**CCSS Analysis Concept Proposal:** Mental health outcomes in adult survivors of childhood acute lymphoblastic leukemia treated with chemotherapy-only protocols
**Working Group:** Psychology
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## Background

Acute lymphoblastic leukemia (ALL) is the most common malignant cancer of childhood and accounts for 29% of all new pediatric cancer diagnoses.[1] Though ALL was once lethal, with contemporary therapy, 5-year survival exceeds 90% in children without high-risk disease.[2,3] Despite improvements in overall survival, survivors of childhood ALL may develop various treatment-related late complications. A report from the Childhood Cancer Survivor Study (CCSS) found that, out of 10,397 adult survivors of childhood cancer studied, 62.3% reported at least one chronic health condition, and 27.5% reported a severe or life-threatening condition.[4] Another group observed that, compared to non-cancer controls, survivors of childhood ALL were twice as likely to report poor functional status, defined as requiring help with personal care or routine needs, or difficulty holding a job or attending school.[5] As a result, reducing treatment-related adverse late effects has emerged as an additional therapeutic focus.

A report from the CCSS in 2003 described the prevalence and type of adverse health outcomes among 9535 adults who had survived at least 5 years after treatment for childhood cancer between 1970 and 1986 and compared these to outcomes of non-cancer controls.[6] Six health domains were measured: general health, cancer-related anxiety, cancer-related pain, functional impairment, mental health, and activity limitation. Among adult survivors of childhood leukemia, 40.3% reported moderate to extreme adverse health status, and 17.5% reported moderate to extreme degrees of adverse mental health. Cranial radiotherapy (CRT) was associated with adverse health status outcome. A subsequent report from the CCSS in 2017 compared the health status of 15,556 adult survivors of childhood cancer treated between 1970 and 1999

according to decade of treatment. Despite a reduction in mean cumulative doses of chemotherapy and radiation and a lower proportion of survivors reporting a medically significant, disabling, or severe chronic health condition, patient-rated health status did not improve over time compared to that of 3,149 non-cancer controls.[7] Poor general health and cancer-related anxiety were reported most frequently in survivors treated between 1990 and 1999, and least often in survivors treated between 1970 and 1979. Survivors reported adverse health outcomes more frequently than siblings did across all health domains. Among ALL survivors specifically, the percentage of survivors who received CRT decreased across treatment decade from 82.8% (1970-1979) to 50.4% (1980-1989) to 23.9% (1990-1999). Despite this reduction, the percentage of ALL survivors who reported poor general health, cancer-related pain, and cancer-related anxiety increased across treatment decade.

Prophylactic CRT, which was once integral in preventing central nervous system (CNS) relapse, is associated with increased risk of adverse psychological late effects such as social-emotional difficulties and psychologic distress,[8,9] and is now reserved only for treatment of high-risk disease. The manifestations of adverse mental health can vary depending on a survivor's age at diagnosis and treatment.[10] Survivors diagnosed in adolescence experience more post-traumatic stress and arousal symptoms and have lower psychological health-related quality of life than survivors diagnosed before adolescence.[11] In addition, survivors are more likely to experience difficulties in school, be unemployed, have problems with personal and financial independence, and face challenges in interpersonal relationships, including being less likely to marry than the general population.[12-14]

The CCSS has delivered valuable data regarding the prevalence of adverse mental health in adult survivors of childhood ALL treated between 1970 and 1999, but the evolution of contemporary therapy may have influenced these findings. The detailed treatment histories of the CCSS sample makes possible a comparison of adverse mental health outcomes over time while controlling for therapy received. Previous work has emphasized treatment decade to measure changes in health status over time, but there may be additional unmeasured variables influencing these outcomes. One such variable is the era in which a survivor grew up, where differences can shape an individual's opinions, expectations, and core values. In the 1970's, a cancer diagnosis was often perceived as a death sentence, and it was rarely discussed openly.[15] Since then, scientific advances have led to changes in public opinion regarding cancer. Cancer is no longer considered a death sentence, and it is now openly discussed in American society through the media, research literature, and both local and federal governments.[16,17] Given the absence of concrete variables to measure prevailing societal attitudes about cancer treatment and follow-up care, to account for changes in public opinion regarding these issues, the current study will examine the association between treatment year and adverse mental health status. Adjusting for survivors' age at diagnosis and therapy received may reveal specific changes in mental health outcomes based on a survivor's age at the time of treatment, a novel combination. The detailed medical histories of the CCSS sample allows further investigation into the impact of chronic health conditions on mental health outcomes. Finally, examining the relationship between adverse mental health and social attainment outcomes may yield real-world applications of these demographic and treatment variables, and perhaps allow opportunities for intervention to improve outcomes.

