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Original article

Association between HCV infection and diabetes type 2 in Egypt: is it time to split up?

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ABSTRACT

Purpose: There is a conflicting evidence about the association between hepatitis C virus (HCV) infection and diabetes mellitus. The objective of this study was to assess this association in Egypt, the country with the highest HCV prevalence in the world.
Methods: The source of data was from the Egypt Demographic and Health Survey conducted in 2008. Using multivariable logistic regression analyses to account for known confounders, the association was investigated at two levels']: (1) HCV exposure (HCV antibody status) and diabetes mellitus and (2) diabetes mellitus and chronic HCV infection (HCV RNA status) among HCV-exposed individuals.
Results: We found no evidence for an association between HCV antibody status and diabetes (adjusted odds ratio [OR] = 0.87; 95% confidence interval [CI], 0.63–1.19). However, among HCV-exposed individuals, we found an evidence for an association between diabetes and active HCV infection (adjusted OR = 2.44, 95% CI, 1.30–4.57).
Conclusions: Although it does not appear that HCV exposure and diabetes are linked, there might be an association between diabetes and chronic HCV infection. The HCV–diabetes relationship may be more complex than previously anticipated. Therefore, a call for an "amicable divorce" to the HCV–diabetes relationship could be premature.

Introduction

Hepatitis C virus (HCV) infection and diabetes mellitus are the major public health challenges with increasing morbidity and mortality disease burden [1, 2]. HCV is a multifaceted infection affecting different processes such as mitochondrial function, insulin resistance, lipid metabolism, and signaling pathways among others [3, 4]. HCV infection can lead to inflammation of the liver, progression to fibrosis, and development of cirrhosis or hepatocellular carcinoma [4]. Diabetes has been also recognized as part of the spectrum of HCV-associated diseases [5]. Diabetes mellitus is a complex disease with pathophysiology that includes increased hepatic glucose production, defects in insulin secretion, and/or insulin resistance [6, 7].

The precise biological mechanisms underlining glucose intolerance and diabetes in HCV-infected individuals are not completely understood. Several hypotheses, however, have been proposed for the development of diabetes mellitus in HCV-infected individuals. Alterations in hepatic lipid and carbohydrate metabolism with HCV infection have been commonly observed, potentially causing fat accumulation in hepatocytes [8, 9]. This intracellular fat accumulation could induce insulin resistance and may lead to the development of diabetes [10]. Moreover, studies have suggested that expression of the HCV core protein can induce hepatic insulin resistance through alterations in signaling in the insulin receptor substrate-1 pathway [11, 12]. Results derived from animal models have also suggested a more direct effect of HCV infection on insulin resistance in the liver through the activity of hepatic tumor necrosis factor-α on the insulin signaling pathway [13].

Emerging epidemiologic evidence has suggested a link between HCV infection and diabetes [5,14–17]. However, most epidemiologic studies reported analyses from data derived from tertiary liver care centers [16, 17]. Such clinic-based studies may suffer from selection bias, and recruited liver patients may not represent the

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early stages of infection or disease present in the general population. Only few population-based studies have been conducted to assess this association, and their results were inconclusive [18–21]. Notably, a recent landmark study on a nationally representative sample of the U.S. population, the National Health and Nutrition Examination Survey (NHANES), failed to identify a statistically significant association between HCV infection and diabetes [22]. The study included more than 15,000 participants, of whom 277 participants were HCV antibody positive [22]. The lack of a clear association between HCV infection and diabetes in this study, along with the accumulating conflicting evidence from other studies [16, 17, 19, 20, 23], casts doubt on the existence of a causal link leading to a call for an "amicable divorce" to this association [7].

A major concern about the U.S.-based study and the other population-based studies has been the relatively small number of HCV infected individuals included in the analyses, because of the low HCV prevalence in the population [16, 20]. For example, HCV prevalence in the U.S. population is only 1.7% [22]. Therefore, there may not have been sufficient statistical power in these studies to characterize the complexity of the association between HCV and diabetes. It is critical, as has been suggested recently [22], to replicate such studies on nationally representative samples in countries with high HCV prevalence where such samples may include a large number of HCV infected individuals.

