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REVIEW

Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies

G. Cheng,[1] C. Huang,[2] H. Deng[1] and H. Wang[2]

[1]Department of Nuclear Medicine and Endocrinology, The First Affiliated Hospital, Chongqing Medical University, Chongqing and [2]Department of Geriatrics, The Third Hospital of Mianyang, Mianyang, China

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Correspondence
Huacong Deng, Department of Endocrinology, The First Affiliated Hospital, Chongqing Medical University, Chongqing 400016, China.
Email: huanghj_319@yahoo.cn

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Abstract

This study examined the association of diabetes with the onset of dementia (including Alzheimer's disease (AD), vascular dementia (VD) and any dementia) and mild cognitive impairment (MCI) by using a quantitative meta-analysis of longitudinal studies. EMBASE and MEDLINE were searched for articles published up to December 2010. All studies that examined the relationship between diabetes and the onset of dementia or MCI were included. Pooled relative risks were calculated using fixed and random effects models. Nineteen studies met our inclusion criteria for this meta-analysis, and 6184 subjects with diabetes and 38 530 subjects without diabetes were included respectively. All subjects were without dementia or MCI at baseline. The quantitative meta-analysis showed that subjects with diabetes had higher risk for AD (relative risk (RR):1.46, 95% confidence interval (CI): 1.20–1.77), VD (RR: 2.48, 95% CI: 2.08–2.96), any dementia (RR: 1.51, 95% CI: 1.31–1.74) and MCI (RR: 1.21, 95% CI: 1.02–1.45) than those without. The quantitative meta-analysis showed that diabetes was a risk factor for incident dementia (including AD, VD and any dementia) and MCI.

Introduction

Dementia is one of the most common and most devastating diseases of late life; approximately 4.6 million new cases of dementia are estimated to occur worldwide every year, and the number of people affected is predicted to double every 20 years, to 81.1 million by 2040.[1] People with mild cognitive impairment (MCI) are at increased risk of developing dementia, although the conversion rates reported range from 1% to 25% or more per year.[2] Diabetes mellitus is associated with changes in cognition. In type 2 diabetes, cognitive changes mainly affect learning and memory, mental flexibility, and mental speed. Several large longitudinal population-based studies have shown that the rate of cognitive decline is accelerated in elderly people with type 2 diabetes.[3,4] The determinants of this accelerated cognitive decline, however, are less clear.[5] The association between diabetes and these modest changes in cognition is now well established, but the relation between diabetes and MCI or dementia is an area of controversy.[6,7] In an earlier systematic review, the author concluded that diabetes was a risk factor for developing dementia (including Alzheimer's disease (AD), vascular dementia (VD) and any dementia), but at that time, there were few detailed epidemiological data on the associations of diabetes with risk factors of dementia, and further high-quality studies need to be initiated.[8] In the systematic reviews, major studies showed diabetes was a risk factor for dementia, but not all.[9–13] Since 2006, several large sample longitudinal studies that focused on the association between diabetes and risk factor for dementia and MCI had been conducted.[7,14–20] Some studies mentioned in the earlier systematic reviews have been continued, and some data available in the field have been reported recently.[21] Therefore, to confirm diabetes as a risk factor for dementia or MCI, it is possible and necessary to conduct a quantitative meta-analysis. In this study, based on the previous systematic review, we evaluated the association of diabetes with dementia (including AD, VD and any dementia) or MCI using a quantitative meta-analysis of longitudinal studies.

Methods

Search method

Studies were identified by searches of MEDLINE (from 1966 to December 2010) and EMBASE (from 1966 to December 2010), with the search terms 'diabet* AND (Alzheim* OR dement* or congnit*)'. Searches were restricted to papers published in English or Chinese, and the EMBASE search was restricted to 'human studies'. The bibliographies of relevant original and review articles were screened. This systematic review aimed to include all published studies that provide an estimate of the incidence of dementia or MCI among patients with diabetes mellitus in the general population. The titles and abstracts of all articles identified by the search were screened, and potentially relevant articles were retrieved and assessed according to the criteria in the section that follows. Additional relevant articles for the discussion on methodological issues, potential risk factors and underlying mechanisms were identified through MEDLINE.