## Specific Aims and Hypotheses

Among survivors of childhood ALL treated with chemotherapy who did not receive CRT (from here, referred to as "chemotherapy-only"), where "mental health" refers to self-reported global mental health as well as symptoms of depression, anxiety, and somatization:

1. Determine the prevalence of adverse mental health (global and by domain) outcomes and compare it to that of childhood ALL survivors exposed to CRT (any dose) and to that of non-cancer (sibling) controls.

*Hypothesis: Survivors of childhood ALL who did not receive CRT have better mental health outcomes than those who did receive CRT, but have worse mental health outcomes than that of non-cancer controls.*

2. Identify demographic and treatment-related factors associated with adverse mental health outcomes.

*Hypothesis: Older age at treatment, female sex, low socioeconomic status, and higher cumulative doses of specific chemotherapy agents are associated with worse mental health outcomes.*

3. Examine the association between chronic health conditions and adverse mental health outcomes.

*Hypothesis: The presence of a chronic health condition is associated with more mental health problems.*

4. Examine the influence of prevailing societal beliefs regarding cancer treatment and follow-up care on adverse mental health outcomes.

*Hypothesis: After adjusting for age at cancer diagnosis, the mental health outcomes of childhood ALL survivors treated in an earlier year are better compared to those of survivors treated more recently.*

5. Examine the impact of adverse mental health outcomes on social attainment outcomes.

*Hypothesis: Adverse mental health is associated with lower social attainment.*

## Population

Survivors of childhood ALL in the original and expansion cohorts who answered the baseline questionnaire will be included if they have attained an age of 18 years or older at the time of their respective follow up survey. To ensure that time between diagnosis and follow-up is consistent between cohorts, we will use responses from the Follow-Up 2 questionnaire for survivors from the original cohort and responses from the Follow-Up 5 questionnaire for survivors from the expansion cohort.

*Inclusion criteria:*

- Diagnosis of ALL
- Age at diagnosis 0-20 years
- Original cohort completed Follow-Up 2 survey; Expansion cohort completed Follow-Up 5 survey
- Original sibling cohort completed Follow-Up 2 survey; Expansion sibling cohort completed Follow-Up 5 survey

There will be two cohorts to which the responses of ALL survivors who did not receive CRT will be compared. The first comparison cohort will be composed of sibling (non-cancer) controls. The second comparison cohort will be composed of survivors who received CRT. This second comparison cohort will be excluded from the main analysis. Survivors younger than 18 years at the time of follow up survey will also be excluded from all analyses.

**Dependent Variables**

1. *Adverse mental health,* as defined as either one of the following:
    a. Score of greater than or equal to 63 on the BSI (Brief Symptom Inventory)-18 on any two of the three subscales (anxiety, somatization, depression) or global mental health.
        i. Follow-Up 2 G1-20
        ii. Follow-Up 5 L1-L20
    b. Currently taking antidepressant, anxiolytic, or other psychotropic medication versus not.
        i. Follow-Up 2 Q8-9
        ii. Follow-Up 5 C2.9,11
2. *Symptoms of anxiety*: score of greater than or equal to 63 on the BSI-18 on the anxiety subscale, or currently taking anxiolytic medication.
3. *Symptoms of depression*: score of greater than or equal to 63 on the BSI-18 on the depression subscale, or currently taking antidepressant medication.
4. *Symptoms of somatization*: score of greater than or equal to 63 on the BSI-18 on the somatization subscale.
5. *Social attainment:* Will be determined based on level of education attained, employment and marital status, current personal income, and independent living. Indices of social attainment will only be measured in survivors aged 25 years and older at time of follow up.