In the present study, we aimed to examine the association between HCV infection and diabetes in a large nationally representative population-based sample in Egypt, the country with the highest HCV prevalence worldwide (14.7%) [24–26], with genotype 4 being the dominant genotype (responsible for more than 90% of HCV infections) countrywide [26]. This sample offers a rare opportunity to examine this association as it is one of the largest samples ever to study HCV infection [24] and conducted in a country where HCV prevalence is more than 10-fold higher than that in the United States. [24, 25]. The sample included more than 1400 HCV antibody-positive individuals [24], compared to only 277 in the U.S. study [22]. The first objective of our study was to assess the association between diabetes mellitus and HCV exposure (antibody positivity) in Egypt. The second objective was to assess the association between chronic HCV infection (HCV RNA positivity) and diabetes mellitus in the subsample of HCV antibody-positive individuals.

Materials and methods

Conceptual framework

The association between HCV infection and diabetes can be manifested at different levels. At one level, HCV-exposed individuals (i.e., HCV antibody positive) could be at higher risk of developing diabetes. Conversely, diabetic patients could also be more frequently exposed to HCV through medical procedures, and thus have a higher likelihood of becoming infected. Therefore, we assessed the association between diabetes mellitus and HCV antibody serological status in the whole sample (Model 1).

On another level, diabetic patients could be less likely to clear the infection if they are exposed to the virus. Alternatively, individuals with chronic HCV infection (i.e., HCV RNA positive) could be more likely to develop diabetes. Therefore, we also examined the relationship at this level by assessing the association between HCV RNA status and diabetes mellitus among only the subsample of HCV antibody-positive individuals (Model 2).

Data sources

Our source of data was the Egypt Demographic and Health Survey (EDHS) conducted in 2008 [24]. All women and men aged 15 to 59 years present in the sampled households were eligible for the survey, and 11,126 (87.1%) of these individuals were tested for HCV antibody and HCV RNA. The HCV testing protocol included an initial round of testing to detect the presence of antibodies against the virus [24]. A third generation Enzyme Immunoassay (ELISA), Adlatis EIAgen HCV Ab test (Adaltis Inc., Montreal, Canada) was used to test for antibodies against HCV. This test showed 100% of sensitivity and 98.1% of specificity, with a cut-off value (signal-to-cut-off ratio, S/CO) of 1.0 or more to be considered reactive for anti-HCV antibodies, whereas those S/CO less than 1.0 were considered nonreactive [27]. All positives with this test were confirmed by a Chemiluminescent Microplate Immunoassay (CIA) [24]. All confirmed HCV antibody-positive specimens were tested by Quantitative real time PCR (RT-qPCR) for the detection of HCV RNA [24]. Further methodologic details related to specimen handling and laboratory methods used for the detection of HCV antibody and HCV RNA can be found in El-Zanaty et al. [24].

We used the binary answer to the question "has a doctor or other health professional ever told you that you had diabetes?" as the measure for diabetes mellitus. After excluding participants with missing HCV antibody status or diabetes status, the final analyses were conducted on 10,143 participants (Fig. 1).

Statistical analyses

We conducted two separate analyses. In the first model, the dichotomous HCV antibody serological status (indicator of exposure to HCV) was included as independent variable, and diabetes status was the main outcome (model 1). In the second model, diabetes status was included as independent variable, and HCV RNA status (indicator of active infection) among HCV antibody-positive individuals was the main outcome (model 2). To adjust for confounders, several variables known to be associated with HCV infection or diabetes were first analyzed in bivariate analyses. Variables included were age, place of residence (urban or rural), sex, level of education, body mass index (BMI), hypertension, ever had dental treatment, ever had surgery, ever had blood transfusion, ever had received parenteral antischistosomiasis therapy (PAT), and ever been hospitalized. BMI was stratified in three categories: normal (BMI < 25), overweight (BMI $= 25–30$), and obese (BMI > 30) [28].

