Scandinavian Journal of Gastroenterology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/igas20

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To cite this article: Fredrik Åberg, Annie Britton & Panu K. Luukkonen (2022): Changes over time in the Chronic Liver Disease risk score predict liver-related outcomes: longitudinal analysis of the Whitehall II study, Scandinavian Journal of Gastroenterology, DOI: 10.1080/00365521.2022.2113130

To link to this article: https://doi.org/10.1080/00365521.2022.2113130

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY
https://doi.org/10.1080/00365521.2022.2113130

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ORIGINAL ARTICLE

Changes over time in the Chronic Liver Disease risk score predict liver-related outcomes: longitudinal analysis of the Whitehall II study

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ABSTRACT

Background and Aims: The Chronic Liver Disease (CLivD) risk score was recently shown to predict future advanced liver disease in the general population. We here investigated the impact of individual CLivD-score changes over time.

Methods: Participants of both phase 3 (baseline, 1991–1994) and phase 5 (follow-up, 1997–1999) examinations of the Whitehall II study were followed for liver-related outcomes (hospitalization, cancer, death) until December 2019 through linkage with electronic healthcare registers. The CLivD score, its modifiable components (alcohol use, waist–hip ratio [WHR], diabetes, and smoking), and their individual changes were studied.

Results: Among 6590 adults (mean age 50 years, 30% women) with a median 21-year follow-up, there were 80 liver outcomes. A rise in the CLivD score between baseline and follow-up examinations significantly increased the risk for liver-related outcomes (adjusted hazard ratio [aHR] 1.62, 95% confidence interval [CI] 1.01–2.60), more so in subjects with baseline intermediate–high CLivD scores (HR 2.4 for a CLivD-change) compared to minimal-low CLivD scores. Adverse changes over time in alcohol use and WHR, and new-onset diabetes also predicted liver outcomes. In contrast to WHR, changes in body weight (kg) showed a U-shaped association with liver outcomes.

Conclusions: A change in the CLivD score over time corresponds to a true change in the risk for liver-related outcomes, suggesting the usefulness of the CLivD score for assessing response to liver-directed lifestyle interventions. Changes in WHR predicted liver outcomes better than changes in body weight or waist circumference, independent of body mass index, supporting the WHR in assessing risk for future liver disease.

Abbreviations: CLivD: Chronic Liver Disease; WHR: waist–hip ratio; HES: hospital episode statistics

ARTICLE HISTORY
Received 22 June 2022
Revised 4 August 2022
Accepted 9 August 2022

KEYWORDS
CLivD; cirrhosis; fibrosis; obesity; alcohol

Introduction

Chronic Liver Disease (CLivD) and cirrhosis are major healthcare burdens leading to substantial morbidity, mortality, and healthcare cost [1]. Alcohol use, obesity, and metabolic dysfunction are the most common etiologies for nonviral cirrhosis [1]. Liver cirrhosis tends to develop silently without signs or symptoms until the development of complications such as ascites or variceal bleeding, whereby prognosis is poor [2].

We recently developed and validated a Chronic Liver Disease risk score – the CLivD score – for the prediction of severe liver-related outcomes (liver-related hospitalization, cancer, and death) [3]. The non-laboratory version of this score is based on simple and widely available variables that are well-acknowledged population risk factors for cirrhosis: age, sex, waist–hip ratio (WHR), diabetes, alcohol use, and smoking [4–10]. Similar to risk prediction scores such as the Framingham score or SCORE used in the cardiovascular field [11], the CLivD score enables the identification of individuals in the general population at high risk of developing liver-related outcomes before advanced liver disease arises. The CLivD score can be useful as a motivational tool to support healthier lifestyle habits including a reduction in alcohol use and weight loss.

Alcohol use, abdominal obesity, and smoking are modifiable risk factors [12–14]. Type 2 diabetes is also at least partially preventable through healthy lifestyle habits [15,16]. However, it remains unproven whether lifestyle modifications to reduce an individual's CLivD score would also reduce the true risk of liver outcomes for that individual. The CLivD score was built by measuring the risk factors at one point in time, namely at the study baseline, which is also the reality when making risk predictions in the clinic. However, this does not account for dynamic lifestyle modifications over time, such as changes in alcohol use or weight loss or weight gain.

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/00365521.2022.2113130

Obesity can be assessed by multiple anthropometric measures, such as body weight, body mass index (BMI), waist circumference, and WHR. WHR has repeatedly been shown to be the best anthropometric predictor of future severe liver disease [9,17,18]. WHR can be decreased with dietary and exercise interventions [13,14,19–21]. However, it remains unclear whether WHR is the most optimal response measure for a change in obesity when making predictions of the risk of liver disease.

