

# Specific causes of late-mortality, excess risk of death and modifiable risk factors:

Results over five decades of follow-up in the Childhood Cancer Survivor Study

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**CCSS**

Childhood Cancer  
Survivor Study



St. Jude Children's  
Research Hospital

Finding cures. Saving children.

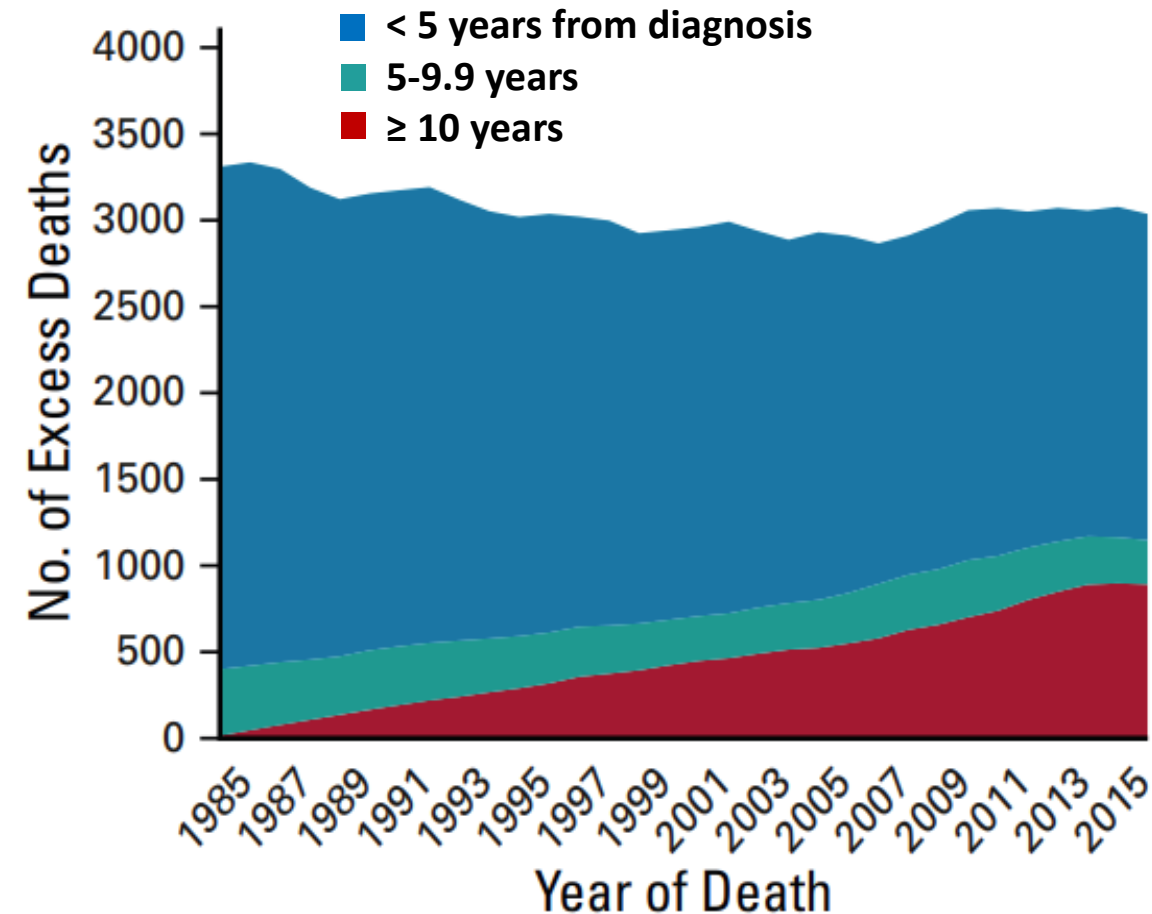
# Background

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Five-year survival for childhood cancer now exceeds 85%.

But, survivors are at increased risk for late mortality and experience excess deaths compared to the general population >5 years from diagnosis.

Yet, specific causes of late mortality, excess deaths and the impact of modifiable risk factors are not well established.



Compare all-cause and cause-specific late mortality among survivors over five decades compared to that expected in the general population.

Evaluate patterns of causes of death using ICD-9 and ICD-10 codes from the National Death Index.

Evaluate risk factors for late mortality including modifiable lifestyle and cardiovascular risk factors.

# Eligible Study Population

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Included original and expansion cohort, diagnosed **1970 to 1999**

Detailed treatment data with imputation for eligible non-participants

The cohort of 34,230 eligible survivors were included in this analysis

For modifiable risk analysis the subset of participants who completed at least one survey at age 18 or greater were included (n=20,051)

## Late Mortality

Death >5 years after diagnosis from the National Death Index through 2017 for evaluation of:

1. All-cause mortality
2. Cause-specific mortality due to:
  - Recurrence or progression of primary cancer
  - External/accidental cause
  - Other health-related cause (includes treatment-related conditions)
3. Causes-of-death using ICD-9 and -10 classification codes

## Modifiable Risk Factors

- 1) Traditional cardiovascular risk factors (CVRFs): hypertension, diabetes, dyslipidemia of CTCAE grade  $\geq 2$
- 2) Modifiable lifestyle factors (smoking status, alcohol use, physical activity, obese/underweight) were assessed, assigned a score (0-1) and summed to create a total lifestyle score (0-4), categorized below.

Modifiable lifestyle category	Score range
Unhealthy	0 – 2.0
Moderately healthy	2.5 – 3.0
Healthy	3.5 – 4.0

