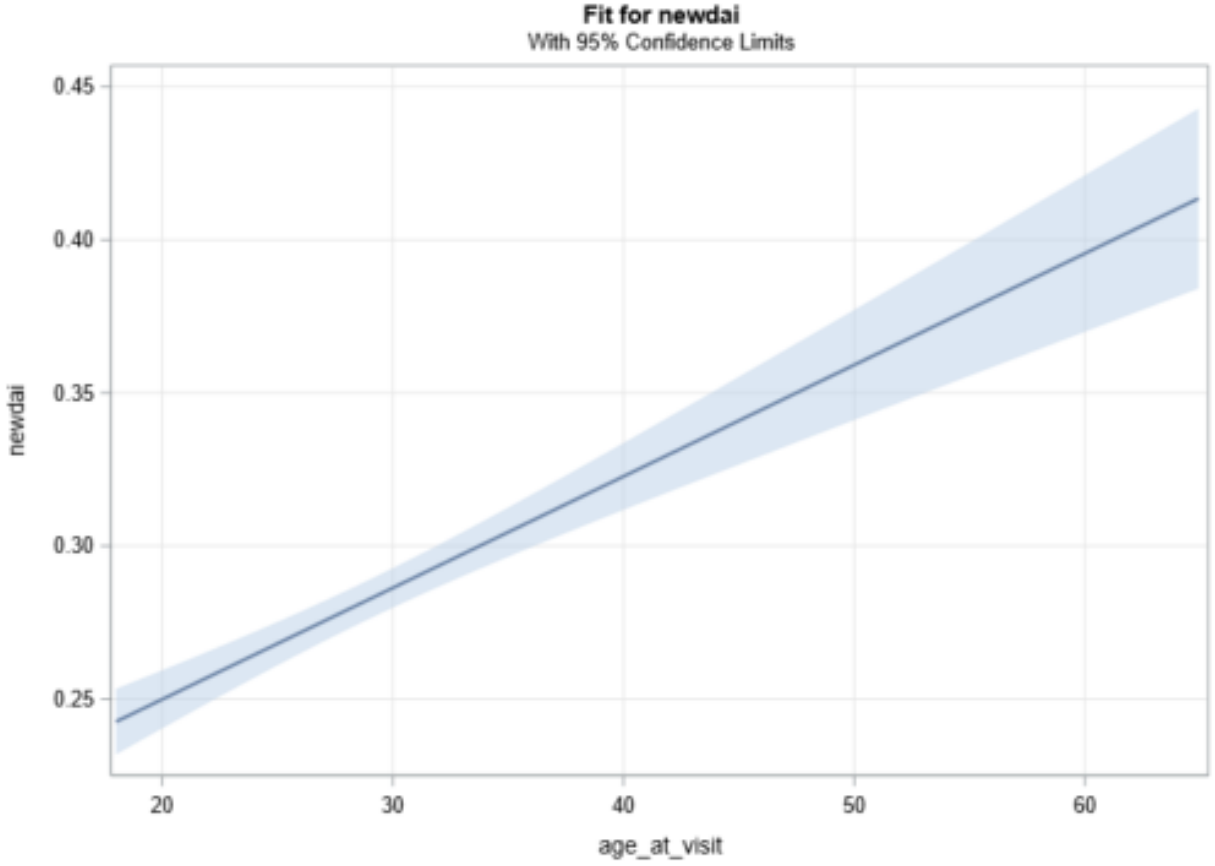


Figure 3: Correlation between the questionnaire-based DAI and 44-item clinical DAI