We used the Whitehall II study population with longitudinal clinical measurements and registry linkage for liver outcomes to study whether a change in the CLivD score and/or in its individual components over time corresponds to a change in the true risk for incident liver outcomes. We also compared the predictive performance for incident liver outcomes of a change over time in WHR to that in body weight or waist circumference.

Material and methods

The study was based on data from the Whitehall II study, which is an ongoing cohort study of civil servants in London-based offices [22]. A total of 10 308 adults (6895 men and 3413 women, aged 35–55) were originally recruited from 1985 to 1988. Follow-up clinical examinations have taken place every 4–5 years, with each wave taking 2 years to complete. Written informed consent from participants and research ethical approvals were renewed at each contact. Subjects were linked electronically to national registers of hospitalization, cancer, and mortality up to December 2019 [23]. In studies of chronic diseases, the sensitivity and specificity of the Hospital Episode Statistics (HES) database are high [23,24]. Because the hospitalization register achieved a high level of national coverage from January 1997 onward, we set the start of follow-up time for liver-related outcomes at the Whitehall II study's fifth follow-up examination (phase 5) which was undertaken in 1997–1999.

The variables necessary to calculate the CLivD score had been recorded starting in phase 3 of the Whitehall II study, and again at phase 5. Phase 3 was undertaken from 1991 to 1994 and phase 5 from 1997 to 1999. In this study, we considered phase 3 as the baseline examination and phase 5 as the follow-up examination, while the follow-up for liver-related outcomes started after phase 5. We therefore included subjects who participated in both phase 3 (baseline) and phase 5 (follow-up) examinations and who had all the variables necessary to calculate the CLivD score at phase 3 (baseline). The complete-case cohort included individuals with all necessary data to calculate the CLivD score at both the baseline (phase 3) and follow-up (phase 5) examinations. We excluded those with a baseline diagnosis of CLivD, missing registry follow-up, and missing data to calculate the CLivD score at phase 3 (baseline) (Figure S1 in Supplementary Material).

Baseline and follow-up variables retrieved for the study included age, sex, smoking status (current, former, or never smoker), alcohol use (drinks per week), WHR, weight, height, waist circumference, and diabetes. One alcohol drink was defined as 10 grams of ethanol. New-onset diabetes was defined as a diabetes diagnosis at the follow-up examination (phase 5) without a diabetes diagnosis at baseline (phase 3). Detailed protocols for these measurements have been previously reported [25,26]. The CLivD score was calculated based on age, sex, smoking status, alcohol use, WHR, and diabetes as described in the original CLivD-score publication [3] and in the Supplementary material.

Study endpoints were fatal and non-fatal advanced liver disease requiring hospital admission or a diagnosis of liver cancer or liver-related death, defined in the same way as in the original CLivD score publication [3]. The ICD codes used for defining the outcomes are listed in Table S1 in Supplementary Material.

Statistical analyses

Correlations were calculated as Pearson correlations. To test the association of sequential change in the CLivD score, we fitted a Cox regression model with baseline (phase 3) CLivD score and change in the CLivD score between the baseline (phase 3) and follow-up (phase 5) examinations as covariates and time to first liver event as the outcome. To test the association of sequential change in alcohol use and the WHR, we fitted a Cox regression model with baseline CLivD score, changes in alcohol use, and WHR between baseline and follow-up as covariates. To test the association of incident diabetes, we fitted a Cox regression model with the same variables and new-onset diabetes among those without diabetes at baseline (phase 3). Moreover, we fitted a Cox regression model with alcohol use at baseline and change in alcohol use from baseline to follow-up as covariates, and another model with the WHR at baseline and change in WHR from baseline to follow-up as covariates. Both of these models were also adjusted for age and sex. To compare the performance of different anthropometric measures, we further fitted similar Cox models as above, but with waist circumference or body weight as covariates instead of the WHR.

In the subgroup of individuals without diabetes at baseline, we further fitted a Cox regression with new-onset diabetes between baseline and follow-up as the covariate, and age and sex as adjustments. There were too few outcome events (1 and 8) among subjects who started smoking or stopped smoking between baseline and follow-up to allow for meaningful analyses of a change in smoking behaviors.

