

Mortality in Siblings of Patients Co-infected with HIV and Hepatitis C

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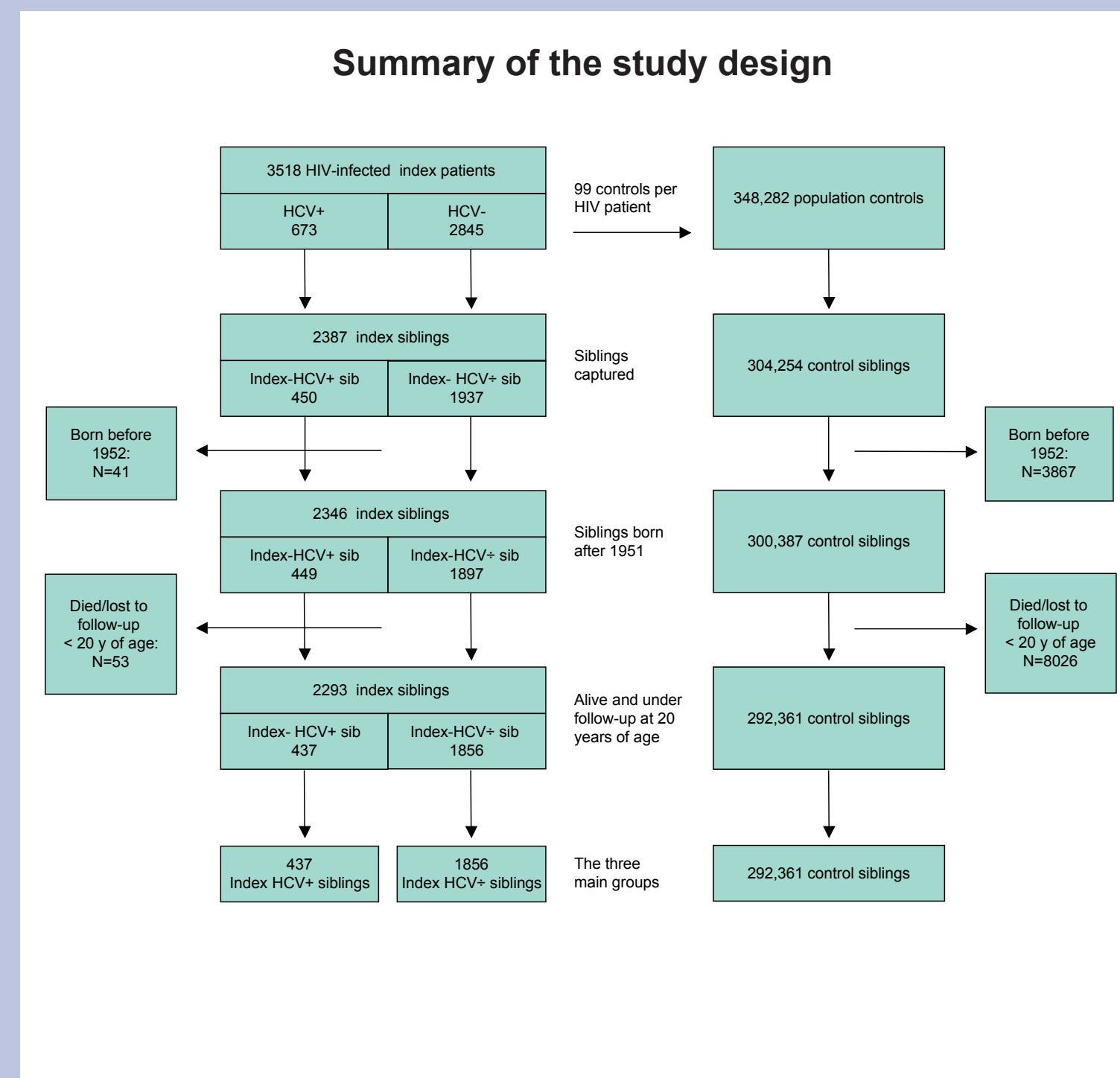
Introduction

Several studies have examined the impact of hepatitis C virus (HCV) co-infection on HIV disease progression and mortality in HIV-infected patients but with discordant results and conclusions.

In the Danish HIV Cohort Study (DHCS), co-infection with HCV in HIV-infected patients was associated with a 2.4 fold increase in overall mortality compared with HIV monoinfected patients. Only part of this excess mortality was liver-related, and the excess non-liver related mortality remained after adjusting for available covariates.