Inclusion/exclusion criteria

Inclusion criteria: (i) the study cohort was recruited at the population level (i.e. not hospital-based), (ii) the study had a longitudinal design, (iii) the incidence of AD, VD, any dementia or MCI could be compared between patients with and without diabetes, (iv) at baseline, subjects with MCI or dementia were excluded, (v) dementia and MCI were defined according to the criteria generally accepted and (vi) diabetes was defined according to the criteria generally accepted.

Exclusion criteria: (i) the quality score of study was lower than 5 (see the quality assessment) according to the quality assessment criteria in the section that follows, (ii) there were insufficient data to estimate a relative risk (odds ratio, risk RR or hazard ratio) and (iii) it was based on convenience sampling (nonrandom and small sampling) in a retrospective study.

Quality assessment

The quality of reporting of all included studies was appraised with checklists developed for longitudinal observational study designs according to the earlier systematic review and the guidelines for reporting meta-analyses of observational studies[8,22] (see Table 1). These checklists included external validity (recruitment, participation at follow up), internal validity (duration of follow up, assessment of exposure, outcome status and covariates, analytical approach) and descriptive issues. Assessment of quality was based on the criteria developed by two of the authors (Gang Cheng and Changquan Huang), and the two authors independently evaluated each of the potentially included studies according to these criteria, and discrepancies were resolved by discussion.

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Conflict of interest: None.

Table 1 Quality assessment of studies

Population selection and recruitment (maximum 2 points)
Well-defined population sample (1 point)
Baseline response rate 70% or more (1 point)
Duration at follow up (maximum 2 points)
Duration at follow up <1 year (0 point)
Duration at follow up 1–3 years (1 point)
Duration at follow up >3 years (2 points)
Participation at follow up (maximum 2 points)
Participation rate at follow up 60–69.9% (1 point)
Or 70% response or more (2 points)
Diabetes assessment (maximum 2 points)
Or random glucose measurement (1 point)
Or fasting glucose/oral glucose tolerance test (2 points)
Dementia assessment and diagnosis (maximum 2 points)
Or active screening with ad hoc criteria (1 point)
Or on recognised international criteria by a central consensus committee (2 points)

Data extraction

Two authors (Gang Cheng and Hui Wang) independently extracted data from the studies, in particular regarding the following: (i) name of the first author, (ii) publication year, (iii) study design, (iv) follow-up time in years, (v) number of patients in the analysis, (vi) sex of patients, (vii) age of patients, (viii) method of dementia or MCI assessment, (ix) method of diabetes assessment, (x) method used for exclusion of dementia or MCI at baseline, (xi) overall incidence of dementia or MCI and (xii) RR of dementia or MCI in participants with diabetes. The discrepancies were resolved by discussion.

Statistical analysis

Data were entered into the RevMan 4.2 meta-analysis program (Cochrane Collaboration, Oxford, UK; see http://ims.cochrane.org/revman). In the meta-analysis of longitudinal studies for incidence rates of dementia or MCI, RR and 95% confidence intervals (95% CI) were calculated. We estimated the between-study heterogeneity across all eligible comparisons using the Chi-squared. Heterogeneity was considered significant for $P < 0.05$. Data were combined using both fixed-effects (Mantel–Haenszel) and random-effects (DerSimonian and Laird) models. When the heterogeneity was non-significant, the RR from fixed-effects model was chosen. If heterogeneity was present, the RR from random-effects method was chosen. To provide visual assessment of publication bias, a funnel plot was drawn, in which the RR was plotted on a logarithmic scale on the vertical axis against its corresponding standard error for each study on the horizontal axis. Asymmetry of the funnel plot was an indicator of publication bias.