The functional form of the association between various covariates and liver-related outcomes was assessed using restricted cubic splines with degrees of freedom selected using the Akaike Information Criterion. Effect modification was evaluated by subgroup analyses based on the previously defined CLivD risk categories: minimal risk (CLivD score <-0.412), low risk (CLivD score -0.413–1.912), and intermediate–high (CLivD score ≥ 1.913) [3]. The intermediate and high-risk categories were combined due to small numbers. To assess the effect of modification of baseline BMI, we compared the various anthropometric measures in subgroup analyses by baseline BMI ($\leq$ or $>25\,kg/m^2$). Finally, we estimated the impact of both baseline (phase 3) CLivD score and change in the CLivD score between the baseline (phase 3) and follow-up (phase 5) examinations on the absolute

20-year cumulative incidence of liver-related outcomes and non-liver death using Fine-Gray competing-risk regression. A value of $p < .05$ was considered statistically significant. Data were analyzed with R software version 3.6.1.

Results

The study cohort included 6 590 persons that participated in both the baseline (phase 3) and follow-up examinations (phase 5) of the Whitehall II studies and had complete data to calculate the CLivD score at baseline (overall cohort). Of these, 4388 (67%) had complete data to calculate the CLivD score at both the baseline and follow-up (complete-case cohort). Follow-up data for WHR was missing in 2072 (31%) participants of the overall cohort; otherwise missingness rates ranged from 0% to 8% (Figure S1 in Supplementary Material). Baseline characteristics were similar in the overall and complete-case cohorts (Table 1).

The median time between the baseline and follow-up examinations was 5.9 years (range 4.2–7.9, IQR 5.6–6.1). During this time, there was a slight increase in mean alcohol use (+3.2 drinks per week, standard deviation [SD] 10.4), waist circumference (+5.1 cm, SD 6.0), hip circumference (+3.0 cm, SD 4.3), and body weight (+2.5 kg, SD 4.7) (Table 2); the distributions of these changes are shown in Figure S2 in Supplementary Material. The mean WHR did not change over the follow-up. Eighty-nine subjects (1.4%) developed new-onset diabetes, 220 (3.5%) stopped smoking and 58 (0.9%) started smoking (Table 2). The CLivD score increased on average by 0.41 units (SD 0.59) over this follow-up. The CLivD score increases by 0.044 units per year of follow-up from the effect of aging alone.

Change in alcohol intake between the baseline and follow-up examinations did not correlate with the corresponding changes in WHR ($r = 0.04$), waist circumference ($r = 0.03$), or weight ($r = 0.07$). The correlation coefficient between change in WHR and change in waist circumference was 0.63 ($p < .001$), that between change in WHR and change in body weight was 0.37 ($p < .001$), and that between change in waist circumference and change in body weight was 0.72 ($p < .001$).

During a median follow-up of 21.4 years (range 0.1–22.5, IQR 20.8–21.8, 132 178 person-years) from the follow-up examination (phase 5) until the first liver-related event, death or December 2019, there were 80 liver-related events in the overall cohort, and 47 in the complete-case cohort. The respective incidence rates were 60.5 and 52.6 per 100 000 person-years. There were 1141 deaths without liver disease.

Change over time in the CLivD score

When adjusted for the baseline CLivD score, the change in CLivD score between the baseline and follow-up examination was significantly associated with incident liver outcomes; the hazard ratio (HR) for a 1-unit change in the CLivD score was 1.62 (95% confidence interval [CI] 1.01–2.60) (Table 3). A 1-unit change in the CLivD score corresponds approximately to an 1 SD change in the population. The findings were similar when also adjusting for the time between baseline and follow-up examinations (Table 3).

The HRs for a change in the CLivD score over time increased along with baseline risk as estimated by the baseline CLivD score, from 1.3 in the minimal- and low-risk groups to 2.4 in the intermediate–high-risk groups (Table 3). The functional form of the change in CLivD score over time and the subsequent risk of liver outcomes are visualized in Figure 1.

Table 2. Change over the follow-up in clinical characteristics and the CLivD score from the baseline (phase 3) to the follow-up examination (phase 5) of the Whitehall II study.

Change in alcohol use (drinks/week), mean (SD)	+3.2 (10.4)
Nonsmoker at baseline and follow-up, *n* (%)	5330 (86.0)
Current smoker at baseline and follow-up, *n* (%)	590 (9.5)
Current smoker at baseline, had stopped smoking at follow-up, *n* (%)	220 (3.5)
Nonsmoker at baseline, started smoking, *n* (%)	58 (0.9)
New-onset diabetes, *n* (%)	89 (1.4)
Change in waist–hip ratio, mean (SD)	0.00 (0.04)
Change in waist circumference (cm), mean (SD)	+5.1 (6.0)
Change in hip circumference (cm), mean (SD)	+3.0 (4.3)
Change in body weight (kg), mean (SD)	+2.5 (4.7)
Change in the CLivD score, mean (SD)	+0.41 (0.59)

Table 1. Demographics at baseline (phase 3) and follow-up (phase 5) in the overall and complete-case cohort of the Whitehall II study.