**Independent Variables**

1. Age at diagnosis
    a. 0 – 5 years old
    b. 6 – 12 years old
    c. 13 – 20 years old
2. Treatment year

**Patient Descriptor Variables**

1. Demographics
    a. Age at diagnosis and follow-up
        i. Original cover page and A1
        ii. Expansion cover page and A1
    b. Race/ethnicity (Asian, White non-Hispanic, Hispanic, African American non-Hispanic, other)
        i. Original A4, A4a
        ii. Expansion A5, A5a
    c. Sex
        i. Original A2
        ii. Expansion A2

d. Educational attainment (less than high school, high school diploma, some college or vocational, college graduate)
    i. Original O1-O4
    ii. Expansion R1-R4
e. Marital status (married, married formerly but not currently, never married)
    i. Original L1-L2
    ii. Expansion M1
f. Income
    i. Original Q8 (household income) - Q9 (personal income)
    ii. Expansion T1 (household income) - T3 (personal income)
g. Employment status (employed versus unemployed)
    i. Original O5-O7
    ii. Expansion S1-S2
h. Independent living (rent or own residence versus live with parents)
    i. Original A.9
    ii. Expansion A.9
i. Insurance status (yes or Canadian [original only] versus no)
    i. Original Q2
    ii. Expansion U2

2. Health demographics
    a. Smoking (never, past, current)
        i. Original N1a-d
        ii. Expansion O1-O3
    b. Heavy alcohol intake (7+/week female, 14+ week male)
        i. Original N3, N6-N7
        ii. Expansion O9, O11-O14
    c. Body mass index (BMI; underweight < 18.5 $kg/m^2$, normal 18.5 – 24.9 $kg/m^2$, overweight 25.0 – 29.9 $kg/m^2$, Class 1 obese 30 – 34.9 $kg/m^2$, Class 2 obese 35 – 39.9 $kg/m^2$, Class 3 obese ≥ 40 $kg/m^2$)
        i. Original A10-A11
        ii. Expansion A3-A4
    d. Comorbid Grade 2, 3, or 4 chronic health condition: As per matrix
        i. Original – Common terminology criteria for adverse events (CTCAE) v. 4.03. Bethesda, MD: National Cancer Institute; 2010.
        ii. Expansion – CTCAE (as per 2.d.i)
3. Chemotherapy received
    a. Cumulative doxorubicin equivalent dose
        i. None
        ii. 1-99 $mg/m^2$
        iii. 100-199 $mg/m^2$
        iv. 200-299 $mg/m^2$
        v. ≥300 $mg/m^2$
    b. Cumulative cyclophosphamide equivalent dose
        i. None

ii. 1-999 mg/$m^2$
iii. 1,000-1,999 mg/$m^2$
iv. 2,000-2,999 mg/$m^2$
v. 3,000-3,999 mg/$m^2$
vi. 4,000-4,999 mg/$m^2$
vii. ≥5,000 mg/$m^2$

c. Glucocorticoids
    i. Dexamethasone (yes, no)
    ii. Prednisone (yes, no)
d. Methotrexate
    i. IV (yes, no; if yes, whether or not high-dose [≥4300 mg/$m^2$])
    ii. IT (yes, no; if yes, cumulative dose)
    iii. PO (yes, no)
e. Cytarabine (yes, no)
f. Vincristine (yes, no)
g. 6-Mercaptopurine
    i. IV
    ii. PO
h. Thioguanine (yes, no)
i. CRT
    i. None
    ii. Scatter low
    iii. Scatter high
    iv. 1-1999 cGy
    v. 2000-2999 cGy
    vi. ≥ 3000 cGy

## Analysis

*Sample characteristics*
We will compare demographic, health, and social attainment factors between ALL survivors treated with chemotherapy or chemotherapy plus CRT and sibling controls (**Table 1**). We will also compare treatment variables between survivors who did and did not receive CRT. We will also compare differences between participants who completed the follow up survey to those who did not by attained age at time of survey, gender, and race/ethnicity.

*Aim 1*: *Determine the prevalence of adverse mental health (global and by domain) outcomes and compare it to that of childhood ALL survivors exposed to CRT and to that of non-cancer (sibling) controls.*
We will calculate the prevalence of adverse mental health as defined above among ALL survivors divided into groups of those exposed to chemotherapy only and those exposed to CRT and among siblings. ALL survivors who received chemotherapy only will be compared separately to those who received CRT and to siblings. Analyses will be carried out using log binomial regression models to model probability of impairment or adverse outcome and will *a priori* be adjusted for sex, attained age, race/ethnicity, and other key demographic variables identified. Models including siblings will include robust sandwich variances to account for correlation between family members. Prevalence Ratios (PR), 95% Confidence Intervals (CIs), and *p*-values will be presented (**Table 2**).