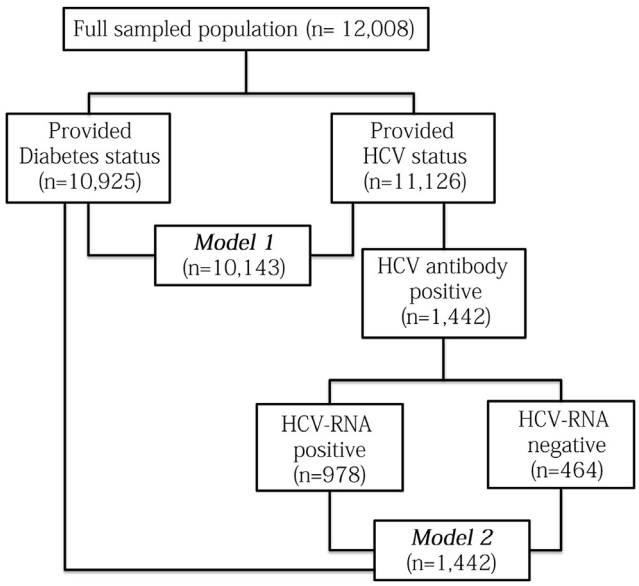

Fig. 1. Determination of study sample.

Hypertension was defined according to the guidelines of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure [29].

Multivariable logistic regressions were performed to determine the association between diabetes and HCV serological status or HCV RNA status. Variables with a *P* value less than .25 in bivariate analyses were included in the final multivariable logistic models. Age was included as a polynomial term to account for nonlinearities in the association with diabetes. Analyses included sample weights to account for unequal selection probabilities and nonresponses. All statistical analyses were conducted using SAS, version 9.3 [30].

Sensitivity analyses

We evaluated the robustness of the results obtained from the multivariable regression models using three different approaches. First, the cut-off of the *P* value in the bivariate analyses was varied to be smaller ($P < .2$) or larger ($P < .5$) than the default cut-off implemented in the selection criteria for the final multivariable model ($P < .25$). Second, alternative multivariable models were performed excluding variables that were not statistically significant in the final multivariable models, but retaining the variables that were statistically significant at $P < .05$. Finally, a study conducted using diabetes self-reported data from NHANES (1988–1994) found no statistically significant association between HCV and diabetes overall, but a significant association among individuals older than 40 years of age [19]. Therefore, we conducted also a subgroup analysis restricted to individuals older than 40 years.

Results

General results

The general characteristics of the study subjects are listed in Table 1. From the sampled population, 351 individuals reported to have diabetes corresponding to a diabetes prevalence of 3.33% (95% confidence interval [CI], 2.94–3.71). Females had higher prevalence of diabetes, 4.01% (95% CI, 3.42–4.60), than males, 2.63% (95% CI, 2.13–3.13). Diabetes was more prevalent in urban areas, 4.72% (95% CI, 3.98–5.46), than in rural areas, 2.35% (95% CI, 1.96–2.76). The