	Overall cohort		Complete-case cohort	
	Baseline examination	Follow-up examination	Baseline examination	Follow-up examination
Subjects	6590		4388	
Age	50 (6)	55 (6)	50 (6)	56 (6)
Female	1965 (29.8)		1319 (30.1)	
Alcohol use (drinks per week)	10.5 (11.8)	13.7 (15.5)	10.5 (11.6)	13.8 (15.7)
Current smoker	884 (13.4)	648 (10.5)	573 (13.1)	468 (10.7)
Diabetes	194 (2.9)	283 (4.3)	130 (3.0)	185 (4.2)
Waist–hip ratio	0.88 (0.09)	0.89 (0.09)	0.88 (0.09)	0.89 (0.09)
Waist circumference (cm)	85.8 (11.6)	90.8 (11.8)	85.7 (11.6)	90.8 (11.8)
Hip circumference (cm)	96.8 (7.3)	99.9 (7.5)	96.9 (7.2)	99.9 (7.5)
Body weight (kg)	74.9 (12.7)	77.5 (13.5)	74.9 (12.6)	77.4 (13.5)
CLivD score	−0.22 (0.90)	0.17 (0.99)	−0.24 (0.89)	0.17 (0.99)
Minimal risk	2922 (44.3)	1313 (29.9)	1979 (45.1)	1313 (29.9)
Low risk	3541 (53.7)	2849 (64.9)	2332 (53.1)	2849 (64.9)
Intermediate–high risk	127 (2.0)	226 (5.2)	77 (1.8)	226 (5.2)

Data are presented as mean (SD) or *n* (%).

Table 3. Associations between a change in the CLivD score, or individual components of the CLivD score, from the baseline (phase 3) to the follow-up (phase 5) examinations of the Whitehall II study and risk for liver-related outcomes after phase 5.

CLivD score	Subjects	Liver events	HR (95% CI)	*p*	Adjustments
All subjects					
Change in CLivD score	4388	47	1.62 (1.01–2.60)	.04	CLivD score at baseline
Change in CLivD score	4388	47	1.61 (1.01–2.57)	.04	CLivD score at baseline, years between baseline, and follow-up examinations
Baseline minimal risk (CLivD score <-0.412)					
Change in CLivD score	1979	12	1.33 (0.45–3.92)	.60	CLivD score at baseline
Baseline low risk (CLivD score -0.413–1.912)					
Change in CLivD score	2332	28	2.15 (1.17–3.93)	.01	CLivD score at baseline
Baseline intermediate–high risk (CLivD score ≥ 1.913)					
Change in CLivD score	77	7	2.35 (1.37–5.91)	.03	CLivD score at baseline
Individual components of the CLivD score					
All subjects					
Change in alcohol use*	6088	70	1.02 (1.00–1.03)	.01	Age, sex, and baseline alcohol use
Change in WHR**	4518	51	1.13 (1.06–1.20)	<.001	Age, sex, and baseline WHR
Baseline minimal risk (CLivD score <-0.412)					
Change in alcohol use*	2703	19	0.98 (0.90–1.08)	.71	Age, sex, and baseline alcohol use
Change in WHR**	2040	12	1.05 (0.92–1.20)	.48	Age, sex, and baseline WHR
Baseline low risk (CLivD score -0.413–1.912)					
Change in alcohol use*	3273	43	1.02 (1.01–1.04)	.009	Age, sex, and baseline alcohol use
Change in WHR**	2398	31	1.16 (1.07–1.26)	<.001	Age, sex, and baseline WHR
Baseline intermediate–high risk (CLivD score ≥ 1.913)					
Change in alcohol use*	112	8	1.01 (0.99–1.03)	.42	Age, sex, and baseline alcohol use
Change in WHR**	80	8	1.17 (0.97–1.40)	.10	Age, sex, and baseline WHR

WHR: waist–hip ratio; HR: hazards ratio; CI: confidence interval.
Analyses are by Cox regression.
*Per 1 weekly drink increase.
**Per 0.01-unit increase.