*Aim 2*: *Identify demographic and treatment-related factors associated with adverse mental health outcomes.*
We will conduct univariate and multivariable log binomial regression analyses to evaluate the associations between demographic and treatment-related factors and adverse mental health outcomes among ALL survivors who did not receive CRT. Results will be displayed as PRs, 95% CIs, and *p*-values for categories of each variable (**Tables 3a and 3b**). Univariate models will be fit first and a multivariable model will be built based on step-up and step-down model fitting.

*Aim 3: Examine the association between chronic health conditions and adverse mental health outcomes.*
We will compare the prevalence of adverse mental health among ALL survivors (excluding those who received CRT) by groups defined as those with a prior report of: a maximum of one grade 1 or grade 2 chronic health condition, two or more maximum grade 1 or grade 2 chronic health conditions, just one grade 3 or grade 4 chronic health condition, or two or more grade 3 or grade 4 chronic health conditions, compared to those not reporting any chronic health conditions. Similar models to those described for the above Aims will be used to make these comparisons in models adjusted for age, sex, race/ethnicity, and other key demographic or treatment factors identified in prior models. Results will be reported as PRs (**Table 4**). For the primary analysis, we will use the Overall, Cardiac, Respiratory, Endocrine, and Neurologic categories of chronic health conditions. In addition, we will explore the association between balance and sensory neuropathy and adverse mental health.

*Aim 4*: *Examine the influence of prevailing societal beliefs regarding cancer treatment and follow-up care on adverse mental health outcomes.*
In the absence of concrete variables to measure societal attitudes about cancer treatment and follow-up care, we will examine treatment year and age at diagnosis as surrogates for understanding how our outcomes are associated with these changes. Therefore, we will repeat the analyses reported in Tables 5a and 5b using treatment year and age at diagnosis as

potential risk factors to explore the degree to which these variables are associated with adverse mental health outcomes. Potential modifications to this approach could include using birth year instead of treatment year along with the associated interactions. Models will be adjusted for key demographic and treatment-related factors identified earlier, and we will present predicted prevalence of adverse mental health outcomes across treatment year (**Table 5**). Models will use year and age variables as continuous variables initially using spline functions to explore shapes of curves, though some categorical versions may be examined for display purposes (**Figure 1**).

*Aim 5: Examine the impact of adverse mental health outcomes on social attainment outcomes.* We will compare measures of social attainment among ALL survivors who did not receive CRT for those reporting adverse mental health outcomes to that in survivors not reporting adverse mental health (**Tables 6a-e**). Log binomial models will be fit to each social attainment outcome, which will be defined as follows:

- Full-time employment: 1 (yes) or 0 (no)
- ≥ $20,000 income: 1 (yes) or 0 (no)
- Living independently: 1 (yes) or 0 (no)
- Education: 1 (High school graduate plus some vocational school or college) or 0 (less than or equal to high school graduate)
- Marital status: 1 (married ever) or 0 (never married)

Separate models will be fit for each outcome and each adverse mental health condition. Outcomes will be included as a binary risk factor adjusted for age, sex, race/ethnicity, and other key demographic or treatment factors identified in prior models.