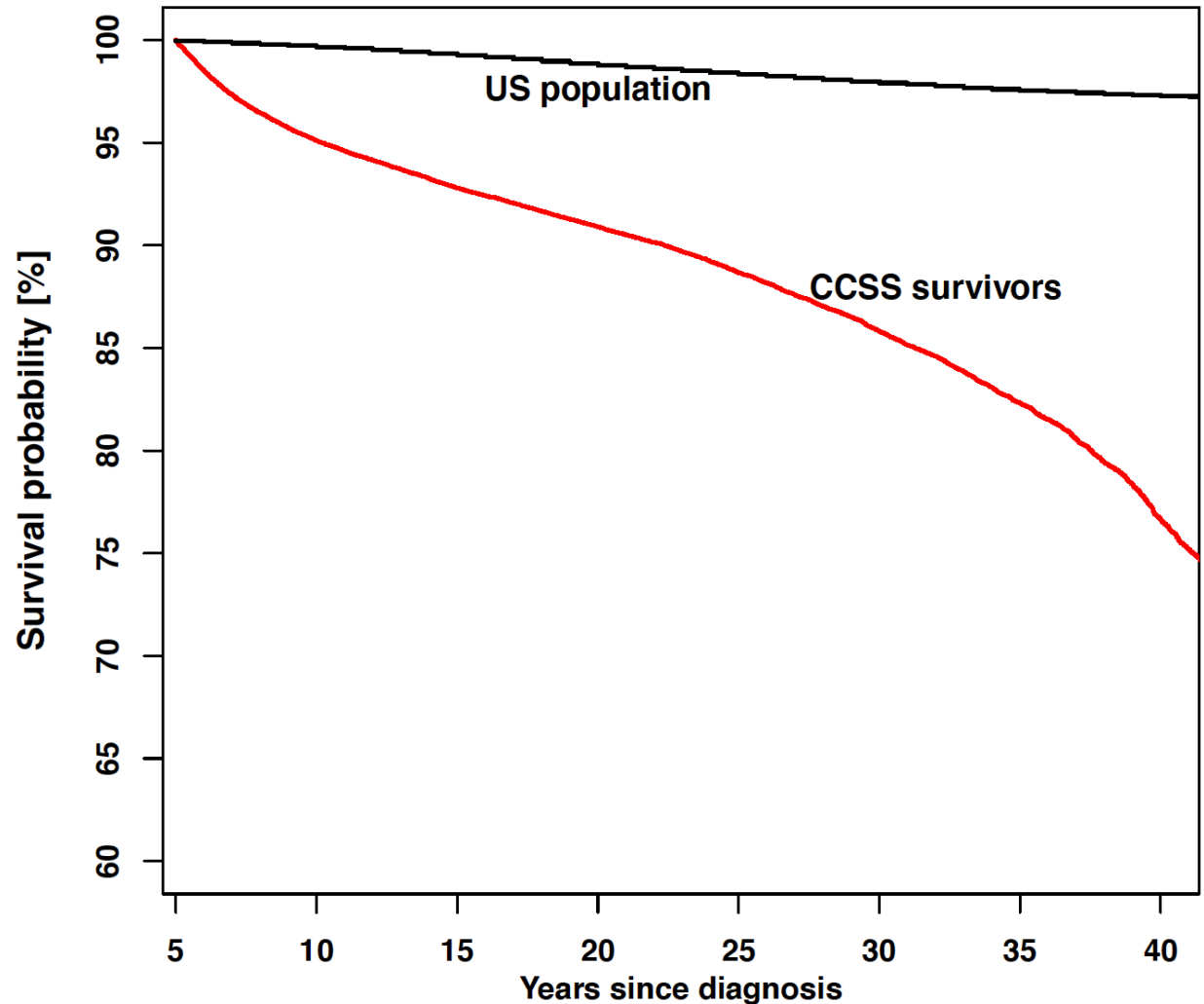
# Study Population

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	Total	Alive	Dead
	<b>34,230</b>	<b>29,469</b>	<b>5,916</b>
<b>Age at diagnosis, median (IQR)</b>	6.0 (3.0-12.2)	5.7 (2.9-11.5)	9.3 (4.0-14.8)
<b>Time from diagnosis, median (range)</b>	29.1 (5.0-48.0)		
<b>Primary diagnosis</b>			
Leukemia	10,587	9,042	1,545
CNS tumor	6,144	4,789	1,355
Hodgkin lymphoma	4,380	3,153	1,227
Non-Hodgkin lymphoma	2,853	2,495	358
Kidney tumor (Wilms)	3,072	2,805	267
Bone tumor	2,869	2,235	634
Neuroblastoma	2,630	2,373	257
Soft-tissue sarcoma	1,695	1,422	273

# All-Cause Late Mortality

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Number at risk

34,230 32,450 31,596 28,369 21,730 16,139 9,924 4,550

## Cumulative mortality among survivors

20-year:  
9.1% (8.8-9.4)

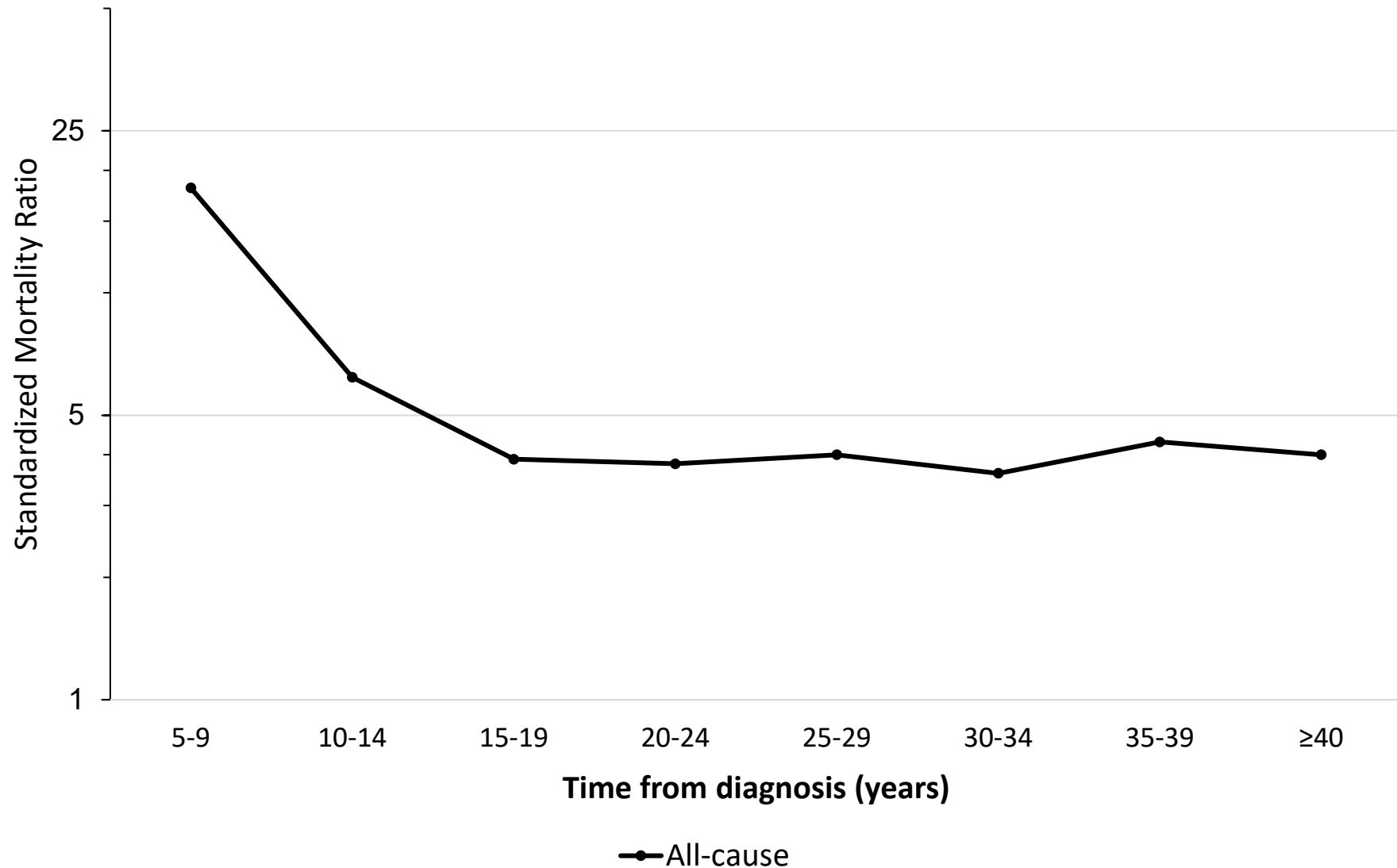
30-year:  
14.2% (13.8-14.6)