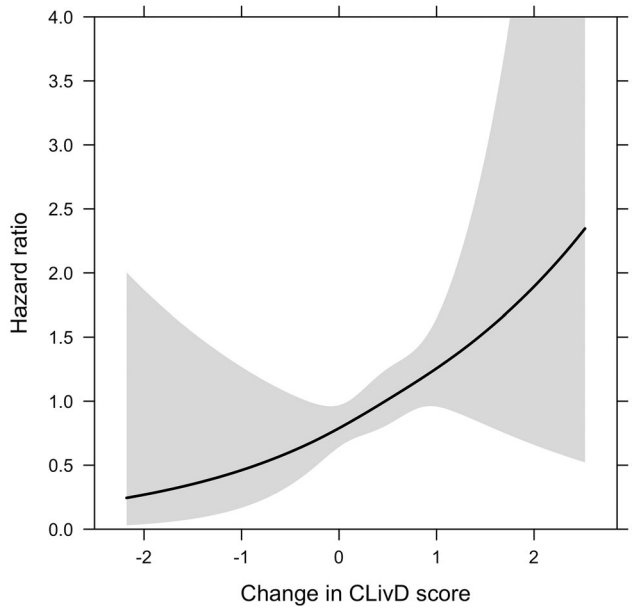

Figure 1. Nonlinear association between the change in the Chronic Liver Disease (CLivD) risk score from the baseline (phase 3) to follow-up (phase 5) measurement and risk for liver-related outcomes after phase 5. Analysis is by Cox regression with restricted cubic spline and adjusted for the CLivD score at baseline.

Change in individual CLivD score components over time

In a Cox regression model with baseline CLivD score, change in alcohol use, and change in WHR as independent variables, an increase in alcohol use by 1 weekly drink increased the relative risk of liver-related outcomes by 1% (HR 1.01, 95% CI 1.00–1.02, $p = .05$). An increase in WHR by 0.01 units increased the relative risk of liver outcomes by 10% (HR 1.10, 95% CI 1.03–1.18, $p = .003$). In subjects without diabetes at baseline, when including new-onset diabetes as an additional independent variable in the model, both alcohol intake and WHR remained significant, and new-onset diabetes was highly significant (HR 10.8, 95% CI 4.24–27.7, $p < .001$).

In Cox models adjusted for age, sex, and baseline alcohol use, the change in alcohol use over time predicted liver-related outcomes in the cohort as a whole (Table 3). Similarly, in models adjusted for age, sex, and baseline WHR, the change in WHR over time predicted liver-related outcomes (Table 3). The functional form of these associations for the group as a whole is shown in Figure 2 and Figure S3 in Supplementary Material.

Alternative measures of obesity

When adjusted for age, sex, and baseline waist circumference, a rise by 1 cm in waist circumference over time increased the relative risk of liver-related outcomes by 5% (HR 1.05, 95% CI 1.00–1.10, p .04). When adjusted for age, sex, and baseline weight, a change in body weight did not significantly alter the risk of liver-related outcomes (HR 1.03, 95% CI 0.97–1.08, $p = .35$). These findings remained unchanged when analyzed in the complete-case cohort (data not shown). The functional forms of the associations with liver outcomes are shown in Figure 2; as seen, change in body weight had a U-shaped association with the risk for liver-related outcomes, meaning that both weight loss and weight gain increased this risk.