Table 1
Demographics and study population characteristics

Variable	Diabetes, *n* (%)		HCV antibody, *n* (%)		HCV RNA, *n* (%)	
	Negative ($n = 9792$)	Positive ($n = 351$)	Negative ($n = 8701$)	Positive ($n = 1442$)	Negative ($n = 464$)	Positive ($n = 978$)
Diabetes						
Negative	—	—	8442 (85.44)	1320 (14.56)	8888 (90.35)	904 (9.65)
Positive	—	—	259 (73.10)	92 (26.90)	277 (77.71)	74 (22.29)
Age (y)						
15–19	1786 (99.77)	6 (0.23)	1723 (96.07)	69 (3.93)	1741 (97.22)	51 (2.78)
20–24	1664 (99.79)	6 (0.21)	1595 (95.39)	75 (4.61)	1629 (97.33)	41 (2.67)
25–29	1390 (99.88)	4 (0.12)	1305 (93.64)	89 (6.36)	1333 (95.91)	61 (4.09)
30–34	1131 (99.04)	12 (0.96)	1022 (88.15)	121 (11.85)	1060 (91.68)	83 (8.32)
35–39	1018 (98.15)	23 (1.85)	912 (86.26)	129 (13.74)	945 (90.03)	96 (9.97)
40–44	939 (95.88)	45 (4.12)	760 (76.16)	224 (23.84)	836 (84.36)	148 (15.64)
45–49	785 (91.42)	74 (8.58)	601 (69.89)	258 (30.11)	688 (80.19)	171 (19.81)
50–54	591 (87.72)	82 (12.28)	420 (60.97)	253 (39.03)	498 (73.64)	174 (23.36)
55–59	488 (83.47)	99 (16.53)	363 (59.05)	224 (40.95)	435 (72.04)	152 (27.96)
Area						
Urban	3885 (40.69)	198 (58.47)	3674 (89.58)	409 (10.42)	3787 (92.61)	296 (88.04)
Rural	5907 (59.31)	153 (41.53)	5027 (81.82)	1033 (18.18)	5378 (88.04)	682 (11.96)
Sex						
Male	4624 (97.37)	136 (2.63)	3932 (81.99)	828 (18.01)	4183 (87.52)	577 (12.48)
Female	5168 (95.99)	215 (4.01)	4769 (87.97)	614 (12.03)	4982 (92.26)	401 (7.74)
Education						
None	2170 (94.87)	123 (5.14)	1778 (75.56)	515 (24.44)	1941 (83.31)	352 (16.69)
Primary	1349 (94.17)	84 (5.83)	1148 (79.03)	285 (20.97)	1257 (86.90)	176 (13.10)
Secondary	4844 (97.96)	107 (2.04)	4448 (89.20)	503 (10.80)	4590 (92.46)	361 (7.54)
Higher education	1429 (97.47)	37 (2.53)	1327 (90.79)	139 (9.21)	1377 (94.09)	89 (5.91)
BMI						
Normal (less than 25)	748 (97.93)	16 (2.07)	660 (86.03)	104 (13.97)	699 (91.24)	65 (8.76)
Overweight (25–30)	870 (98.20)	17 (1.80)	764 (86.39)	123 (13.61)	801 (91.13)	86 (8.87)
Obese (more than 30)	1186 (95.38)	63 (4.62)	1075 (85.24)	174 (14.76)	1140 (90.90)	109 (9.10)
Hypertension						
Normal	8436 (97.00)	269 (3.00)	7564 (86.06)	1141 (13.94)	7930 (90.61)	775 (9.39)
Prehypertensive	1356 (94.62)	82 (5.38)	1137 (78.74)	301 (21.26)	1235 (85.79)	203 (14.21)
Ever had dental treatment						
Yes	5816 (95.86)	263 (4.14)	5089 (82.91)	990 (17.09)	5398 (88.34)	681 (11.66)
No	3970 (97.94)	88 (2.06)	3608 (88.37)	450 (11.63)	6079 (92.45)	3763 (7.55)
Ever had a surgical procedure						
Yes	3989 (95.24)	202 (4.76)	3491 (82.62)	700 (17.38)	3704 (87.88)	487 (12.12)
No	5793 (97.74)	148 (2.26)	5201 (86.81)	740 (13.19)	5452 (91.46)	489 (8.54)
Ever had a blood transfusion						
Yes	381 (91.16)	31 (8.84)	320 (75.10)	92 (24.90)	350 (83.12)	62 (16.88)
No	9392 (96.88)	320 (3.12)	8365 (85.42)	1347 (14.58)	8799 (86.48)	913 (9.39)
Ever received PAT						
Yes	859 (95.50)	46 (4.50)	633 (69.07)	272 (30.93)	722 (79.38)	183 (20.62)
No	8789 (96.77)	298 (3.23)	7947 (86.59)	1140 (13.41)	8309 (90.93)	778 (9.07)
Ever been hospitalized						
Yes	299 (97.1)	9 (2.9)	260 (84.4)	48 (15.6)	274 (88.9)	34 (11.1)
No	9493 (96.4)	342 (3.5)	8441 (85.2)	1394 (14.2)	8891 (90.4)	944 (9.6)

mean age of individuals who reported to have diabetes was 48 years (95% CI, 47–49), compared with 32 years (95% CI, 31–33) of those who did not.

