

Hepatitis C Virus Infection and Incident Type 2 Diabetes

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Although hepatitis C virus (HCV) infection is more common among adults with type 2 diabetes, it is uncertain whether HCV precedes the development of diabetes. Thus, we performed a prospective (case-cohort) analysis to examine if persons who acquired type 2 diabetes were more likely to have had antecedent HCV infection when enrolled in a community-based cohort of men and women between the ages of 44 and 65 in the United States (Atherosclerosis Risk in Communities Study [ARIC]). Among 1,084 adults free of diabetes at baseline, 548 developed diabetes over 9 years of follow-up evaluation. Incident cases of diabetes were identified by using fasting glucose and medical history and HCV antibodies were assessed at baseline. *A priori*, persons were categorized as low-risk or high-risk for diabetes based on their age and body mass index, factors that appeared to modify the type 2 diabetes–HCV infection incidence estimates. The overall prevalence of HCV in this population was 0.8%. Among those at high risk for diabetes, persons with HCV infection were more than 11 times as likely as those without HCV infection to develop diabetes (relative hazard, 11.58; 95% confidence interval, 1.39–96.6). Among those at low risk, no increased incidence of diabetes was detected among HCV-infected persons (relative hazard, 0.48; 95% confidence interval, 0.05–4.40). In conclusion, pre-existing HCV infection may increase the risk for type 2 diabetes in persons with recognized diabetes risk factors. Additional larger prospective evaluations are needed to confirm these preliminary findings. (HEPATOLOGY 2003; 38:50–56.)

Nearly 4 million persons in the United States and 170 million persons worldwide have been infected with the hepatitis C virus (HCV).^{1,2} HCV infection primarily causes liver disease,^{3,4} but also has been linked to other conditions including type 2 diabetes mellitus.^{4,5} The association between HCV infection and type 2 diabetes has been clearly shown by cross-sectional studies that included prevalent cases of diabetes,^{5–13} but there is insufficient evidence to conclude that HCV infection causes type 2 diabetes. Although most of the

evidence supports that HCV infection antedates type 2 diabetes, it also is possible that persons with diabetes are at increased risk for acquiring HCV infection because of frequent hospital interventions and daily use of syringes. To ascertain if HCV infection causes type 2 diabetes, the temporal relationship needs to be established. In a community-based sample of adults in the United States, we assessed whether persons with HCV antibodies were at increased risk for type 2 diabetes. Because previous studies have suggested that among individuals with HCV infection, those with diabetes are more likely to have traditional risk factors of diabetes,^{6,7,13,14} we also examined whether this relationship between HCV infection and type 2 diabetes was modified by known risk factors of diabetes including age and obesity.

Methods

Study Population. The Atherosclerosis Risk in Communities (ARIC) study is a multicenter cohort designed to study the etiology and natural history of atherosclerosis. The details of the study design have been published elsewhere.¹⁵ Briefly, between 1987 and 1989, 15,792

Abbreviations: HCV, hepatitis C virus; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; IQR, interquartile range.

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men and women aged 45 to 64 were recruited from 4 communities in the United States—Forsyth County, NC; Jackson, MI; northwest suburbs of Minneapolis, MN; and Washington County, MD. At baseline and 3 follow-up visits (1990-1992, 1993-1995, 1996-1998), subjects underwent an interview, examination, and blood draw. Written informed consent was obtained from all participants and a repository of plasma and serum aliquots from each visit was stored frozen at -70°C .¹⁵

A total of 5,517 (35%) individuals were excluded from this analysis because of prevalent or missing diabetes status at baseline ($n = 2,018$), missing baseline plasma specimens due to use in other substudies ($n = 2,506$), missing information on essential covariates ($n = 14$), restricted access to stored specimens ($n = 7$), race other than African American or white ($n = 95$), failure to return for any follow-up ($n = 851$), and insufficient information to characterize diabetes in even one follow-up visit ($n = 26$), leaving 10,275 (65%) individuals in the sampling frame.