40-year:  
23.3% (22.7-24.0)



# Standardized Mortality Ratios (SMRs): Compared to the US Population

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## 5-9 Year Survival SMR (95% CI)

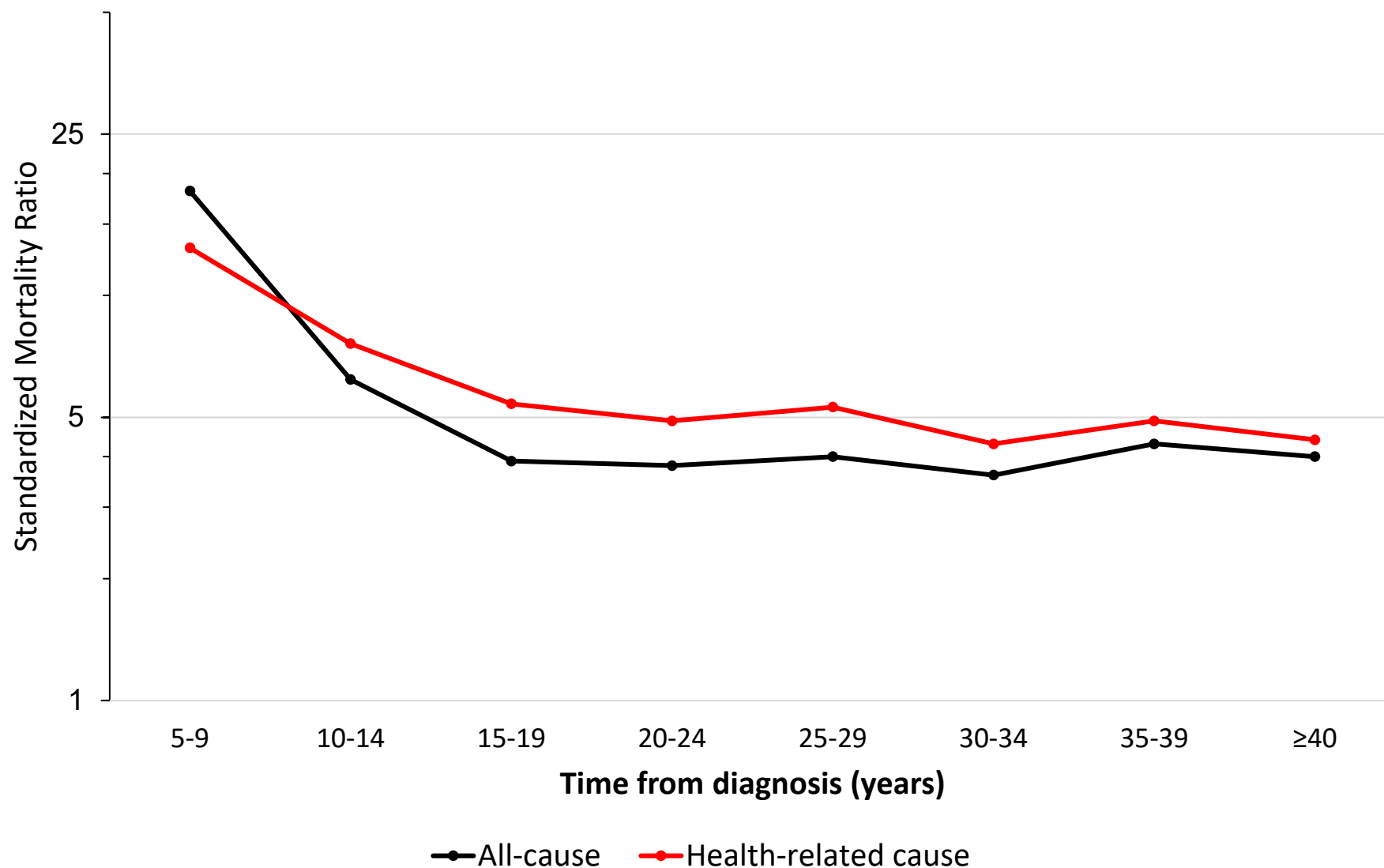
All-cause:  
18.1 (17.3 – 18.9)

## ≥40 Year Survival SMR (95% CI)

All-cause:  
4.0 (3.5 – 4.5)

# Standardized Mortality Ratios (SMRs): Compared to the US Population

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## 5-9 Year Survival SMR (95% CI)

All-cause:  
18.1 (17.3 – 18.9)

Health-related:  
13.1 (11.9 – 14.4)

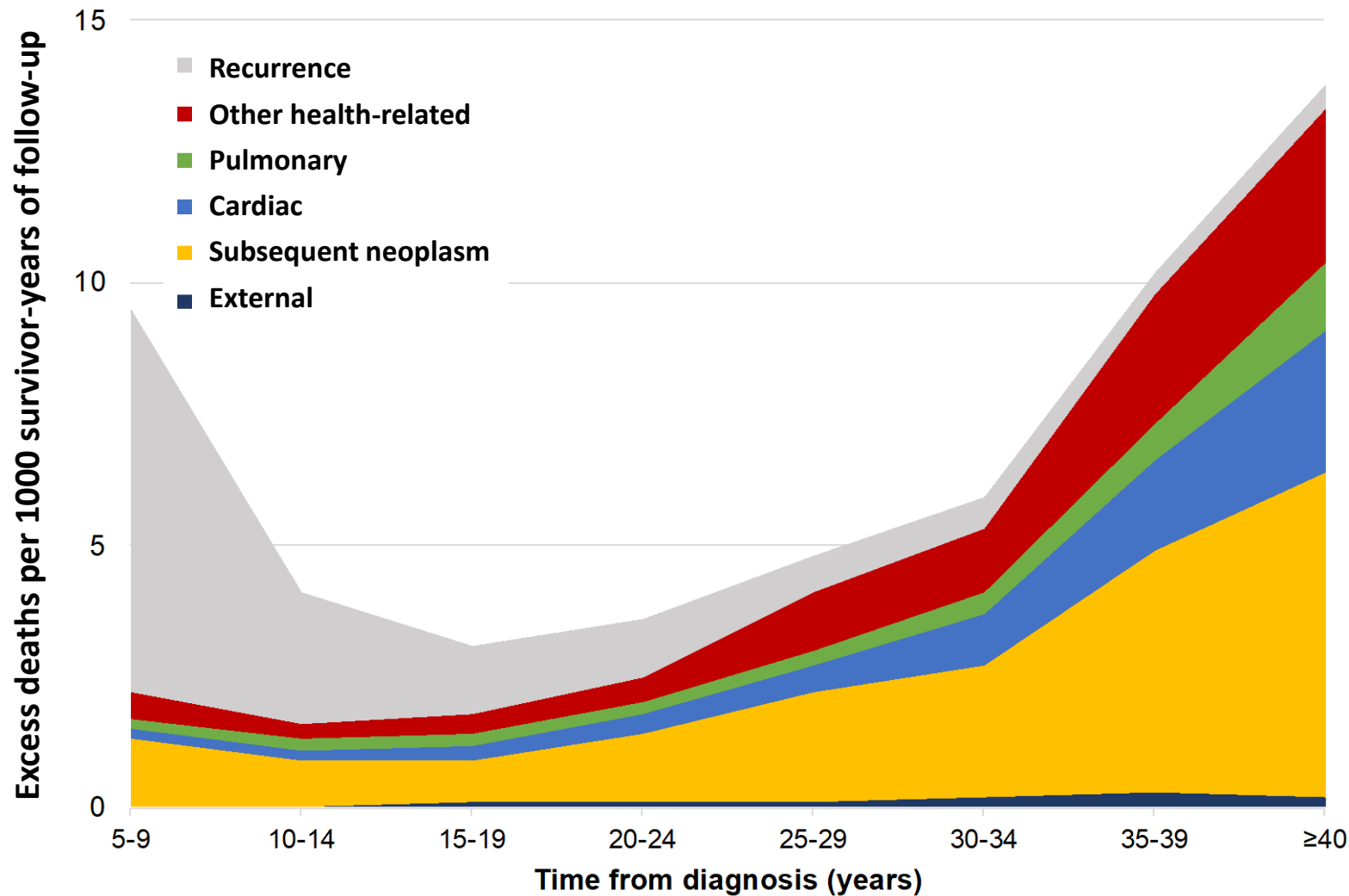
## ≥40 Year Survival SMR (95% CI)