## Tables and figures

Table 1. Study population demographic and health information

| | Survivors | | Siblings (%) | Pairwise comparison (*p* value) | |
|---|---|---|---|---|---|
| | Chemo only (%) | CRT (%) | | Chemo vs. CRT | Chemo vs. siblings |
| Age at questionnaire (years; mean, SD) | | | | | |
| Sex | | | | | |
| Female | | | | | |
| Male | | | | | |
| Race/ethnicity | | | | | |
| Asian | | | | | |
| Black (non-Hispanic) | | | | | |
| Hispanic | | | | | |
| White (non-Hispanic) | | | | | |
| Other | | | | | |
| Social attainment[+] | | | | | |
| Educational attainment | | | | | |
| Less than High school | | | | | |
| High school diploma | | | | | |
| High school, some college or vocational | | | | | |
| College graduate | | | | | |
| Marital status | | | | | |
| Married currently | | | | | |
| Married, not currently | | | | | |
| Never married | | | | | |
| Employment status | | | | | |
| Employed full-time | | | | | |
| Not employed full-time | | | | | |
| Independence | | | | | |
| Living independently | | | | | |
| Living as dependent | | | | | |
| Household income | | | | | |
| None | | | | | |
| Less than $20,000 | | | | | |
| $20,000 - $39,999 | | | | | |
| $40,000 - $59,999 | | | | | |
| $60,000 - $79,999 | | | | | |
| Over $80,000 | | | | | |
| Insurance status | | | | | |
| Yes/Canadian | | | | | |
| No | | | | | |
| Body mass index | | | | | |
| Underweight | | | | | |
| Normal | | | | | |
| Overweight | | | | | |
| Obese | | | | | |
| Class 1 | | | | | |
| Class 2 | | | | | |
| Class 3 | | | | | |
| Smoking | | | | | |
| Current | | | | | |
| Past | | | | | |
| Never | | | | | |
| Heavy drinking | | | | | |
| Yes | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| No | | | | | |
| Birth year | | | | | |
| Before1979 | | | | | |
| 1980-1989 | | | | | |
| 1990-1999 | | | | | |
| Treatment decade | | | N/A | | N/A |
| 1970-1979 | | | N/A | | N/A |
| 1980-1989 | | | N/A | | N/A |
| 1990-1999 | | | N/A | | N/A |
| Cumulative anthracycline dose (doxorubicin equivalents) | | | N/A | | N/A |
| None | | | N/A | | N/A |
| 1-99 mg/m$^2$ | | | N/A | | N/A |
| 100-199 mg/m$^2$ | | | N/A | | N/A |
| 200-299 mg/m$^2$ | | | N/A | | N/A |
| ≥300 mg/m$^2$ | | | N/A | | N/A |
| Cumulative alkylator dose (cyclophosphamide equivalents) | | | N/A | | N/A |
| None | | | N/A | | N/A |
| 1-999 mg/m$^2$ | | | N/A | | N/A |
| 1,000-1,999 mg/m$^2$ | | | N/A | | N/A |
| 2,000-2,999 mg/m$^2$ | | | N/A | | N/A |
| 3,000-3,999 mg/m$^2$ | | | N/A | | N/A |
| 4,000-4,999 mg/m$^2$ | | | N/A | | N/A |
| ≥5,000 mg/m$^2$ | | | N/A | | N/A |
| Prednisone | | | N/A | | N/A |
| Yes | | | N/A | | N/A |
| No | | | N/A | | N/A |
| Dexamethasone | | | N/A | | N/A |
| Yes | | | N/A | | N/A |
| No | | | N/A | | N/A |
| Methotrexate (cumulative dose) | | | N/A | | N/A |
| IT | | | N/A | | N/A |
| IV | | | N/A | | N/A |
| High-dose (≥4300 mg/m$^2$ ) | | | N/A | | N/A |
| No high-dose | | | N/A | | N/A |
| PO | | | N/A | | N/A |
| Cytarabine | | | N/A | | N/A |
| Yes | | | N/A | | N/A |
| No | | | N/A | | N/A |
| Vincristine | | | N/A | | N/A |
| Yes (cumulative dose) | | | N/A | | N/A |
| No | | | N/A | | N/A |
| 6-mercaptopurine | | | N/A | | N/A |
| IV | | | N/A | | N/A |
| PO | | | N/A | | N/A |
| Thioguanine | | | N/A | | N/A |
| Yes | | | N/A | | N/A |
| No | | | N/A | | N/A |

+Social attainment will only be measured in survivors aged 25 years and older at Follow-up

Table 2. Prevalence of adverse mental health and chronic health conditions in study population, adjusted for age, sex, race/ethnicity, and other key demographic or treatment factors identified in prior models

| | Survivors | | Siblings N (%) | Pairwise comparison (*p* value) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Chemo only N (%) | CRT N (%) | | Chemo vs. CRT | | | Chemo vs. siblings | | |
| | | | | PR | 95% CI | *p* | PR | 95% CI | *p* |
| Adverse mental health | | | | | | | | | |
| Global | | | | | | | | | |
| Depression | | | | | | | | | |
| Anxiety | | | | | | | | | |
| Somatization | | | | | | | | | |
| Chronic health conditions | | | | | | | | | |
| None | | | | | | | | | |
| One Maximum Grade 1-2 | | | | | | | | | |
| ≥2 Maximum Grade 1-2 | | | | | | | | | |
| One Grade 3-4 | | | | | | | | | |
| ≥2 Grade 3-4 | | | | | | | | | |

Tables 3a and 3b. Univariate (3a) and multivariable (3b) models for adverse mental health according to demographic and treatment factors adjusted for age, sex, race/ethnicity, and other key demographic or treatment factors identified in prior models. Similar tables will be used for univariate models and multivariable models with reduced number of key important factors included.