Definition of Cases. Fasting serum glucose measurements were performed at each follow-up visit by using the hexokinase method.¹⁶ Incident cases of diabetes were defined as participants meeting one of the following criteria at any of 3 follow-up visits: (1) self-reported use of hypoglycemic medications; (2) fasting (>8 hours) serum glucose level greater than 7.0 mmol/L (126 mg/dL); (3) nonfasting serum glucose level greater than 11.1 mmol/L (200 mg/dL); or (4) self-report of physician diagnosis. For individuals classified by physician diagnosis or medication use, date of diabetes onset was considered to be the midpoint between the last visit when an individual was not diabetic and the first visit when an individual was diabetic. For those diagnosed by fasting or nonfasting glucose level, date of diabetes onset was the estimated date at which blood sugar level crossed a threshold (7.0 mmol/L for fasting and 11.1 mmol/L for nonfasting), assuming a linear increase in glucose level between visits.

Exposure and Other Covariate Information. Baseline visit plasma samples were tested for HCV antibodies with the third-generation Ortho HCV enzyme immunoassay (Ortho Diagnostics, Raritan, NJ). Specimens positive by enzyme immunoassay were tested using the third-generation Chiron recombinant immunoblot assay HCV Test System (Chiron Corporation, Emeryville, CA, and Ortho Diagnostics). Only specimens positive by both enzyme immunoassay and recombinant immunoblot assay were considered positive for HCV antibody. Specimens negative by recombinant immunoblot assay were considered negative for HCV antibody, and those with indeterminate results were from the primary analysis.

Supplemental HCV testing was performed on persons with HCV antibodies. All specimens that were positive by

enzyme immunoassay were tested further with the HCV core antigen assay (Ortho-Clinical Diagnostics, Raritan, NJ) according to the manufacturer's recommendations. This assay has a cut-off value of 1.5 pg/mL of core antigen that corresponds to approximately 12,000 IU/mL of HCV RNA.¹⁷ All core antigen-negative serum specimens were tested further using a nested reverse-transcriptase polymerase chain reaction assay, which amplifies the HCV genome from core through E1 and has a lower limit of detection of less than 50 IU/mL, as previously described.¹⁸

Other covariate information was obtained from the baseline examination and interview. Information on general demographics, education (highest grade completed), cigarette smoking, alcohol use, and medical history including personal and family history of diabetes was obtained from the home interview. Body mass index was calculated based on weight and height measurements taken during the baseline clinic examination. Medication use was documented by asking study participants to bring all medications taken during the past 2 weeks to the study clinic.

Statistical Analysis. We performed a case-cohort analysis. Because sampling of the cohort is performed *a priori* without regard to case status or time, a true relative risk can be obtained without testing all cohort members for the presence of hepatitis C.¹⁹ We included stratified random samples of both incident cases of type 2 diabetes and members of the cohort at baseline (selected without respect to diabetes status). The case group ($n = 1,155$) and the eligible cohort ($n = 10,275$) were stratified by race and simple random samples were drawn from each race category. Initially, 581 incident cases of type 2 diabetes and 693 cohort members were selected for analysis. However, 117 individuals were excluded due to insufficient sample volume ($n = 108$) or indeterminate HCV antibody results ($n = 9$), leaving 529 cases (261 African American and 268 white) and 628 cohort members (307 African American and 321 white). Of the 628 individuals in the cohort sample, 92 developed type 2 diabetes during 9 years of follow-up, of whom 73 also were sampled as part of the case group, leaving a total 536 noncases and 19 cases, adding to the 529 other cases for a total of 548 cases (Fig. 1).

Because African-American individuals were oversampled in this study to accommodate parallel ARIC investigations, we accounted for sampling fractions in the estimation of all means and proportions and in the analysis of time to diabetes. χ^2 tests were used to determine correlates of type 2 diabetes and HCV infection. Cox proportional hazards regression with staggered entries was used in the analysis of time to diabetes. The methods of