All-cause:  
4.0 (3.5 – 4.5)

Health-related:  
4.4 (3.9 – 5.0)

# Excess Risk of Death Compared to US Population

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**Excess deaths per 1000 person years (95% CI)**

**5-9 years**

All-cause:

9.5 (9.1-10.0)

Health-related:

2.1 (1.9-2.3)

**≥40 years**

All-cause:

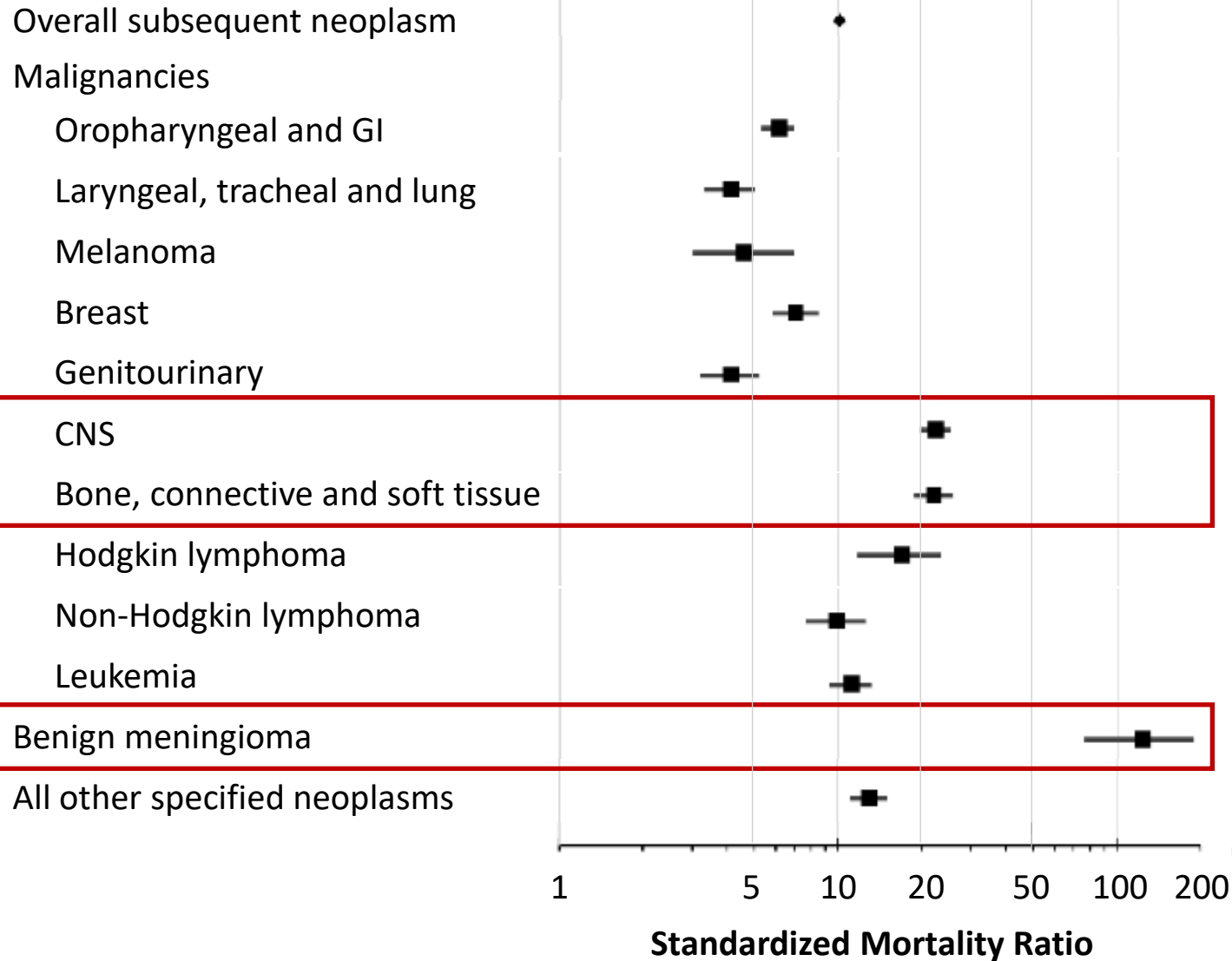
13.8 (11.7-16.1)

Health-related:

13.1 (11.1 – 15.3)