From the sampled population, 1442 individuals were HCV antibody positive corresponding to an HCV antibody prevalence of 14.22% (95% CI, 13.54–14.91) were HCV antibody positive, whereas 9.64% (95% CI, 9.07–10.23) was HCV RNA positive. HCV antibody prevalence was higher in rural areas, 17.04% (95% CI, 16.10–18.01), than in urban settings, 10.02% (95% CI, 9.07–10.23). The mean age of HCV antibody-positive individuals was 43 years (95% CI, 42–44), compared to 31 years (95% CI, 30–32) of those HCV antibody negative.

Association between HCV exposure and diabetes (model 1)

The prevalence of diabetes in HCV antibody-positive individuals was 5.98% (95% CI, 4.67–7.30), whereas the prevalence of diabetes in HCV antibody negative individuals was 2.86% (95% CI, 2.47–3.25). There was an association between diabetes and HCV exposure in bivariate analysis with an unadjusted crude odds ratio (OR) of 2.16 (95% CI, 1.65–2.82). From the covariates included in the study, only ever been hospitalized ($P = 0.5$) was not included in the final multivariable model (model 1). After adjusting for the other variables, HCV exposure status was no longer associated with diabetes status (Table 2). The adjusted OR was 0.87 (95% CI, 0.63–1.19).

Table 2
Unadjusted and adjusted results for diabetes mellitus status as the outcome according to selected covariates (model 1)

Variable	Unadjusted			Adjusted*		
	OR	95% CI	*P*	OR	95% CI	*P*
HCV antibody						
Negative	ref			ref		
Positive	2.16	1.65–2.82	<.01	0.87	0.63–1.19	.38
Area						
Urban	ref			ref		
Rural	0.49	0.38–0.62	<.01	0.60	0.45–0.80	<.01
Sex						
Male	ref			ref		
Female	1.59	1.21–1.98	<.01	1.88	1.39–2.55	<.01
Education						
None	ref			ref		
Primary	1.14	0.83–1.57	<.01	1.30	0.91–1.84	.67
Secondary	0.38	0.28–0.52	<.01	1.23	0.86–1.77	.51
Higher education	0.48	0.31–0.75	.02	1.07	0.66–1.73	.28
BMI						
Normal (less than 25)	ref			ref		
Overweight (25–30)	0.87	0.40–1.90	.06	1.37	0.73–2.54	.44
Obese (more than 30)	2.29	1.26–4.17	<.01	0.61	0.28–1.33	.37
Hypertension						
Normal	ref			ref		
Prehypertensive	1.84	1.39–2.44	<.01	1.17	0.86–1.60	.32
Ever had dental treatment						
No	ref			ref		
Yes	2.05	1.60–2.61	<.01	1.16	0.86–1.56	.33
Ever had a surgical procedure						
No	ref			ref		
Yes	2.26	1.70–2.74	<.01	1.27	0.92–1.78	.06
Ever had a blood transfusion						
No	ref			ref		
Yes	3.01	1.93–4.71	<.01	1.78	0.97–2.97	.06
Ever received PAT						
No	ref			ref		
Yes	1.14	0.99–2.01	.14	1.06	0.71–1.60	.13
Ever been hospitalized						
No	ref					
Yes	0.77	0.35–1.68	.50	—	—	—

* The model also includes adjustment for age.