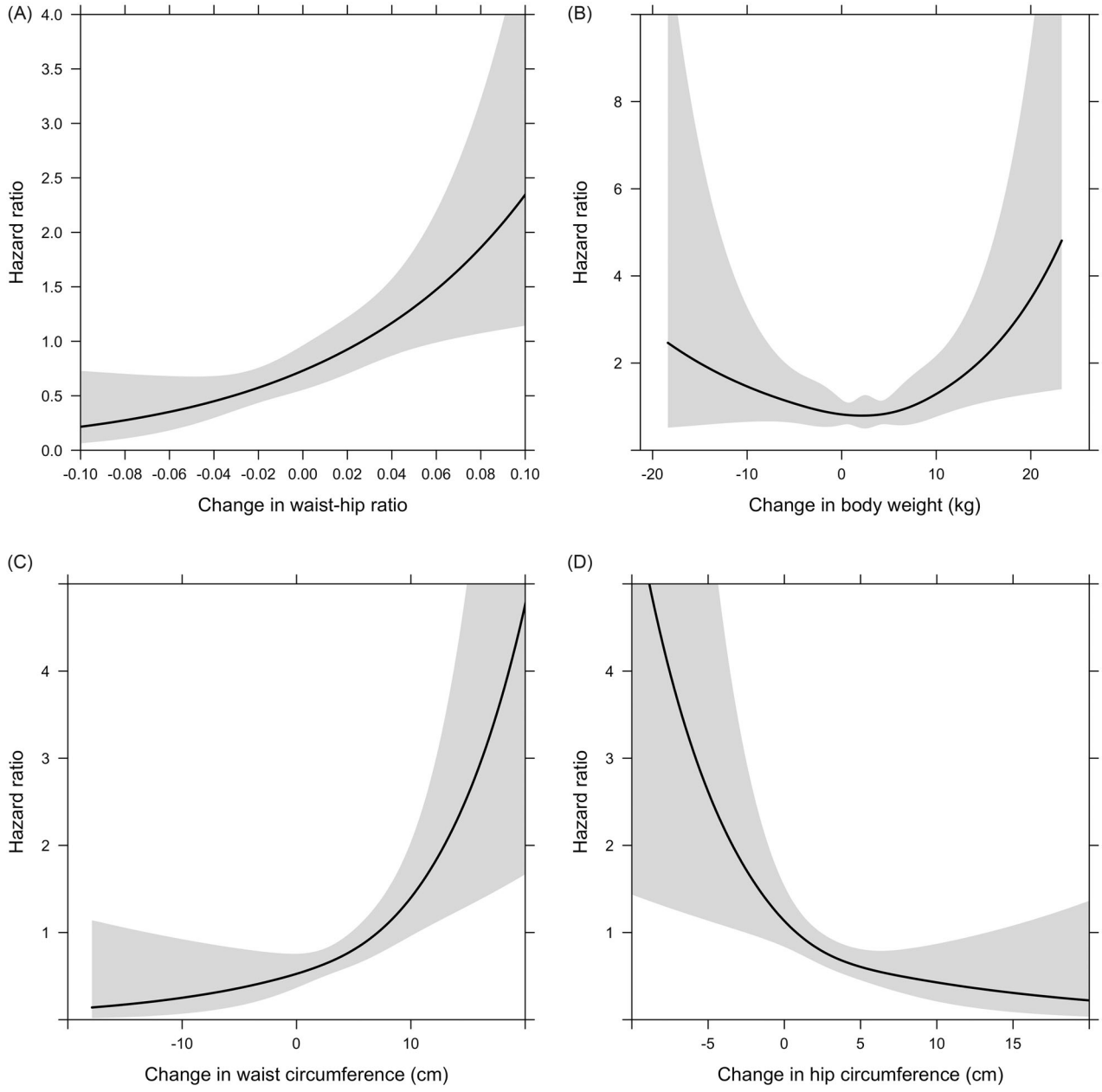

Figure 2. Nonlinear association between a change in (A) waist–hip ratio (WHR), (B) body weight, (C) waist circumference, and (D) hip circumference from the baseline to follow-up measurement and risk for liver-related outcomes by adjusted Cox regression analyses.

In a Cox model including age, sex, baseline waist and hip circumferences, and changes in the waist and hip circumferences, the change in hip circumference was associated with a reduced risk of liver-related outcomes (HR 0.89, 95% CI 0.82–0.98, $p = .02$) while the change in waist circumference was associated with an increased risk (HR 1.11, 95% CI 1.04–1.18, $p < .001$) with a slightly stronger risk effect than in the model above where hip circumference was not considered (Figure 2).

To examine whether the association between WHR and future risk of liver-related outcomes was dependent on BMI, we performed subgroup analyses by baseline BMI. A change in WHR over time was significantly associated with future risk of liver-related outcomes both among normal-weight individuals (baseline BMI $\leq$ 25 kg/m^2) and overweight/obese individuals (baseline BMI >25 kg/m^2), while changes in waist circumference or body weight were both non-significant (Table S2 in Supplementary Material).

Cumulative incidences by competing-risk analysis

In a Fine-Gray competing-risk model adjusted for the baseline CLivD score, the change in CLivD score between the baseline and follow-up examination was associated with incident liver outcomes with a similar risk estimate (subdistribution HR 1.59, 95% CI 1.02–2.46, $p = .04$) as in the Cox model. The change in CLivD score did not predict non-liver death (subdistribution HR 1.02, 95% CI 0.90–1.15, $p = .79$). The combined impact of baseline CLivD score and the change in CLivD score between the baseline and follow-up examination on the absolute 20-year cumulative incidence of liver-related outcomes and non-liver death is shown in Table 4.