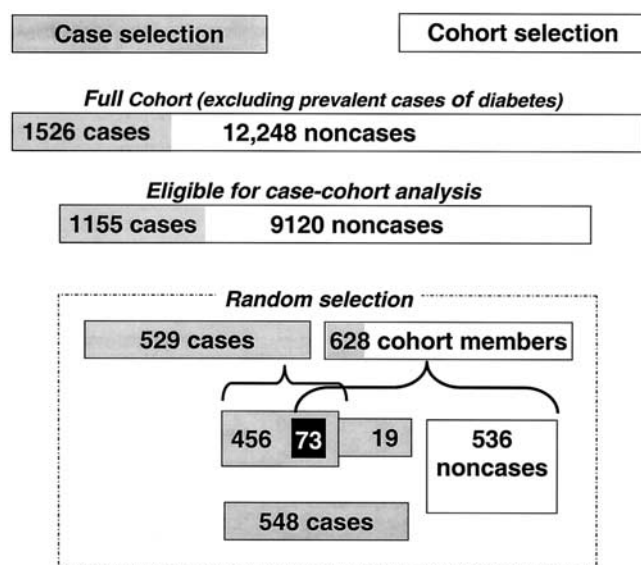


Fig. 1. Determination of study sample. Of the 15,792 persons enrolled in the ARIC cohort, 2,018 had prevalent diabetes at baseline, 1,526 developed incident diabetes, and 12,248 were free of type 2 diabetes throughout follow-up evaluation. Of the 13,774 individuals without diabetes at entry, 10,275 were eligible for this study, 1,155 of whom developed type 2 diabetes. We included random samples, stratified by race, of both incident cases of type 2 diabetes ($n = 529$; 268 African American and 261 white) and members of the cohort at baseline ($n = 628$; 307 African American and 321 white). Of the 628 cohort members selected, 92 developed type 2 diabetes during follow-up (73 also were selected as part of the case group). The 19 cases selected only in the cohort sample also contributed to the case group for a total of 548 cases and 536 noncases.

Barlow et al.¹⁹ were used to account for case-cohort sampling, with the sampling fractions varying by race strata. Although cases in the cohort sample ($n = 92$) were observed from their entry into the study until failure, cases outside the cohort sample ($n = 456$) were observed only at the time of failure and thus were entered into the analysis immediately before their occurrence (staggered entry). Robust variance estimates were calculated in STATA (College Station, TX) using the robust option.^{20,21}

Potential interactions between HCV and age, race, body mass index (BMI), alcohol use, and family history of diabetes were assessed by adding interaction terms to Cox regression models and testing the statistical significance of resulting coefficients. The relationship between HCV infection and diabetes appeared to be modified by both age and BMI. Because too few persons were anti-HCV positive to examine each age and BMI category separately, persons were categorized into low- and high-risk groups, created based on a combination of age and BMI without knowledge of the data. The high-risk group included all persons over the age of 60 years and all those with a BMI greater than 35 kg/m², as well as those 50 to 59 years of age with a BMI of 30 to 34.9 kg/m², and those 55 to 59

years of age with a BMI of 25 to 29.9 kg/m². All other persons were in the low-risk group. Analysis was performed using STATA software version 7.0.

Results

Cases of type 2 diabetes tended to be older, male, and African American when compared with noncases (Table 1) and the cohort sample (data not shown). Persons with type 2 diabetes also tended to have lower educational attainment, higher BMI, and were more likely to report a family history of diabetes than those without type 2 diabetes.

Because the cohort sample was sampled to be representative of the original ARIC cohort, the association between HCV infection and diabetes risk factors was examined in these 628 persons, of whom 8 (0.8%) were anti-HCV positive (Table 2). The prevalence of HCV

Table 1. Baseline Characteristics of Incident Cases of Type 2 Diabetes and Noncases, ARIC Study, 1987-1998

	Noncases* (n = 536)	Cases* (n = 548)	P Value
Center			
Forsyth County, NC	26.0	18.4	
Jackson, MS	17.2	32.5	
Minneapolis, MN	24.5	19.2	
Washington County, MD	32.3	29.8	<.001
Age (y)			
45-49	36.6	27.6	
50-54	27.5	31.6	
55-59	20.9	22.5	
60-65	15.0	18.3	.15
Male gender	34.8	43.4	.03
African-American race	20.0	37.8	<.0001
Education			
Less than high school	17.4	28.2	
High school	45.1	39.9	
Some college	37.5	31.9	<.01
BMI (kg/m ²)			
Lean/normal (<25)	38.2	16.1	
Overweight (25-29.9)	41.0	33.6	
Obese (30-34.9)	14.3	27.1	
Morbidly obese (>35)	6.5	23.2	<.00001
Cigarette smoking			
Never smoker	47.3	42.0	
Former smoker	31.2	37.7	
Current smoker	21.5	20.3	.24
Alcohol intake (g/d)†			
None	57.3	61.6	
Light	37.3	29.1	
Heavy	5.4	9.3	.07
Family history of diabetes‡	21.2	33.8	<.001

*Weighted proportions taking into account the stratified selection of the case and cohort samples. Case group includes both cases inside ($n = 92$) and outside ($n = 456$) the cohort sample.