It is not clear to what extent HCV per se has a negative impact on the clinical course of HIV and the response to HAART, and to what extent increased non liver-related mortality in co-infected patients can be ascribed to other risk factors not readily measured in clinical studies.

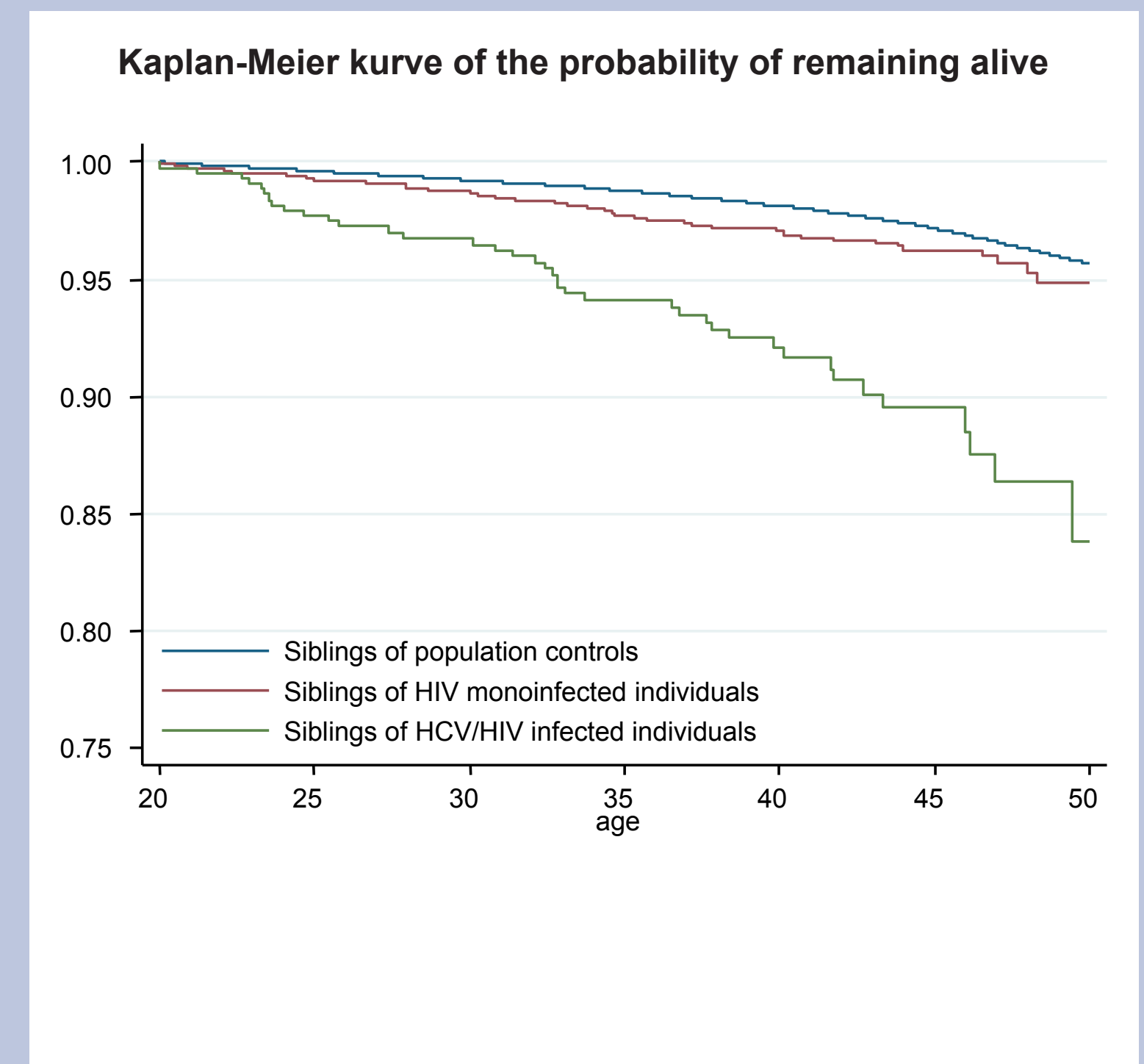
We compared the mortality in three groups of siblings; siblings of HCV/HIV-coinfected patients, siblings of HIV-monoinfected patients and siblings of HIV-negative population controls to examine the extent to which HCV/HIV co-infection is a marker for other family-shared risk factors.