| | Adverse global mental health PR (95% CI), *p* value | Depression PR (95% CI), *p* value | Anxiety PR (95% CI), *p* value | Somatization PR (95% CI), *p* value |
|---|---|---|---|---|
| Attained age (years) | | | | |
| 18-19 | | | | |
| 20-24 | | | | |
| 25-29 (Ref) | | | | |
| 30-34 | | | | |
| ≥35 | | | | |
| Age at diagnosis | | | | |
| 0-5 years (Ref) | | | | |
| 6-12 years | | | | |
| 13-20 years | | | | |
| Sex | | | | |
| Female | | | | |
| Male (Ref) | | | | |
| Race/ethnicity | | | | |
| Asian | | | | |
| Black (non-Hispanic) | | | | |
| Hispanic | | | | |
| White (non-Hispanic; Ref) | | | | |
| Other | | | | |
| Educational attainment | | | | |
| Less than high school | | | | |
| High school diploma | | | | |
| High school, some college or vocational | | | | |
| College graduate (Ref) | | | | |
| Marital status | | | | |
| Married currently (Ref) | | | | |
| Married, not currently | | | | |
| Never married | | | | |
| Employment status | | | | |
| Employed full time (Ref) | | | | |
| Not employed full time | | | | |
| Independence | | | | |
| Living independently (Ref) | | | | |
| Not living independently | | | | |
| Household income | | | | |
| None | | | | |
| Less than $20,000 | | | | |
| $20,000 - $39,999 | | | | |
| $40,000 - $59,999 | | | | |
| $60,000 - $79,999 | | | | |
| ≥$80,000 (Ref) | | | | |
| Insurance status | | | | |
| Yes/Canadian (Ref) | | | | |
| No | | | | |
| Body mass index | | | | |
| Underweight | | | | |
| Normal (Ref) | | | | |
| Overweight | | | | |

| | | | | |
|---|---|---|---|---|
| Obese | | | | |
| Class 1 | | | | |
| Class 2 | | | | |
| Class 3 | | | | |
| Smoking | | | | |
| Current | | | | |
| Past | | | | |
| Never (Ref) | | | | |
| Heavy drinking | | | | |
| Yes | | | | |
| No (Ref) | | | | |
| Therapy received[+] | | | | |
| Cumulative anthracycline dose (doxorubicin equivalents) | | | | |
| None (Ref) | | | | |
| 1-99 mg/m$^2$ | | | | |
| 100-199 mg/m$^2$ | | | | |
| 200-299 mg/m$^2$ | | | | |
| ≥300 mg/m$^2$ | | | | |
| Cumulative alkylator dose (cyclophosphamide equivalents) | | | | |
| None (Ref) | | | | |
| 1-999 mg/m$^2$ | | | | |
| 1,000-1,999 mg/m$^2$ | | | | |
| 2,000-2,999 mg/m$^2$ | | | | |
| 3,000-3,999 mg/m$^2$ | | | | |
| 4,000-4,999 mg/m$^2$ | | | | |
| ≥5,000 mg/m$^2$ | | | | |
| Prednisone | | | | |
| Yes | | | | |
| No (Ref) | | | | |
| Dexamethasone | | | | |
| Yes | | | | |
| No (Ref) | | | | |
| Methotrexate | | | | |
| IT | | | | |
| IV | | | | |
| High-dose (≥4300 mg/m$^2$) | | | | |
| No high-dose (Ref) | | | | |
| Cytarabine | | | | |
| No (Ref) | | | | |
| Yes | | | | |
| Vincristine | | | | |
| Yes (Cumulative dose) | | | | |
| No (Ref) | | | | |
| Thioguanine | | | | |
| No (Ref) | | | | |
| Yes | | | | |
| 6-Mercaptopurine | | | | |
| IV | | | | |
| Yes | | | | |
| No (Ref) | | | | |
| PO | | | | |

[+] We will exclude any exposure in which ≥95% of ALL survivors received and for which we do not have cumulative doses

Table 4. Percent of ALL survivors and siblings reporting adverse mental health according to presence of a chronic health condition adjusted for age, sex, race/ethnicity, and other key demographic or treatment factors identified in prior models. Similar sections will be added to this table for each of the types of chronic conditions examined.