Table 4. Combined impact of baseline CLivD score and the change in CLivD score between the baseline (phase 3) and follow-up (phase 5) examination on the subsequent absolute 20-year cumulative incidence of liver-related outcomes and non-liver death.

	Baseline CLivD score							
Change in CLivD score	−1	−0.5	0	0.5	1	1.5	2	2.5
Liver-related outcomes								
−1	0.2%	0.3%	0.4%	0.7%	1.0%	1.6%	2.4%	3.7%
−0.5	0.2%	0.4%	0.5%	0.8%	1.3%	2.0%	3.1%	4.7%
0	0.3%	0.4%	0.7%	1.1%	1.6%	2.5%	3.8%	5.9%
0.5	0.4%	0.6%	0.9%	1.3%	2.0%	3.1%	4.8%	7.3%
1	0.5%	0.7%	1.1%	1.7%	2.6%	3.9%	6.0%	9.2%
1.5	0.6%	0.9%	1.4%	2.1%	3.2%	4.9%	7.5%	11.4%
2	0.7%	1.1%	1.7%	2.6%	4.1%	6.2%	9.4%	14.1%
2.5	0.9%	1.4%	2.2%	3.3%	5.1%	7.7%	11.7%	17.5%
Competing risk of death without a liver outcome								
−1	9.1%	11.2%	13.8%	17.0%	20.7%	25.2%	30.4%	36.5%
−0.5	9.2%	11.3%	13.9%	17.1%	20.9%	25.4%	30.6%	36.7%
0	9.2%	11.4%	14.0%	17.2%	21.0%	25.6%	30.9%	36.9%
0.5	9.3%	11.5%	14.1%	17.4%	21.2%	25.7%	31.1%	37.2%
1	9.4%	11.6%	14.3%	17.5%	21.4%	25.9%	31.3%	37.4%
1.5	9.5%	11.7%	14.4%	17.6%	21.5%	26.1%	31.5%	37.7%
2	9.5%	11.8%	14.5%	17.8%	21.7%	26.3%	31.7%	37.9%
2.5	9.6%	11.9%	14.6%	17.9%	21.8%	26.5%	31.9%	38.2%

Analyses are by Fine-Gray competing-risk regression.

Discussion

A decrease in the CLivD risk score over time implies that the individual has adopted healthier lifestyle habits with regard to the liver. Conversely, an increase in the CLivD score exceeding the increase from aging alone (0.044 units per year) implies that adverse lifestyle changes have been made.

We here show that a change in the CLivD risk score over time mirrors a true change in the incidence of clinical liver-related outcomes, namely hospitalization, cancer, and death. This implies that the CLivD score could be used for assessing response to lifestyle interventions aimed at preventing the development of severe liver disease.

The relative effect of a change in the CLivD score on incident liver outcomes over follow-up was higher (HR 2.4 vs. 1.3) among individuals with intermediate or high baseline risk according to the CLivD score compared to those with minimal or low baseline risk. These findings further support the notion that lifestyle interventions are best targeted to individuals with intermediate or high CLivD risk scores.

Regarding changes in the individual components of the CLivD score, we found that reductions in alcohol use and in WHR over time were both significantly associated with decreased incidence of liver-related outcomes, independent of each other. Development of new-onset diabetes during the follow-up was a particularly strong predictor of liver outcomes.

Interestingly, body recomposition in a way that reduced WHR, but not necessarily body weight measured in kilograms per se, was associated with decreased risk of liver outcomes. In fact, a substantial loss in body weight (>10 kg) tended to increase the incidence of liver outcomes in our study. A U-shaped association between BMI and future risk for liver disease was also reported in the Million Women Study [27]. One potential explanation for this seemingly paradoxical finding may be that substantial weight loss could be secondary to a new-onset illness and loss of lean body mass rather than an active choice to adopt a healthier lifestyle. We speculate that a reduction in WHR rather than in body weight may more specifically reflect improvement in metabolic dysfunction and reduction in visceral or liver fat [28,29]. In contrast to body weight, WHR might be a useful response measure also among lean individuals (BMI <25 kg/m^2) [30].

Changes in waist circumference and hip circumference over time had independent and opposite associations with liver-related outcomes. A previous study similarly reported that increased waist circumference was more strongly associated with incident severe liver disease when accompanied by a low, compared to high, hip circumference [31]. A high waist circumference with low hip circumference (high WHR) seems to reflect a more severe metabolic dysfunction, relatively more visceral fat, and/or less gluteal muscle mass than the same level of waist circumference with high hip circumference (low WHR) [31]. These aspects are largely captured in the WHR [31], which supports previous observations that the WHR is superior to waist circumference alone and other anthropometric measures in predicting liver-related outcomes [9,17,18].