†Light alcohol intake represents <20 g/d for women and <30 g/d for men. Heavy alcohol intake represents >20 g/d for women and >30 g/d for men.

‡Persons were classified as having a family history of diabetes if they reported that any first-degree relative had diabetes.

Table 2. Percentage of Persons With HCV Antibody in the Cohort Sample (n = 628) by Diabetes Risk Factors

	Number in Cohort Sample	Number of HCV Cases	Percent*	P Value
Center				
Forsyth County, NC	125	2	0.6	
Jackson, MS	273	5	1.8	
Minneapolis, MN	98	1	1.0	
Washington County, MD	132	0	0	.22
Age (y)				
44-49	244	3	1.1	
50-54	179	1	0.3	
55-59	120	4	1.4	
60-65	85	0	0	.33
Sex				
Female	418	3	0.4	
Male	210	5	1.5	.04
Race				
White	321	1	0.3	
African American	307	7	2.4	.03
Education				
Basic or none (<11 y)	148	4	1.6	
Intermediate (12-16 y)	244	2	0.3	
Advanced (17-21 y)	227	2	0.9	.28
BMI (kg/m²)				
Lean/normal (<25)	195	5	1.0	
Overweight (25-29.9)	246	2	0.8	
Obese (30-34.9)	112	1	0.5	
Morbidly obese (>35)	75	0	0	.77
Cigarette smoking				
Never smoker	299	2	0.3	
Former smoker	185	1	0.8	
Current smoker	144	5	1.8	.23
Alcohol intake (g/d)†				
None	390	3	0.4	
Light	193	5	1.5	
Heavy	36	0	0	.18
Family history of diabetes‡				
No	402	4	0.7	
Yes	150	1	0.3	.14

*Weighted percentages taking into account the stratified nature of the cohort sample.

†Light alcohol intake represents <20 g/d for women and <30 g/d for men. Heavy alcohol intake represents >20 g/d for women and >30 g/d for men. Numbers do not add up to 628 because of missing values.

‡Persons were classified as having a family history of diabetes if they reported that any first-degree relative had diabetes. Numbers do not add up to 628 because of missing values.

infection was higher among men than women (1.5% vs. 0.47%, $P = .04$) and African Americans than whites (2.47% vs. 0.3%, $P = .03$). However, there were no differences in HCV prevalence by other correlates of type 2 diabetes (e.g., age, BMI, or family history of diabetes).

Overall, persons with HCV infection were nearly twice as likely as those without HCV infection to develop diabetes, but this difference was not statistically significant (relative hazard, 1.9; 95% confidence interval, 0.6-6.2). After stratification for underlying diabetes risk, a significant increase in the incidence of diabetes was not detected among anti-HCV-positive persons who were at low risk

for diabetes (relative hazard, 0.48; 95% confidence interval, 0.05-4.40). However, compared with persons without HCV infection at high risk for diabetes, those with HCV infection at high risk were more than 11 times as likely to develop type 2 diabetes (relative hazard, 11.58; 95% confidence interval, 1.39-96.6; P value for test of interaction = 0.04) (Table 3). When the analysis was restricted to include only the 12 persons who had ongoing HCV infection, the relationship between HCV and type 2 diabetes among high-risk persons was attenuated (relative hazard, 7.61; 95% confidence interval, 0.85-68.4, $P = .07$).

At baseline, among the 15 individuals with HCV infection, those who developed diabetes had higher fasting insulin levels (136 pmol/L; interquartile range [IQR], 108-230 pmol/L) and more insulin resistance (4.8 pmol/L; IQR, 4.0-9.8) as measured by the HOMA-IR method (fasting insulin [Uu/mL] \times fasting glucose [mmol/L]/22.5) compared with those who did not develop diabetes (72 pmol/L; IQR, 50-176 and 2.5; IQR, 1.5-5.9, respectively), but these differences were not statistically significant ($P = .18$ and $.13$, respectively). Albumin levels at baseline were significantly lower among HCV-infected persons who developed diabetes (median, 3.6; IQR, 3.5-3.9) compared with HCV-infected persons who did not develop diabetes (median, 4.1; IQR, 4.0-4.2; $P = .02$), a result driven by differences in the high-risk group. However, median platelet counts did not differ between the 2 groups (225 and 210 for persons who did and did not develop diabetes, respectively, $P = .89$).