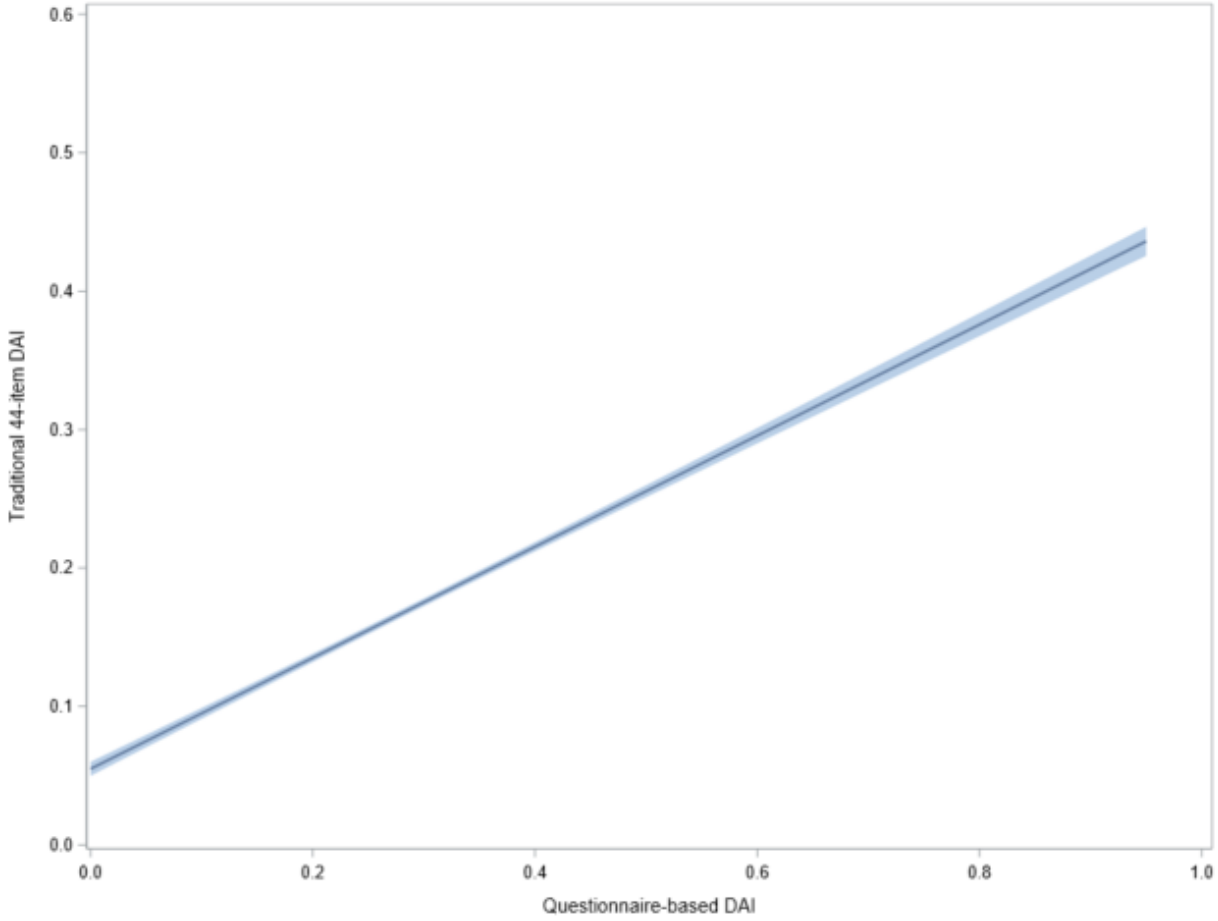
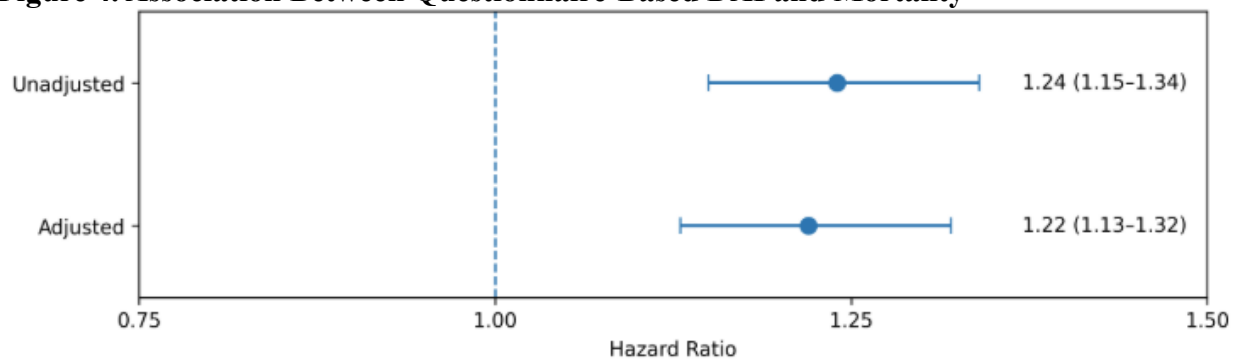


Figure 4. Association Between Questionnaire-Based DAI and Mortality



Adjusted for age at visit, sex, race/ethnicity, and year of diagnosis.

Expected Impact

This questionnaire-based DAI may provide an easier way to identify survivors with health impairments when detailed clinical information is unavailable. This instrument is constructed entirely from participant-reported cognitive, emotional, and physical/functional symptoms and limitations and therefore does not require prior clinical evaluation or knowledge of a medical diagnosis. The DAI score reflects the overall burden of accumulated deficits, while

latent class analysis helps identify different patterns of impairment among childhood cancer survivors. This distinction is important because individuals with a similar level of overall impairment may have different underlying problems, such as cognitive concerns, mental health problems, or impairments across multiple domains. Understanding these differences may help better characterize survivor health, facilitate risk stratification, identify high-risk survivor subgroups, and prioritize follow-up evaluation in settings where comprehensive clinical frailty assessments are not available.