HIV-infected index patients and population controls			
Index patients/controls	HCV-positive (Index HCV+)	HCV-negative (Index HCV-)	Population controls (Controls)
Number	673	2845	348,282
Number with siblings (%)	277 (41)	1080 (38)	178,160 (51)
No. of siblings per index patient with siblings	1.6	1.8	1.7

Characteristics of siblings			
Characteristics	Index HCV+ siblings	Index HCV- siblings	Control siblings
Number	437	1856	292,361
Median birth year (interquartile range)	1964 (1959-1968)	1963 (1959-1968)	1964 (1960-1970)
Born in Denmark (%)	417 (95.4)	1837 (99.0)	288,653 (98.7)
Transmission* group (%)			
IDU	293 (67)	24 (1)	NA
hemophilia	35 (8)	0	
Died between 20 and 50 years of age (%)	39 (8.9)	58 (3.1)	6096 (2.1)
Emigrated (%)	11 (2.5)	61 (3.3)	10279 (3.5)
Lost to follow-up (%)	0	2 (0.1)	242 (0.1)

* Transmission group refers to the HIV transmission group of the index-person. IDU: Intravenous drug use. NA: not applicable



Methods

Study population and data sources

HIV-infected index patients

The Danish HIV Cohort Study encompasses all HIV-infected patients treated in Danish HIV clinics since 1 January 1995. 3518 patients living in Denmark at time of diagnosis and having at least one HCV test were included as index patients. Patients were classified as (1) index HCV+ (having at least one serological test positive for HCV and/or detection of HCV-RNA) and (2) index-HCV- (consistently tested negative for HCV).

General population controls

The Danish Civil Registration System (DCRS) contains information on all persons residing in Denmark since April 1 1968. We used DCRS to identify 99 population controls per HIV-infected individual, sampled on gender, date of birth, and residency.

Siblings

For both index patients and population controls all registered siblings having both parents in common were identified, and data on dates of death, emigration, or loss to follow up were obtained from DCRS. For individuals born before 1952 kinship was irregularly registered, and siblings born before 1 January 1952 were excluded from analyses. Index siblings were grouped as (1) *index-HCV+ siblings* or (2) *index-HCV- siblings* according to HCV status of index patients.

Outcome measure and statistical analysis

The main outcome measure was time from 20 years of age to death in the siblings. Subjects were censored at emigration, loss to follow up, May 1 2005, or 50 years of age, whichever came first. We performed Cox's proportional hazards regression analyses to estimate mortality rate ratios (MRR) with 95% confidence intervals.

Results

2293 index siblings and 292,361 control siblings were included in the study, totalling 45,670 and 5,657,353 person-years of observation after age 20 years.

The mortality was considerably increased when comparing index HCV+ siblings with either index HCV- siblings, MRR = 2.97 (95%CI, 1.98-4.45) or control siblings, MRR = 4.23 (95% CI, 3.08-5.79). Index-HCV- siblings had moderately increased mortality with an MRR of 1.42 (95% CI, 1.10-1.84) compared with control siblings.

Restricting analysis to siblings born after 1 April 1968, siblings born in Denmark, or only one sibling per index patient/control (firstborn or lastborn) did not change the conclusions of the study.

When only siblings of index patients infected through homosexual or heterosexual contact were included, index-HCV+ siblings still had increased mortality compared with both index-HCV- siblings, MRR=3.09 (95% CI, 1.58-6.04) and control siblings, MRR=4.59 (2.47-8.53).

We also grouped siblings according to IDU of index patients: Siblings of patients with IDU had increased mortality compared with either siblings of patients without IDU, MRR= 2.60 (95% CI, 1.67-4.05 or control siblings, MRR=4.18 (95% CI, 2.87-6.10).

Conclusion

We demonstrated a strong familial risk with three- to fourfold increased mortality in siblings of HIV/HCV co-infected patients compared with siblings of HIV mono-infected patients or siblings of population controls. In contrast, HIV mono-infection was only associated with minor adverse familial risk of death.

Interpretations

Our results imply that factors other than pathogenicity of the HCV contribute substantially to the increased mortality in co-infected patients. Differences in familial background may explain part if not all of the reported differences regarding impact of HCV on morbidity and mortality.

Prognosis and mortality studies that do not ascertain causes of death and adjust for socioeconomic risk factors may substantially overestimate mortality attributable to HCV.

Further studies are needed to clarify the contribution of socioeconomic or genetic factors (including genetic influence on behavioural issues) to the excess mortality observed in siblings of HCV/HIV co-infected individuals.

During the continued analytic approach we decided to analyse only adult mortality due to few events and incomplete follow-up during childhood. This is in contrast to the abstract where the outcome measure was time from birth to death. Figures in the Method and the Result section therefore vary from the abstract, but no conclusions are affected.