Among all high-risk persons, fasting insulin levels and insulin resistance were slightly higher in those who were HCV-infected compared with those who were not, but these differences were not statistically significant (Table 4). However, among persons with a high BMI (>30 kg/m²), median insulin levels and insulin resistance were significantly higher among HCV-infected persons compared with HCV-uninfected persons.

Table 3. Relative Hazards of Type 2 Diabetes From Cox Proportional Hazards Regression Analysis

Risk Group*	HCV Antibody Status	Total Number	Cases of Diabetes	Relative Hazard (95% Confidence Interval)
Low	-	545	212	1
Low	+	8	1	0.48 (0.05-4.40)
High	-	524	329	1
High	+	7	6	11.59 (1.39-96.64)†

*Persons were categorized *a priori*, according to age and BMI, into 2 groups: low- and high-risk for diabetes. The high-risk group included all persons who either were >60 years of age or had a BMI >35 kg/m², as well as persons who were between 50 and 59 years of age with a BMI between 30 and 35 kg/m² and those between 55 and 59 years of age with a BMI between 25-29.9 kg/m². The low-risk group included all others.

† P value of test for interaction, .04.

Table 4. Fasting Insulin and Insulin Resistance by HCV Antibody Status and Diabetes Risk

	Fasting Insulin (pmol/L)			Insulin Resistance*		
	HCV Positive, Median (IQR)	HCV Negative, Median (IQR)	P Value†	HCV Positive, Median (IQR)	HCV Negative, Median (IQR)	P Value
Low risk‡	72 (50-194)	65 (43-93)	.32	2.5 (1.5-6.7)	2.2 (1.4-3.3)	.40
High risk‡	136 (100-230)	100 (72-158)	.21	4.4 (3.8-9.8)	3.8 (2.4-5.9)	.33
BMI (kg/m ²)						
<30	79 (36-136)	65 (43-86)	.24	2.9 (1.1-4.4)	2.2 (1.4-3.2)	.34
>30	244 (197-315)	118 (86-165)	<.01	10.4 (7.3-13.0)	4.4 (3.0-6.3)	.01

*Insulin resistance measured by HOMA-IR method (fasting insulin [Uu/mL] × fasting glucose [mmol/L]/22.5).

†P values from Mann Whitney tests.

‡Persons were categorized *a priori*, according to age and BMI, into 2 groups: low- and high-risk for diabetes. The high-risk group included all persons who either were >60 years of age or had a BMI >35 kg/m², as well as persons who were between 50 and 59 years of age with a BMI between 30 and 35 kg/m² and those between 55 and 59 years of age with a BMI between 25-29.9 kg/m². The low-risk group included all others.

Discussion

In this investigation, the incidence of type 2 diabetes was increased substantially for persons with recognized diabetes risk factors and HCV infection compared with those with similar diabetes risk factors but not HCV infection. Detection of an increased risk for type 2 diabetes among those with HCV infection supports many of the previous investigations that have documented an association between HCV infection and type 2 diabetes in other settings, including liver clinics,^{5-9,11,22} diabetes clinics,^{9,10,12} and the general U.S. population.¹³ In addition, the present study extends this research by showing that HCV infection antedated the development of type 2 diabetes, providing preliminary epidemiologic evidence supporting the hypothesis that HCV infection causes type 2 diabetes. Further studies are needed to confirm these preliminary findings and to elucidate the underlying biologic mechanism before causality can be firmly established.

The conclusions that can be made from this study are limited by the unexpected low prevalence of HCV infection in this population. With only 15 cases of HCV infection, it is possible that some cases were highly influential. However, in a sensitivity analysis, systematic removal of cases did not significantly alter the results. Additionally because the sampling weights varied quite widely, we investigated the sensitivity of the results to the weights. The hazard ratios remained large despite reductions in the weights of up to 50%. When the largest weights were reduced dramatically (40%), some results were no longer statistically significant, but this is probably more because of the small number of cases rather than the weighting scheme itself. The small number of HCV cases also prohibited multivariate analysis. Although we indirectly accounted for age and BMI through the risk group classification, we were not able to account for other known correlates of diabetes including race and socioeconomic status. However, in our previous analysis, adjust-

ment for these factors actually strengthened the association between HCV infection and type 2 diabetes,¹³ suggesting that the relative hazard observed in this study might even be an underestimate of the relationship between HCV and type 2 diabetes.