Association between chronic HCV infection and diabetes among HCV exposed (model 2)

Among HCV antibody-positive individuals, 82.84% (95% CI, 74.25–91.44) of the individuals who reported diabetes were HCV RNA positive. In contrast, only 66.26% (95% CI, 63.55–68.98) of the individuals who did not report diabetes had an active HCV infection. There was an association between HCV RNA status and diabetes in bivariate analysis with unadjusted crude OR of 2.46 (95% CI, 1.34–4.53). From the covariates included in the study age ($P = 0.79$), BMI ($P = 0.89$), hypertension ($P = 0.86$), ever had a blood transfusion ($P = 0.91$), ever received PAT ($P = 0.76$), and ever been hospitalized ($P = 0.39$) were not included in the final multivariable model (model 2). After adjusting for the other remaining variables, individuals who were HCV antibody positive and reported diabetes had more than two times higher odds of having an active infection than HCV antibody-positive individuals who did not report diabetes (Table 3). The adjusted OR was 2.44 (95% CI, 1.30–4.57). It is worth noting that sex was also associated with HCV RNA status. Our analysis suggests that in females the likelihood of having an active infection is lower compared to males, with an adjusted OR of 0.72 (95% CI, 0.56–0.91).

Sensitivity analyses

Sensitivity analyses indicated that modifying the cut-off of the *P* value for inclusion in the final multivariable models did not affect our results. Likewise, by removing the variables that lacked statistical significance in the final multivariable models, or by including only individuals older than 40 years, the associations estimated in both models for HCV exposure (model 1) or diabetes (model 2) were almost the same as the estimations using the full final models (data not shown).

Discussion

HCV exposure was not associated with diabetes in this nationally representative population-based survey in Egypt, the country with the highest HCV prevalence in the world. After adjusting for confounders, our results indicated that HCV antibody-positive individuals did not have higher odds of having diabetes, thereby corroborating results of the recent U.S.-based survey [22]. As the Egypt sample was composed of more than 10,000 subjects, with more than 1400 HCV antibody-positive individuals, it is not likely that the lack of association could be explained by insufficient statistical power. Although we found no association between HCV exposure and diabetes, we identified an association between diabetes and chronic HCV infection in those who have been exposed to HCV. Diabetics were found to be less likely to have a cleared HCV infection than those who were not diabetic. To our knowledge, this is the first evidence that suggests the possibility of a biological interaction between the two conditions, but only among those HCV antibody-positive individuals. This finding highlights how the conflicting evidence about the association between HCV infection and diabetes could have been obscured by the complexity of this association and underlying causal links. Although HCV exposure and diabetes do not appear to be associated, diabetes and HCV chronic infection appear to be associated with a sizeable effect size. Additional research is justified to investigate this association and to identify possible causal links between these two conditions.

We conducted several sensitivity analyses to examine the robustness of our findings. These analyses indicated that the results are consistent regardless of changes in the *P* value for the variable inclusion criteria or exclusion of individuals younger than 40 years. The latter contrasts with a similar study, using the NHANES 1988–1994 self-reported data, which found no

Table 3
Unadjusted and adjusted results for HCV RNA status among HCV antibody-positive individuals as the outcome according to selected covariates (model 2)

Variable	Unadjusted			Adjusted*		
	OR	95% CI	*P*	OR	95% CI	*P*
Diabetes						
Negative	ref			ref		
Positive	2.46	1.34–4.53	<.01	2.44	1.30–4.57	<.01
Area						
Urban	ref			ref		
Rural	0.79	0.60–1.05	.10	0.83	0.62–1.11	.19
Sex						
Male	ref			ref		
Female	0.80	0.64–0.99	.05	0.72	0.56–0.91	<.01
Education						
None	ref			ref		
Primary	0.77	0.56–1.08	.16	0.68	0.48–1.06	.10
Secondary	1.07	0.81–1.16	.10	0.97	0.72–1.31	.19
Higher education	0.83	0.55–1.26	.55	0.70	0.46–1.08	.14
BMI						
Normal (less than 25)	ref			ref		
Overweight (25–30)	1.12	0.61–2.03	.38	—	—	—
Obese (more than 30)	0.96	0.56–1.63	.89	—	—	—
Hypertension						
Normal	ref			—	—	—
Prehypertensive	0.98	0.73–1.29	.86	—	—	—
Ever had dental treatment						
No	ref			ref		
Yes	1.16	0.91–1.49	.24	1.08	0.84–1.37	.50
Ever had a surgical procedure						
No	ref			ref		
Yes	1.25	1.00–1.57	.05	1.26	0.98–1.59	.06
Ever had a blood transfusion						
No	ref			—	—	—
Yes	1.03	0.62–1.70	.91	—	—	—
Ever received PAT						
No	ref			—	—	—
Yes	0.96	0.71–1.29	.76	—		—
Ever been hospitalized						
No	ref			—	—	—
Yes	1.33	0.69–2.57	.39	—	—	—