# Discrete Neoplastic Causes of Death Compared to the US Population

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**SMR (95% CI)**

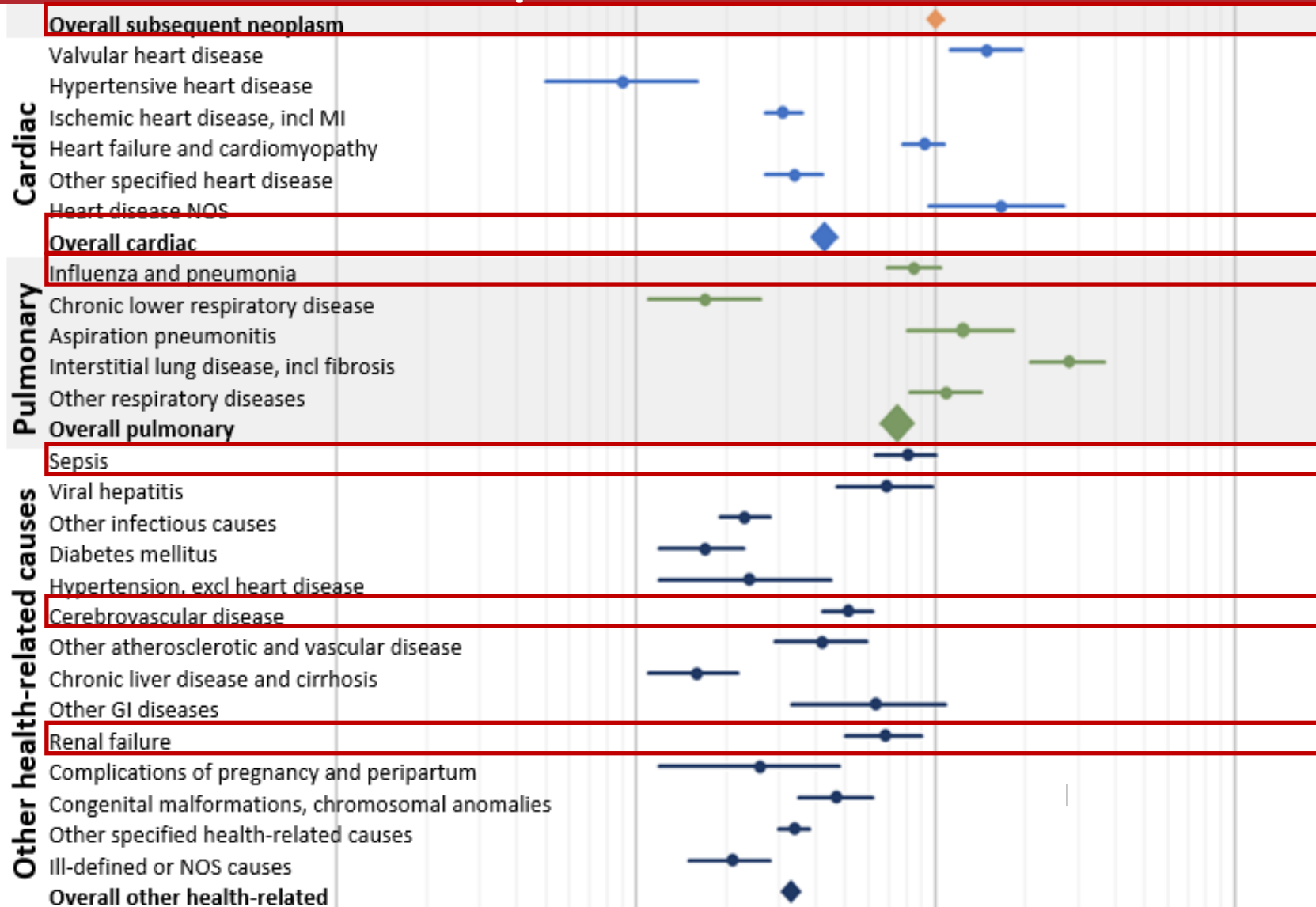
CNS: 22 (20 – 25)

Bone: 22 (19 – 26)

Meningioma: 123 (76 – 188)

# Discrete Causes of Death Compared to the US Population

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## SMR (95% CI)

SN: 10.1 (9.6 – 10.6)

Heart disease: 4.3 (3.9 – 4.7)

Flu & pneumonia: 8.5 (6.9 – 10.4)

Sepsis: 8.1 (6.3 – 10.1)

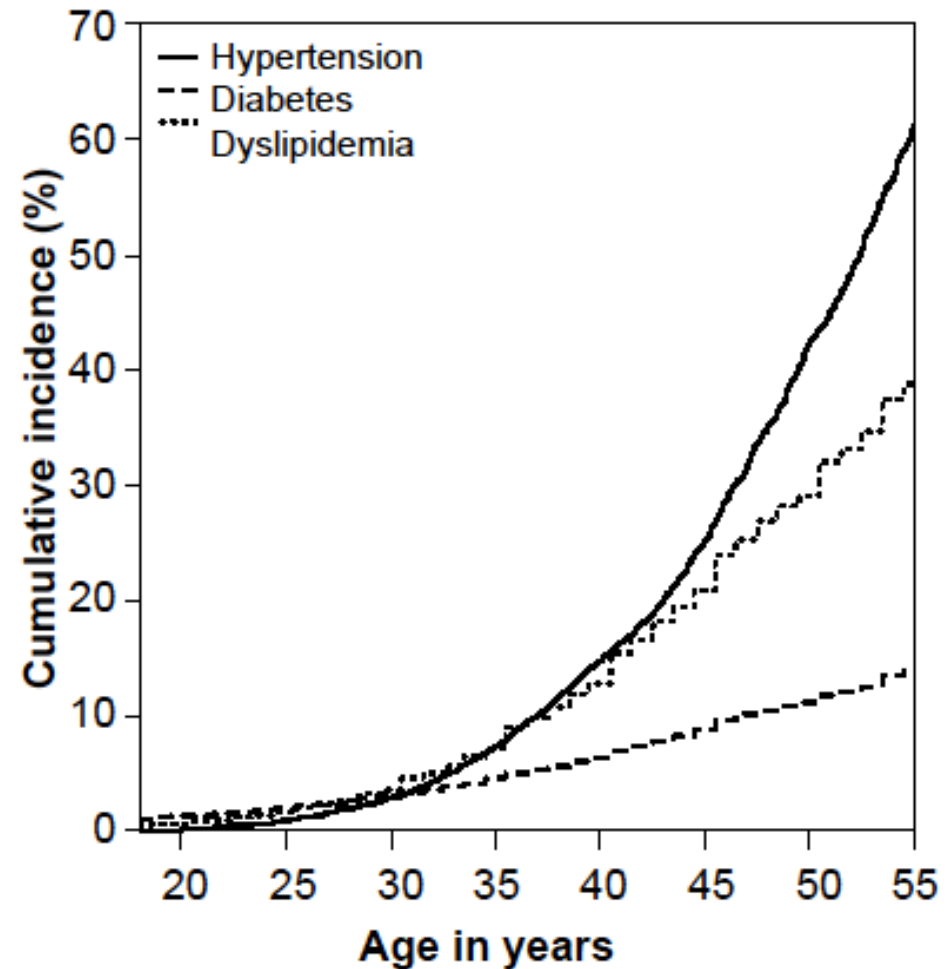
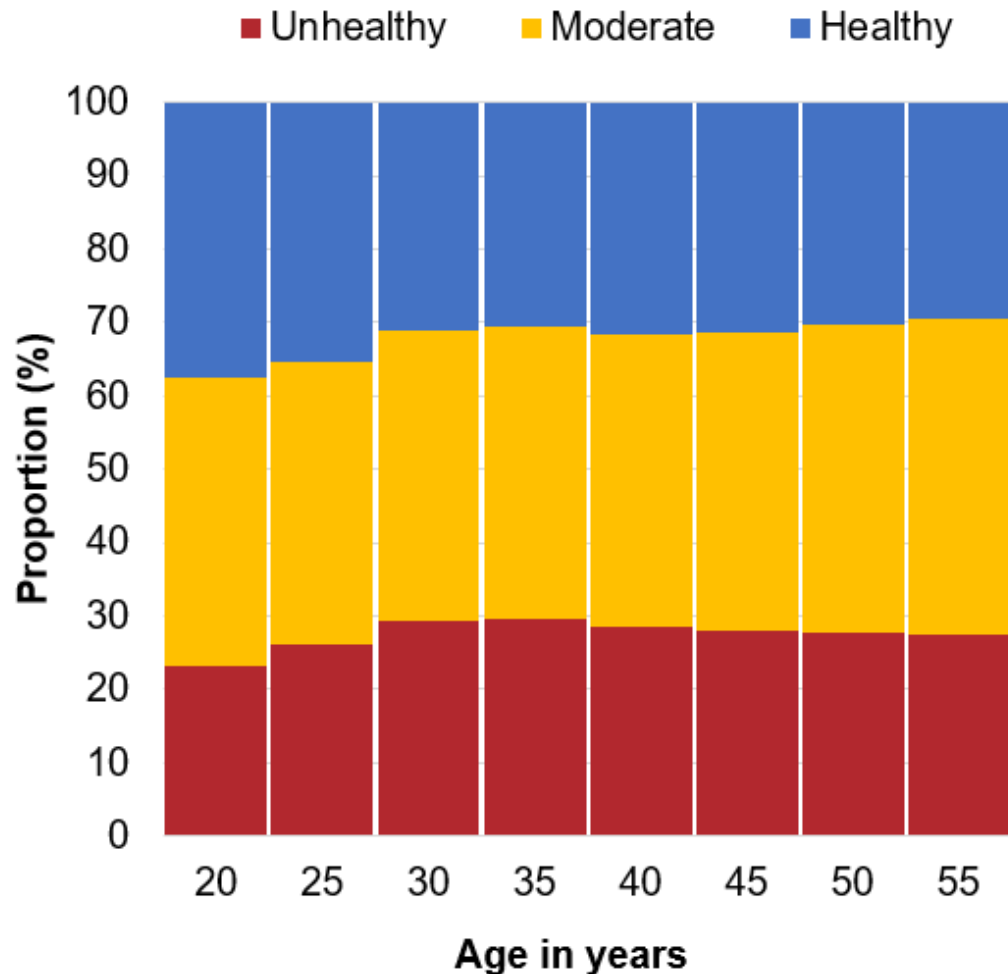
Stroke: 5.1 (4.2 – 6.2)