| Comorbid chronic health condition | Adverse global mental health RR (95% CI) | | Depression RR (95% CI) | | Anxiety RR (95% CI) | | Somatization RR (95% CI) | |
|---|---|---|---|---|---|---|---|---|
| | Survivors | Siblings | Survivors | Siblings | Survivors | Siblings | Survivors | Siblings |
| None (Ref) | | 1 | | 1 | | 1 | | 1 |
| One Maximum Grade 1-2 | | | | | | | | |
| ≥ 2 Maximum Grade 1-2 | | | | | | | | |
| One Grade 3-4 | | | | | | | | |
| ≥ 2 Grade 3-4 | | | | | | | | |

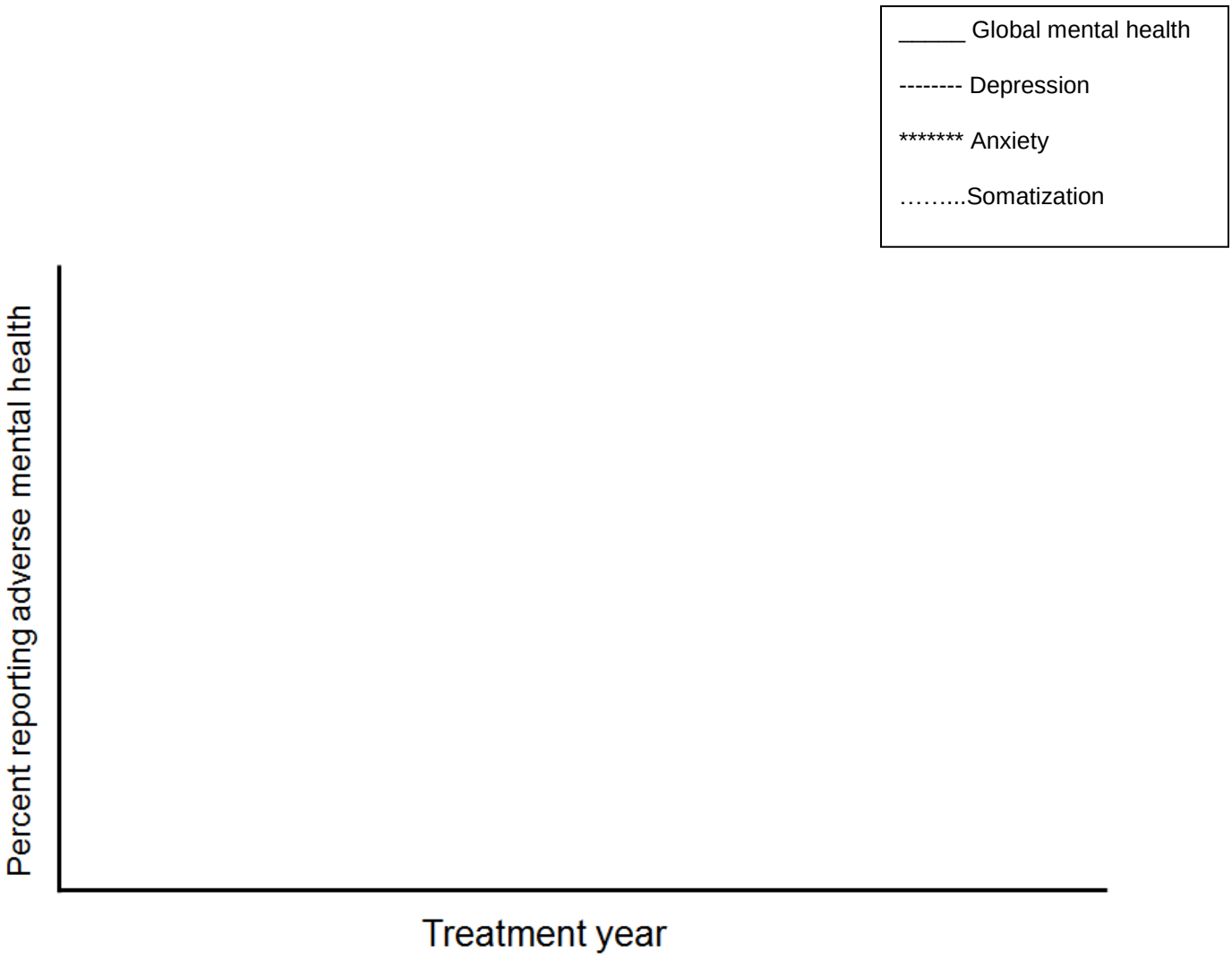
Table 5. Percent of ALL survivors and siblings reporting adverse mental health according to treatment year (top) and age at diagnosis (bottom), adjusted for age, sex, race/ethnicity, and other key variables identified.