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eTable 1. Initial Candidate Items for the Questionnaire-Based Deficit Accumulation Index

DAI Construct	Description	Value/Criteria	DAI Item Weight
prupst	I get upset easily	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prfrgt1	I forget instructions easily	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prwork2	I have problems completing my work	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prrcl	I have difficulty recalling things I had previously learned	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prwork1	It takes me longer to complete my work	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prfrt	I get frustrated easily	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prmood	My mood changes frequently	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prfind	I have trouble finding things in my bedroom, closet or desk	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prfrgt2	I forget what I am doing in the middle of things	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prstrt	I have problems getting started on my own	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prowh	I am easily overwhelmed	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prmlt	I have trouble doing more than one thing at a time	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prmess1	My desk/workspace is a mess	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prremb	I have trouble remembering things, even for a few minutes	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prpriort	I have trouble prioritizing my activities	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prread	I read slowly	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prwork3	I am slower than others when completing my work	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
prpres	I don't work well under pressure	1. Never a problem 2. Sometimes a problem	=1, DAI=0 >1, DAI=1

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		3. Often a problem	
prorg1	I am disorganized	1. Never a problem 2. Sometimes a problem 3. Often a problem	=1, DAI=0 >1, DAI=1
nerve	Nervousness or shaking inside	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
faint	Faintness or dizziness	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
painht	Pains in hear or chest	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
sudsc	Suddenly scared for no reason	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
lonly	Feeling lonely	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
blue	Feeling blue	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
noint	Feeling no interest in things	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
fear	Feeling fearful	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
nause	Nausea or upset stomach	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
breath	Trouble getting your breath	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1

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numb	Numbness or tingling in parts of your body	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
hopls	Feeling hopeless about the future	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
weak	Feeling weak in parts of your body	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
tense	Feeling tense or keyed up	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
panic	Spells of terror or panic	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
nosit	Feeling so restless you couldn't sit still	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
worth	Feelings of worthlessness	1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely	1-2, DAI=0 3-5, DAI=1
limvi	In last 2 years, health limited the kinds or amounts of vigorous activities you can do, like lifting heavy objects, running or participating in strenuous sports	1. Not limited at all 2. Limited for 3 months or less 3. Limited for more than 3 months	=1, DAI=0 >1, DAI=1
limm	In last 2 years, health limited the kinds or amounts of moderate activities you can do, like moving a table, carrying groceries or bowling	1. Not limited at all 2. Limited for 3 months or less 3. Limited for more than 3 months	=1, DAI=0 >1, DAI=1
hill	In last 2 years, health limited walking uphill or climbing a few flights of stairs	1. Not limited at all 2. Limited for 3 months or less 3. Limited for more than 3 months	=1, DAI=0 >1, DAI=1
bend	In last 2 years, health limited bending, lifting, or stooping	1. Not limited at all 2. Limited for 3 months or less 3. Limited for more than 3 months	=1, DAI=0 >1, DAI=1
block	In last 2 years, health limited walking one block	1. Not limited at all 2. Limited for 3 months or less	=1, DAI=0 >1, DAI=1

		3. Limited for more than 3 months	
self	In last 2 years, health limited eating, dressing, bathing, or using the toilet	1. Not limited at all 2. Limited for 3 months or less 3. Limited for more than 3 months	=1, DAI=0 >1, DAI=1
Help	Need help with personal care needs because of any impairment or health problems	1. Yes 2. No	=1, DAI=0 >1, DAI=1
Chore	Need help handling routine needs because of any impairment or health problems	1. Yes 2. No	=1, DAI=0 >1, DAI=1
Nojob	Kept from holding a job or attending school because of any impairment or health problem	1. Yes 2. No	=1, DAI=0 >1, DAI=1
drive	Currently have a driver's license	1. Yes 2. No	=1, DAI=0 >1, DAI=1
disable	Disability status rating	1. Not at all disabled 2. Mildly disabled 3. Moderately disable 4. Severely disabled 5. Completely disabled	1-2, DAI=0 3-5, DAI=1

eTable 2: Final Items Included in the Questionnaire-Based Deficit Accumulation Index