Renal failure: 6.8 (5.0 – 9.0)

# Distribution of Modifiable Lifestyle and Cardiovascular Risk Factors

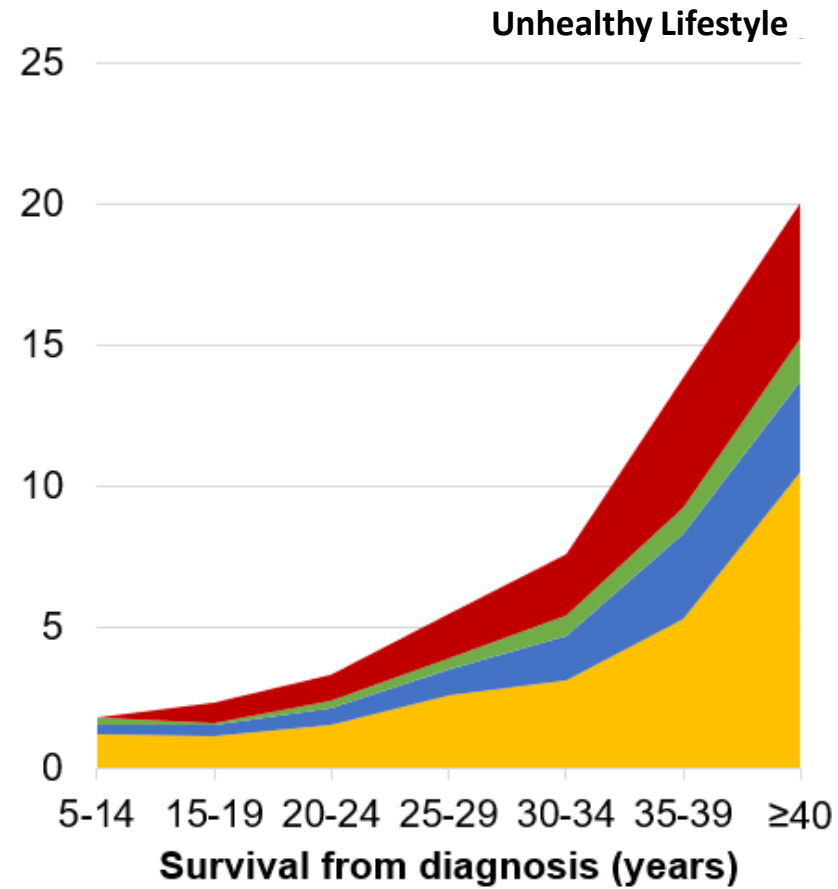
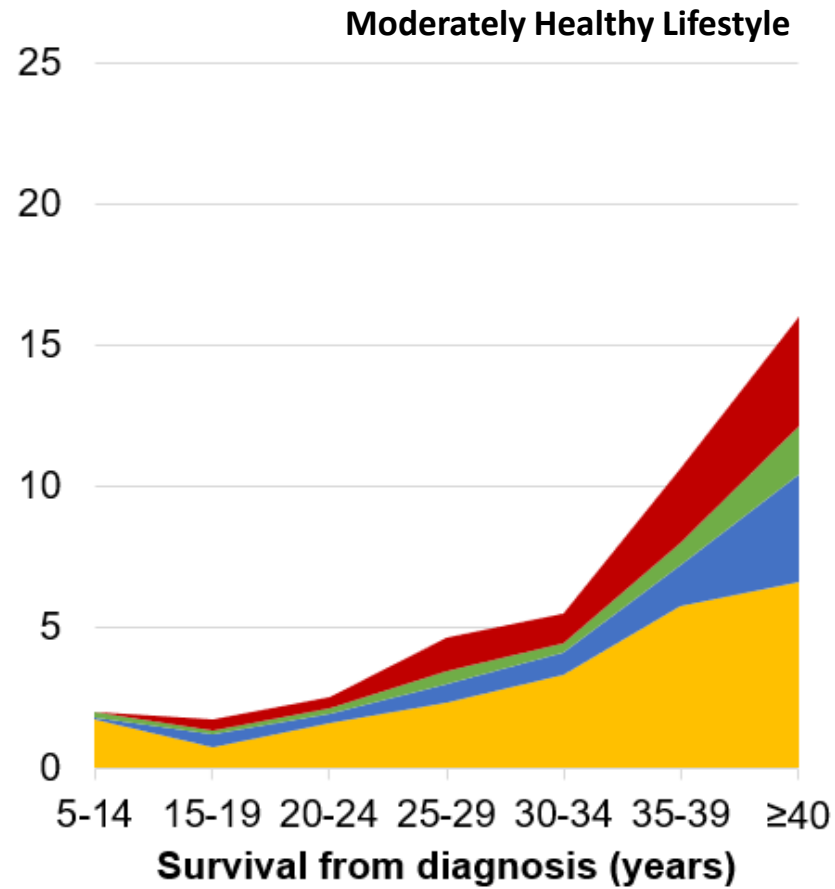
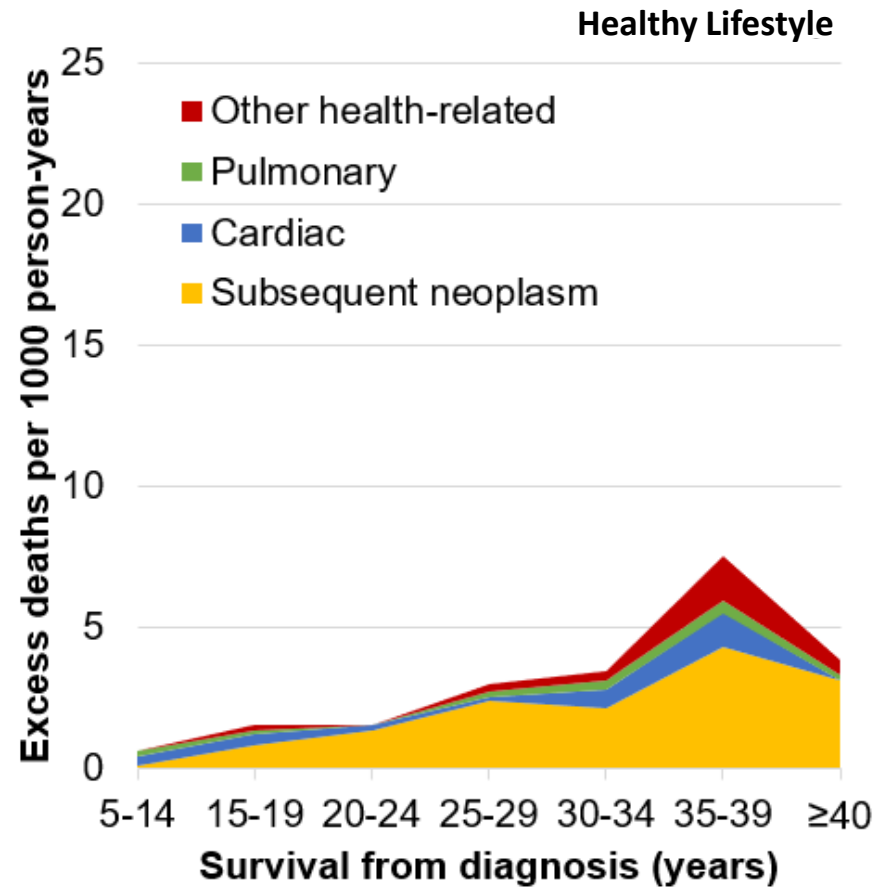
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20,051 adult survivors, median age of 40 years (range 18.7-67.7)