The corollary of these findings is that more focus should be put on measuring WHR when assessing the effect of lifestyle interventions to reduce the risk for severe liver disease. In contrast, a reduction in body weight alone, without considering the simultaneous change in the WHR, may give false impressions of reduced risk of liver disease outside the context of lifestyle interventional studies.

Previous intervention trials have shown that the WHR can be reduced by dietary and exercise interventions [13,14,19–21]. Validity of self-measurements of WHR has been shown to be good [32,33], and recently mobile applications enable valid WHR measurements using digital photography technology [34], which has the potential to increase the utilization of these measurements in the population.

It has also been shown that lifestyle interventions in high-risk subjects can reduce the risk of new-onset type 2 diabetes [15,16], and this will likely simultaneously reduce the

risk of liver disease, although this issue remains to be explicitly proven.

The main strength of this study is the ability to analyze longitudinal changes in individual risk profiles over time and link these changes to clinical liver-related outcomes (hospitalization, cancer, and death related to liver disease). Although the Whitehall II study cohort consists of civil servants working in London and are predominantly white, previous studies have shown that the etiology findings are representative of the general population [35]. Moreover, follow-up was long, median of 21 years. An inevitable disadvantage of long follow-up is that the standard of care may have changed over the years.

As in any observational study, not all behavioral changes reflect an active decision to adopt healthier lifestyles but may instead reflect changes made secondary to a new-onset illness. Larger studies are needed to enable more comprehensive adjustment for such potential confounding. Definitive conclusions would need a large randomized trial to analyze the effect of lifestyle interventions targeting a reduction in the CLivD score on the incidence of clinical liver-related outcomes.

Our study methodology did not reflect lifestyle changes over the entire length of follow-up, only the changes that occurred between phases 3 and 5 of the Whitehall II study. We chose this approach because a substantial proportion of participants did not attend the later follow-up visits, and the lack of later clinical follow-up data could introduce selection bias while simultaneously reducing cohort size and statistical power. In the current approach, all subjects were followed passively through registry linkage. Although the overall cohort was relatively large, the number of liver-related events was small. There were too few subjects with a change in smoking habits to allow for meaningful analyses. Therefore, more study is needed to clarify whether smoking cessation reduces the incidence of liver outcomes.

Implications

The CLivD score can be used interactively with the patient to communicate the personal risk of severe liver disease and facilitate a discussion as to how lifestyle modifications can reduce that risk. The knowledge of being at high risk for the severe liver disease can serve as a motivational tool to take action in changing behavior, such as reducing drinking, adopting healthier dietary habits, and increasing physical activity. For instance, the level of drinking that becomes harmful to the liver in any given individual likely depends on several other risk factors [36]. The CLivD score accounts for many of these factors and therefore allows a more comprehensive evaluation of the individual risks of drinking. This observational study suggests that the CLivD score could be used to assess the response to lifestyle interventions targeted to prevent the development of severe liver disease. Finally, the CLivD score can be used for targeting the resources of interventional programs to prevent severe forms of liver disease. Such resources should likely be targeted to persons with intermediate or high CLivD scores.

In conclusion, a change in the individual risk profile over time resulting in a change in the CLivD risk score leads to a corresponding change in the incidence of clinical liver-related outcomes. The CLivD score could thus likely be used for assessing response to lifestyle interventions in persons at risk for severe liver disease. WHR appears to be a better measure of change in adiposity with regard to risk for liver disease than waist circumference or body weight.

Acknowledgments

We thank all participants in the Whitehall II Study, Whitehall II researchers, and support staff who made the study possible. The UK Medical Research Council (MR/K013351/1; G0902037), British Heart Foundation (RG/13/2/30098), and the US National Institutes of Health (R01HL36310, R01AG013196) have supported the collection of data in the Whitehall II Study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Dr. Åberg was supported by the Academy of Finland [grant number 338544] and Sigrid Jusélius Foundation. Dr. Luukkonen was supported by the Novo Nordisk, Sigrid Jusélius, and Instrumentarium Science Foundations.

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Data availability statement

Whitehall II data are available to bona fide researchers for research purposes. Please refer to the Whitehall II data sharing policy at http://www.ucl.ac.uk/whitehallII/data-sharing.

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