Results

Eligible studies

The MEDLINE search yielded 3105 hits, while the EMBASE search yielded 2764 hits. Screening of titles and abstracts identified 307 potentially relevant papers, including 17 reviews, which were retrieved for screening of the bibliographies. Forty-four papers met the inclusion criteria and went forward to the data extraction stage. When more than one paper reported on the same population and provided the same information, only the paper with the largest population sample and the most detailed information was included. Finally, 19 studies (all published in English) were included in the meta-analysis.[7,9,11–20,23–28] Characteristics of the 19 prospective longitudinal studies included in the meta-analysis are shown in Table 2. Of the studies included in the previous systematic review, three were retrospective studies,[30–32] and one was with the quality scores lower than 5,[10] the four studies were excluded for the meta-analysis. Of these studies, 10 failed to find an association between diabetes and increased incidence of AD.[9,11–13,23–27]

Assessment of publication bias

We assessed publication bias using funnel plots (Fig. 1). The funnel plot of RRs (under a fixed-effects model) was constructed from the 19 studies in Table 2. In the absence of publication bias, the points should be symmetrical about the vertical line at the pooled RRs. The reasonably symmetrical shape did suggest the absence of publication bias.

Diabetes as a risk factor for AD

Sixteen of the included studies compared incidence of AD between subjects with and without diabetes. Of them, ten studies showed that diabetes could not increase the risk for AD,[7,9,11–13,15,20,25,28,29] but six studies showed diabetes as a significant risk for AD[14,17,23,24,26,27] (see Table 2). There was significant heterogeneity among these studies ($\chi^2 = 47.3$ d.f. = 15 $P < 0.001$). There were 5700 and 36 191 subjects with and without diabetes respectively. After pooling these 16 studies, subjects with diabetes had significant higher incidence of AD than those without (RR: 1.46, 95% CI: 1.20–1.77; RR: 1.54, 95% CI: 1.40–1.70 in random-effects and fixed-effects models respectively) (see Table 3).

Table 2 Characteristics of the 20 prospective longitudinal studies included in the meta-analysis

Reference	Country	Follow up (years)	Patients base/FU	Patients with diabetes	Age baseline	Gender (% men)	Quality rating	Dementia/cognitive impairment results (95%CI)
Akomolafe *et al.*[7]	USA	12.7 (1–20)	2611/2210	202/ND	60 or older	40	9	Any dementia RR: 1.19 (0.79–1.78) AD: RR: 1.07 (0.65–1.75) VD: RR 1.81 (0.63–5.23)
Arvanitakis *et al.*[27]	USA	5.5	847/824	91/127	75 or older	31	7	AD: RR 1.7 (1.1–2.5)
Panza *et al.*[16]	Italian	7.6	2963/1556	189/ND	65 or older or older	34	6	Mild cognitive impairment RR 1.1 (0.7–1.9)
Hassing *et al.*[12]	Sweden	6	897/702	ND/108	85 or older	64	6	Any dementia: 1.2 (0.8–1.7) AD: RR 0.8 (0.5–1.5) VD: RR 2.5 (1.4–4.8)
Becker *et al.*[20]	USA	1–9	396/288	32	70 or older	31	9	AD: RR 1.4 (0.7–3.1)
Luchsinger *et al.*[18]	USA	5.7	1129/918	219	65 or older	30	8	Mild cognitive impairment RR 1.2 (1.0–1.4)
Katzman *et al.*[9]	USA	3.7	488/397	46	79 or older	36	6	AD: RR 0.5 (0.1–2.0)
Leibson *et al.*[24]	USA	6.9	11970/10970	1455	55 or older	35	6	Any dementia: RR 1.6 (1.3–2.1) AD: RR 1.6 (1.3–2.0)
Luchsinger *et al.*[26]	USA	4.3	1799/1262	231	65 or older	31	7	AD: RR 2.4 (1.7–3.5) VD: RR 4.7 (2.7–8.1)
MacKnight *et al.*[11]	Canada	5	9131/5574	503	65or older	39	8	Any dementia: RR 1.2 (0.9–1.6) AD: RR 1.2 (0.8–1.9) VD: RR 2.3 (1.5–3.5)
Muller *et al.*[17]	USA	4.4	2476/2259	483	65 or older	38	8	Any dementia: RR 1.6 (1.2–2.2) AD: RR 1.4 (1.0–1.9)
Ott *et al.*[29]	Netherlands	2.1	6370/6370	692	69 or older	39	9	Any dementia: RR 1.9 (1.4–2.6) AD: RR 1.9 (0.8–2.7) VD: RR 2.0 (0.8–4.8)
Peila *et al.*[23]	Japanese-American	2.9	3508/2574	900	65 or older	100	8	Any Dementia: RR 1.4 (0.9–1.9) AD: RR 1.6 (1.0–2.5) VD: RR 2.4 (1.2–2.8)
Rastas *et al.*[19]	Finland	3.5	516/339	91	85 years or older	20	6	Any dementia: RR 1.3 (0.9–1.9)
Tyas *et al.*[28]	Canada	3–5	694/688	44	65 or older	33	8	AD: RR 1.9 (0.7–5.1)
Treiber *et al.*[14]	USA	3–7	5092/3634	461	65 or older	35	9	Any dementia: 2.8 (2.2–3.7) AD: RR 3.3 (2.5–4.3) VD: RR 2.7(1.6–4.7)
Eriksson *et al.*[15]	Swedish	3–6	2287/2214	238	50 years or more	38	8	Any dementia: RR 1.5 (1.2–1.8) AD: RR 1.0 (0.7–1.5) VD: RR 2.6 (1.7–4.0)
Xu *et al.*[13]	Sweden	4.7	1301/1301	114	65 or older	25	8	Any dementia: RR 1.5 (1.1–2.0) AD: RR 1.2 (0.7–2.0) VD: RR 2.2(1.4–5.8)
Yoshitake *et al.*[25]	Japan	7	828/828	70	65 or older	40	8	AD: RR 1.7 (0.8–3.5) VD: RR 2.8 (1.4–5.8)