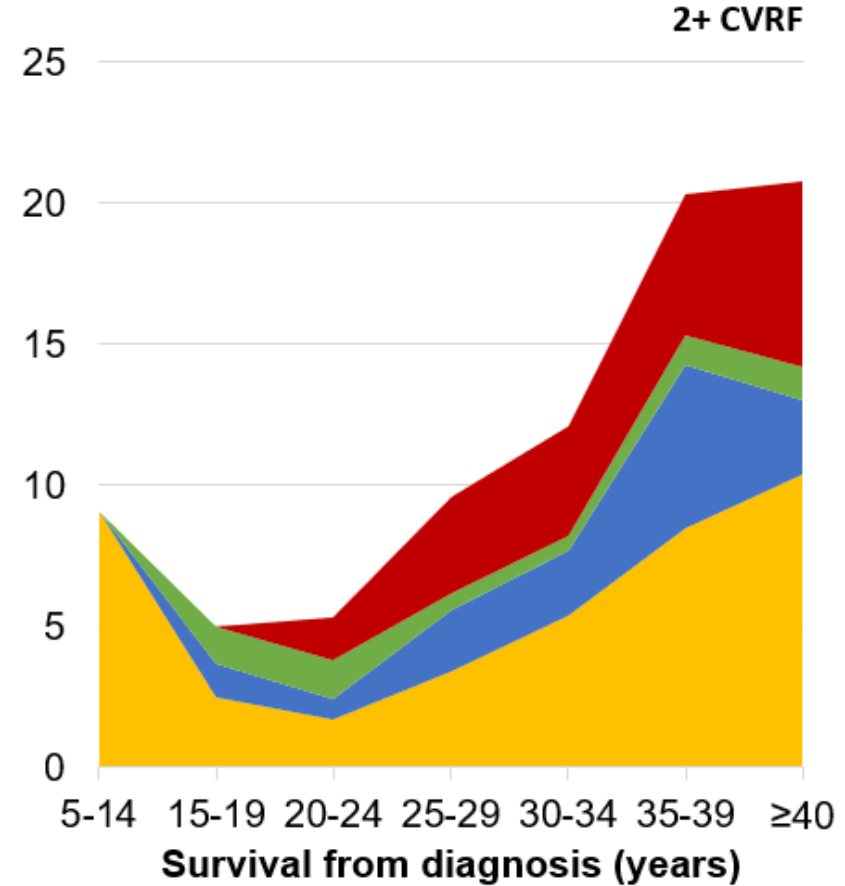
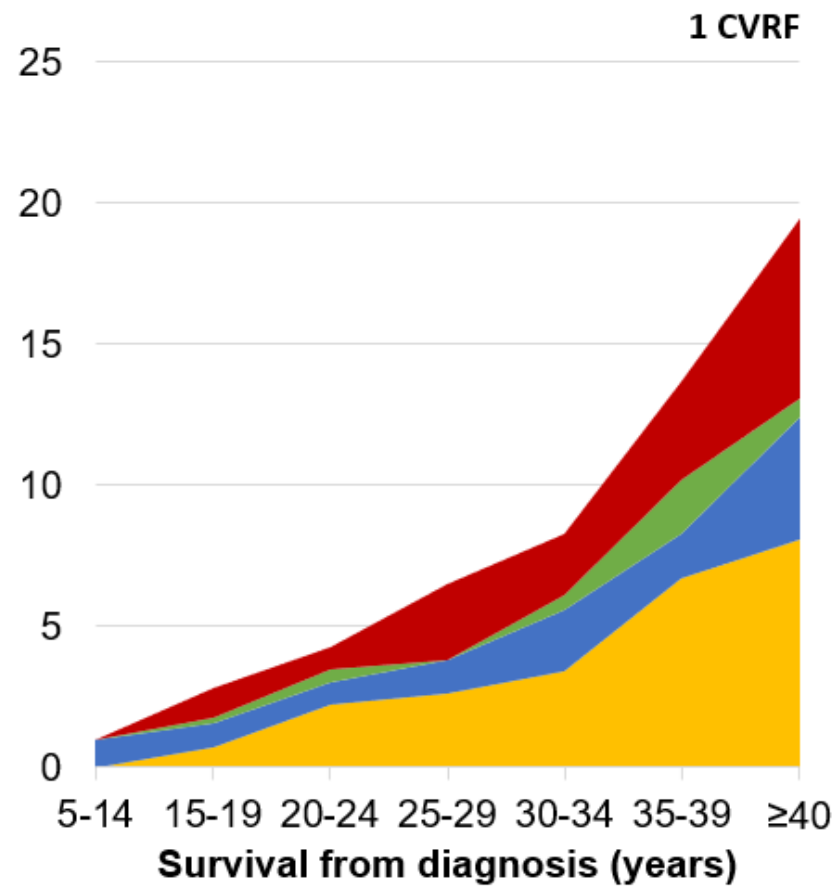
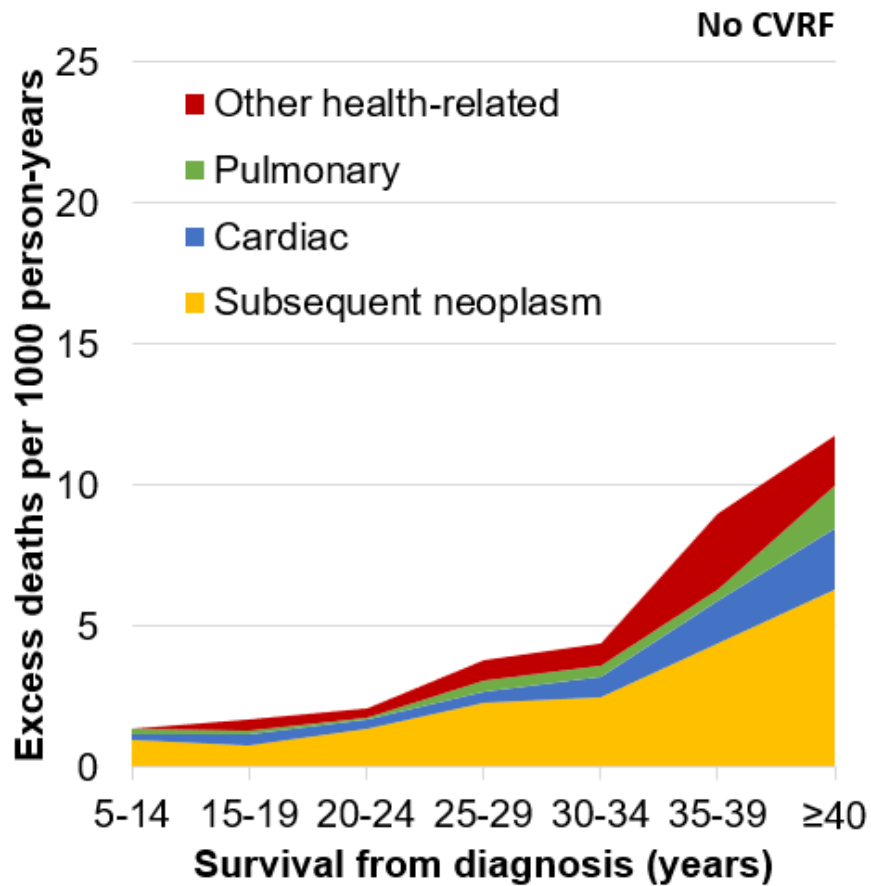
# Absolute Excess Risk of Death from Health-related Causes by Lifestyle Category