| | Global mental health | | | Depression | | | Anxiety | | | Somatization | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment year*^** | Survivors (%) | Siblings (%) | *p* value | Survivors (%) | Siblings (%) | *p* value | Survivors (%) | Siblings (%) | *p* value | Survivors (%) | Siblings (%) | *p* value |
| 1970-79 | | | | | | | | | | | | |
| 1980-89 | | | | | | | | | | | | |
| 1990-99 | | | | | | | | | | | | |
| **Age at diagnosis (years)** | Survivors (%) | Siblings (%) | *p* value | Survivors (%) | Siblings (%) | *p* value | Survivors (%) | Siblings (%) | *p* value | Survivors (%) | Siblings (%) | *p* value |
| 0-5 | | | | | | | | | | | | |
| 6-12 | | | | | | | | | | | | |
| 13-20 | | | | | | | | | | | | |

* For purposes of data display, treatment year is depicted by decade. Analyses will be conducted with treatment year as a continuous variable.

^ If there is an interaction between treatment year and age at diagnosis, it will be included in the model. As described in text, we will also evaluate the model with birth year rather than treatment year.

Figure 1. Percent reporting adverse mental health by treatment year, adjusted for age, sex, race/ethnicity, and other key demographic or treatment factors identified in prior models.



Tables 6a-6e. Measures of social attainment: Full-time employment (**6a**), educational attainment (**6b**), income (**6c**), independent living (**6d**), and marital status (6e) according to adverse mental health, adjusted for age, sex, race/ethnicity, and other key demographic or treatment factors identified in prior models.

6a. Full-time employment

| Mental health status | Yes (N, %, PR, 95% CI) | No (N, %, PR, 95% CI) | *p* |
|---|---|---|---|
| Adverse global mental health | | | |
| Non-adverse global mental health (Ref) | | | |
| Symptoms of depression | | | |
| No symptoms of depression (Ref) | | | |
| Symptoms of anxiety | | | |
| No symptoms of anxiety (Ref) | | | |
| Symptoms of somatization | | | |
| No symptoms of somatization (Ref) | | | |

6b. Educational attainment

| Mental health status | Less than or equal to high school diploma (N, %, PR, 95% CI) | Greater than high school diploma (N, %, PR, 95% CI) | *p* |
|---|---|---|---|
| Adverse global mental health | | | |
| Non-adverse global mental health (Ref) | | | |
| Symptoms of depression | | | |
| No symptoms of depression (Ref) | | | |
| Symptoms of anxiety | | | |
| No symptoms of anxiety (Ref) | | | |
| Symptoms of somatization | | | |
| No symptoms of somatization (Ref) | | | |

6c. ≥ $20,000 income

| Mental health status | Yes (N, %, PR, 95% CI) | No (N, %, PR, 95% CI) | *p* |
|---|---|---|---|
| Adverse global mental health | | | |
| Non-adverse global mental health (Ref) | | | |
| Symptoms of depression | | | |
| No symptoms of depression (Ref) | | | |
| Symptoms of anxiety | | | |
| No symptoms of anxiety (Ref) | | | |
| Symptoms of somatization | | | |
| No symptoms of somatization (Ref) | | | |

6d. Living independently

| Mental health status | Yes (N, %, PR, 95% CI) | No (N, %, PR, 95% CI) | *p* |
|---|---|---|---|
| Adverse global mental health | | | |
| Non-adverse global mental health (Ref) | | | |

| | | | |
|---|---|---|---|
| Symptoms of depression | | | |
| No symptoms of depression (Ref) | | | |
| Symptoms of anxiety | | | |
| No symptoms of anxiety (Ref) | | | |
| Symptoms of somatization | | | |
| No symptoms of somatization (Ref) | | | |

6e. Marital status

| Mental health status | Ever married (N, %, PR, 95% CI) | Never married (N, %, PR, 95% CI) | *p* |
|---|---|---|---|
| Adverse global mental health | | | |
| Non-adverse global mental health (Ref) | | | |
| Symptoms of depression | | | |
| No symptoms of depression (Ref) | | | |
| Symptoms of anxiety | | | |
| No symptoms of anxiety (Ref) | | | |
| Symptoms of somatization | | | |
| No symptoms of somatization (Ref) | | | |

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