95%CI, 95% confidence interval; AD, Alzheimer's disease; FU, follow up; ND, no data; RR, relative risk; VD, vascular dementia.

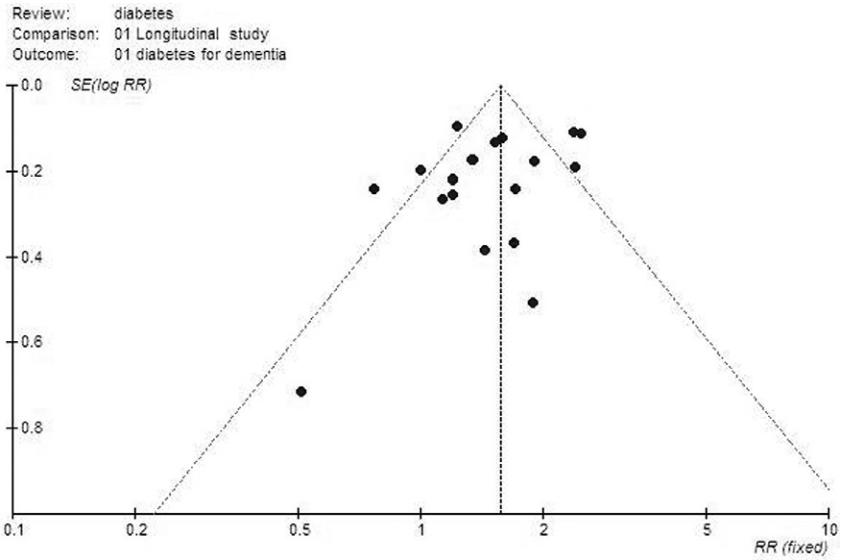

Figure 1 Funnel plot of the 20 studies included in the meta-analysis. In the absence of publication bias, the points should be symmetrical about the vertical line at the pooled odds risk (RRs). The reasonably symmetrical distribution suggests the absence of publication bias.