* The model also includes adjustment for age.

statistically significant association overall, but a significant association among individuals older than 40 years [19].

With the cross-sectional design of our study, the direction of the relationship between diabetes and chronic HCV infection is uncertain. The higher likelihood of diabetics having an active infection could possibly be a manifestation of a biological effect of chronic HCV infection on the development of diabetes, as it has been previously reported [31], or a biological effect of diabetes on the natural history of HCV infection. For example, diabetics may have an impaired ability to clear HCV infection. It is also possible that a nonbiological relationship may explain the association such as diabetics being more exposed to HCV infection through frequent medical procedures. The latter, however, would seem unlikely as we found no evidence for an association between HCV exposure and diabetes (Table 2), and we controlled in our analyses for exposure to different medical procedures (Table 3).

We used self-reported data for diabetes, and such data may not have sufficient sensitivity and specificity. Laboratory diagnosis is the preferred method to investigate the associations examined in this study [22]. Self-reported diabetes will likely underestimate diabetes prevalence as a large fraction of diabetics are unaware of their disease status [32]. Diabetes prevalence in this sample was only 3.3%, much lower than that estimated for Egypt at 10.4% [33]. In addition to underdiagnosis, the EDHS sample included only those aged 15–59 years and excluded older populations who have a higher diabetes prevalence. This explains also part of this difference. Despite this limitation, self-reported diabetes has been proposed as a reasonably good approximation to diabetes status, particularly in population-based studies [34].

An additional shortcoming in our study was the lack of laboratory data to adjust for other factors such as plasma alanine aminotransaminase (ALT) levels. Elevation of liver enzymes such as ALT has been found to increase the risk of diabetes regardless of the underlying liver disease. A study conducted in a Japanese population found that HCV was no longer associated with diabetes after adjusting for ALT [35]. But another study conducted in an Italian cohort found that HCV was associated with diabetes only in subjects with elevated ALT [18]. It has been proposed that failure to adjust for these factors may explain the positive association between HCV and diabetes identified in several studies [22,36].

Other important study limitations may have affected our results. Given the multiple logistical difficulties in conducting DHS studies, some of our measures could be affected by inherent biases in the data, such as response rate or refusal to HCV testing with prior knowledge of being HCV infected [37–39]. Additionally, as we mentioned above, genotype 4 is responsible for more than 90% of the HCV infections in Egypt [26], and whether the association of diabetes and HCV infection in genotype 4 discussed here can be generalized to other genotypes is uncertain.

Conclusions

In sum, using data from one of the largest nationally representative surveys of HCV infection ever conducted, we found no evidence for an association between HCV exposure and diabetes. More importantly, however, we found evidence for an association between diabetes and chronic HCV infection in HCV-exposed individuals. The existence of such association suggests that the HCV–diabetes relationship could be more complex than previously anticipated. A call for an "amicable divorce" to the HCV–diabetes relationship [36] could be premature.

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Authors' contributions: D.F.C. collaborated on project conception, analyzed the data, and wrote the draft article. F.D.M., N.N., and L.J.A.-R. collaborated on project conception, statistical analysis, and helped in writing the article.

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