Variable Name	Description	
prupst	I get upset easily	Emotional regulation
prfrt	I get frustrated easily	
prmood	My mood changes frequently	
prwork2	I have problems completing my work	Task Efficiency
prwork1	It takes me longer to complete my work	
prmlt	I have trouble doing more than one thing at a time	
prwork3	I am slower than others when completing my work	
prpres	I don't work well under pressure	
prorg1	I am disorganized	Organization
prfind	I have trouble finding things in my bedroom, closet or desk	
prmess1	My desk/workspace is a mess	
prfrgt1	I forget instructions easily	Memory
prfrgt2	I forget what I am doing in the middle of things	
prrcl	I have difficulty recalling things I had previously learned	
prremb	I have trouble remembering things, even for a few minutes	
noint	Feeling no interest in things	Depression
lonly	Feeling lonely	
blue	Feeling blue	
worth	Feelings of worthlessness	
hopls	Feeling hopeless about the future	

nause	Nausea or upset stomach	Somatization
faint	Faintness or dizziness	
painht	Pains in hear or chest	
breath	Trouble getting your breath	
numb	Numbness or tingling in parts of your body	
weak	Feeling weak in parts of your body	
nerve	Nervousness or shaking inside	Anxiety
sudsc	Suddenly scared for no reason	
panic	Spells of terror or panic	
fear	Feeling fearful	
limvi	In last 2 years, health limited the kinds or amounts of vigorous activities you can do, like lifting heavy objects, running or participating in strenuous sports	Activities of Daily Living (ADL)
limm	In last 2 years, health limited the kinds or amounts of moderate activities you can do, like moving a table, carrying groceries or bowling	
hill	In last 2 years, health limited walking uphill or climbing a few flights of stairs	
bend	In last 2 years, health limited bending, lifting, or stooping	
block	In last 2 years, health limited walking one block	
self	In last 2 years, health limited eating, dressing, bathing, or using the toilet	
Help	Need help with personal care needs because of any impairment or health problems	Instrumental ADL
Chore	Need help handling routine needs because of any impairment or health problems	
Nojob	Kept from holding a job or attending school because of any impairment or health problem	
drive	Currently have a driver's license	

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CCSS questionnaire

N.4 How old were you when you started drinking?

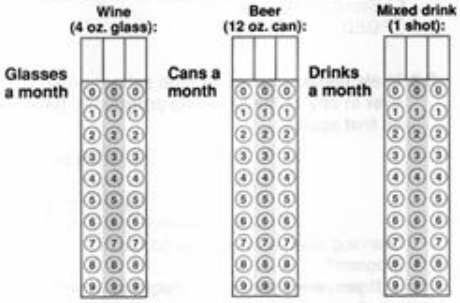
Years old:



N.5 When you drink, do you most often drink alone or with others?

- ○ Alone
- ○ With others

N.6 During the past 2 years, on the average, how many times per month did you drink the following: (If less than one per month, enter 0.)



N.7 On the days that you drink, on average, how many drinks do you have?

- ○ No drinks in the past 2 years
- ○ One drink/day
- ○ Two drinks/day
- ○ Three drinks/day
- ○ Four drinks/day
- ○ Five drinks/day
- ○ Six or more drinks/day

N.8 Have you had at least one drink of beer, wine, or liquor during the past year?

- ○ No
- ○ Yes

Physical Activity

N.9 On how many of the past 7 days did you exercise or do sports for at least 20 minutes that made you sweat or breathe hard (e.g. dancing, jogging, basketball, etc.)

- ○ 0 days
- ○ 1 day
- ○ 2 days
- ○ 3 days
- ○ 4 days
- ○ 5 days
- ○ 6 days
- ○ 7 days

N.10 Because of any impairment or health problems, do you need the help of other persons with personal care needs, such as eating, bathing, dressing, or getting around your home?

- ○ No
- ○ Yes

N.11 Because of any impairment or health problems, do you need the help of other persons in handling routine needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes.

- ○ No
- ○ Yes

N.12 Does any impairment or health problem keep you from holding a job or attending school?

- ○ No
- ○ Yes

N.13 Do you currently have a driver's license?

- ○ No
- ○ Yes

N.14 Over the last 2 years, how long (if at all) has your health limited you in each of the following activities? (Mark one circle on each line)

	Not limited at all	Limited for 3 months or less	Limited for more than 3 months
a. The kinds or amounts of vigorous activities you can do, like lifting heavy objects, running or participating in strenuous sports	○	○	○
b. The kinds or amounts of moderate activities you can do, like moving a table, carrying groceries or bowling	○	○	○
c. Walking uphill or climbing a few flights of stairs	○	○	○
d. Bending, lifting or stooping	○	○	○
e. Walking one block	○	○	○
f. Eating, dressing, bathing, or using the toilet	○	○	○

Health Practices

N.15 Would you say that your health is:

- ○ Excellent
- ○ Very good
- ○ Good
- ○ Fair
- ○ Poor