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# Absolute Excess Risk of Death from Health-related Causes by CVRF

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# Multivariable Association of Health-related Death with Modifiable Risk Factors

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	Health-related cause		Subsequent neoplasm		Cardiac		Pulmonary		Other health-related cause	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
<b>Lifestyle Category</b>										
Healthy (3.5-4)	<b>Ref</b>		<b>Ref</b>		<b>Ref</b>		<b>Ref</b>		<b>Ref</b>	
Moderate (2.5-3)	<b>1.3</b>	<b>1.1 - 1.5</b>	1.1	0.9 - 1.4	1.1	0.8 - 1.7	1.6	0.8 - 3.1	<b>1.8</b>	<b>1.2 - 2.7</b>
Unhealthy (0-2)	<b>1.4</b>	<b>1.2 - 1.6</b>	1.1	0.9 - 1.4	1.3	0.9 - 1.9	1.9	1.0 - 3.7	<b>2.2</b>	<b>1.5 - 3.2</b>
<b>CVRF (ref no)</b>										
Hypertension	<b>1.4</b>	<b>1.2 - 1.7</b>	1.1	0.9 - 1.4	<b>1.5</b>	<b>1.1 - 2.1</b>	1.5	0.9 - 2.5	<b>2.1</b>	<b>1.6 - 2.9</b>
Diabetes	<b>1.3</b>	<b>1.1 - 1.6</b>	1.0	0.7 - 1.4	<b>1.6</b>	<b>1.0 - 2.5</b>	1.3	0.6 - 2.8	<b>1.5</b>	<b>1.0 - 2.3</b>
Dyslipidemia	1.0	0.9 - 1.2	<b>1.3</b>	<b>1.0 - 1.6</b>	1.0	0.7 - 1.5	0.7	0.4 - 1.3	0.8	0.6 - 1.2

Rate ratios are adjusted for age at diagnosis, race, sex, attained age and education, insurance status and income.

Findings reflect outcomes based on treatment from 1970-1999 and may not be generalizable to some contemporary treatment outcomes.

When evaluating specific causes of death, data were obtained from death certificate information which is at risk for misclassification.

Modifiable risk factors analyses were limited to survivors who completed at least one survey as an adult and rely on participant report of health behaviors and traditional cardiovascular risk factors.

Survivors remain at a four-fold increased risk for death 40 years after their cancer diagnosis compared to the general population.

There is a persistent increased risk of death due to health-related causes, including many of the leading causes of death in the general, aging population.

The excess risk of death beyond five-year survival increases by survival time and appears to accelerate from 30 to 40 years from diagnosis.

Fewer excess deaths were observed among adult survivors with a healthy lifestyle and no CVRFs.

Interventions targeting modifiable risk factors may reduce late mortality.

- The Childhood Cancer Survivor Study is an NCI-funded resource (U24 CA55727) to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence.
- Investigators interested in potential uses of this resource are encouraged to visit:

<http://ccss.stjude.org>