It also was not possible to determine whether the observed effect modification by age and BMI was real or caused by random variation. Likewise, it is possible that no increased risk for diabetes was detected among anti-HCV-positive persons who were otherwise at low risk because of limited power. Although power calculations performed before the study was conducted suggested greater than 80% power based on an HCV prevalence of 1.8% among persons without diabetes (the average among U.S. adults),¹ *post hoc* power calculations based on the observed prevalence of 0.8% revealed only 30% power to detect in the low-risk stratum a difference of the same magnitude as was observed in other studies.

It also is possible that HCV infection modified the effect of age and BMI on the risk for diabetes. This is supported by the observation that HCV-infected individuals who were obese (BMI > 30 kg/m²) had significantly higher insulin levels and insulin resistance at baseline compared with HCV-negative individuals who also were obese regardless of diabetes status. In previous studies, HCV-infected persons with diabetes also were more likely than HCV-infected persons without diabetes to be older and obese.^{6,7,13,14} There are insufficient data to explain these observations. However, it is interesting to note that both obesity and older age were associated with more severe liver disease among HCV-infected patients.²³

The link between advanced liver disease and type 2 diabetes has been suggested by a number of studies. Patients with cirrhosis are predisposed to insulin resistance and, consequently, type 2 diabetes.²⁴ Some studies have shown that even among HCV-infected persons without type 2 diabetes or cirrhosis, insulin resistance and glucose

intolerance are present. In these individuals, the degrees of insulin resistance and glucose intolerance still were related closely to the severity of liver damage.²⁵ Steatosis is also a feature of chronic HCV infection. A recent study suggested that greater than 60% of persons chronically infected with HCV had steatosis.²³ In this and other studies, steatosis also was associated with high BMI and fibrosis.^{23,26} Because steatosis also has been associated with type 2 diabetes,²⁷ it may not be surprising that HCV infection, age, and obesity combined dramatically increase a person's risk for type 2 diabetes.

Unfortunately, we were not able to address adequately the role of liver disease because neither liver biopsy specimens nor markers of severe liver disease including total bilirubin and prothrombin time were available. Baseline albumin levels were available and were observed to be significantly lower among HCV-infected persons who developed diabetes compared with those who did not develop diabetes. On the other hand, there were no differences in platelet counts and none of the 15 HCV-infected persons reported a history of liver disease or cirrhosis (asked at the third visit, data not shown).

Further support for the hypothesis that diabetes occurs more frequently among HCV-infected persons because of advanced liver disease would come from showing that the hazard of developing diabetes would be greatest in those with ongoing HCV infection, which was only observed (positive HCV antigen and/or RNA) in 12 individuals in this study. The relative hazard among the high-risk group with ongoing HCV infection remained elevated but was reduced in magnitude and statistical significance compared with the relative hazard for all HCV antibody-positive persons. It is difficult to speculate on the reasons for this because the precision of these estimates is very low given that so few people were HCV-RNA positive. Because the overall number of positives was already low, because we found essentially the same estimates in the ongoing infection group, and because we could not test sera from additional visits to ensure there was not a problem with sample handling or storage, we chose to focus our analysis on HCV antibody-positive persons.

It also is possible that HCV infection was a marker for some other risk factor of type 2 diabetes that was not measured in this population. HCV infection could be a marker for ongoing inflammation, which has been associated with the development of type 2 diabetes.²⁸ Although plasma fibrinogen levels were not different among HCV-infected persons who developed diabetes and those who did not (data not shown), we did not have information on other markers of inflammation such as C-reactive protein. It is less likely that HCV infection was a marker for some other behavioral risk factor of type 2 diabetes

because we had information on most known risk factors for diabetes including alcohol use and exercise, neither of which were associated with HCV infection or the development of type 2 diabetes.

The present findings suggest that the association between HCV infection and type 2 diabetes may be stronger for persons defined as high risk on the basis of their age and BMI. Although this study suggests a temporal relationship between HCV infection and type 2 diabetes, these results should be considered to be of a preliminary nature due to the low prevalence of HCV infection. Larger prospective studies should include persons at high risk for both HCV infection and type 2 diabetes to have enough power to firmly establish a temporal relationship between these 2 conditions.

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