Diabetes as a risk factor for VD

Ten of the included studies compared incidence of VD between subjects with and without diabetes. Except two studies,[7,29] all of them showed that diabetes could significantly increase the risk for VD. There was no obvious heterogeneity in these studies ($\chi^2 = 6.3$ d.f. = 9 $P = 0.71$). There were 3519 and 23 026 subjects with and without diabetes respectively. After pooling these 10 studies, subjects with diabetes had significant higher incidence of VD than those without (RR: 2.49, 95% CI: 2.09–2.97; RR: 2.48, 95% CI: 2.08–2.96 in random-effects and fixed-effects models respectively) (see Table 3).

Diabetes as a risk factor for any dementia

Eleven of the included studies compared incidence of any dementia between subjects with and without diabetes. Of them, five studies showed that diabetes could not increase the risk for any dementia,[7,11,12,19,23] but six studies showed diabetes as a significant risk for any dementia[13–15,17,24,29] (see Table 2). There was significant heterogeneity among these studies ($\chi^2 = 28.9$ d.f. = 10 $P = 0.001$). There were 5247 and 32 900 subjects with and without diabetes respectively. After pooling these 11 studies, subjects with diabetes had significant higher incidence of any dementia than those without (RR: 1.51, 95% CI: 1.31–1.74; RR: 1.54, 95% CI: 1.41–1.67 in random-effects and fixed-effects models respectively) (see Table 3).

Diabetes as a risk factor for MCI

Only two of the included studies compared incidence of MCI between subjects with and without diabetes. Of them, one study showed that diabetes could increase the risk for MCI,[18] the other did not show it[16] (see Table 2). There was no obvious heterogeneity in these studies ($\chi^2 = 0.1$ d.f. = 1 $P = 0.76$). There were 393 and 2091 subjects with and without diabetes respectively. After pooling these two studies, subjects with diabetes had significant higher incidence of any MCI than those without (RR: 1.22, 95% CI: 1.00–1.45; RR: 1.21, 95% CI: 1.02–1.45 in

Table 3 Summary relative risks of AD, VD and any dementia among subjects with diabetes compared with that without

	Heterogeneity test			Random effects		Fixed effects	
	Chi	d.f.	*P*	RR	95%CI	RR	95%CI
Risk for AD	47.3	15	<0.0001	1.46	1.20–1.77	1.54	1.40–1.70
Risk for VD	6.3	9	0.71	2.49	2.09–2.97	2.48	2.08–2.96
Risk for any dementia	28.9	10	0.001	1.51	1.31–1.74	1.54	1.41–1.67
Risk for mild cognitive impairment	0.1	1	0.76	1.22	1.0–1.45	1.21	1.02–1.45

95%CI, 95% confidence interval; AD, Alzheimer's disease; RR, relative risk; VD, vascular dementia.

random-effects and fixed-effects models respectively) (see Table 2).

Discussion

The present study confirmed diabetes as a risk factor for MCI, AD, VD and any dementia using a quantitative meta-analysis of longitudinal studies. Compared with subjects without diabetes, those with diabetes were at more than double the risk of developing VD, and the relative risk of developing AD, MCI and any dementia were 1.46, 1.21 and 1.51 respectively.

A systematic review concluded there was an increased risk of dementia (including AD, VD and any dementia) in people with diabetes.[8] In that review, the authors found relatively few detailed epidemiological studies that associate diabetes with the risk of dementia, and recommended that additional studies needed to be conducted. Since 2005, several large prospective cohort studies have been reported. All of these showed that the relation between diabetes and major types of dementia had always been controversial, and researchers in this field had been working to resolve this issue. In the present study, based on these high-quality studies, we used a quantitative meta-analysis of longitudinal studies and confirmed that diabetes was a risk factor for MCI or dementia (including AD and VD).

Dementia, MCI and diabetes increase with age. Diabetes is one of the most common metabolic disorders. The major gene associated with AD is the apolipoprotein E (APOE) gene. In particular, the ε4 allelic variant is associated with an increased risk for MCI.[33] APOE is also one of the genes that regulate glucose and lipid metabolism.[34] This suggests that the aetiology of AD and MCI includes metabolic factors. There may be the same mechanisms in the development of AD or MCI as that of diabetes. From thus assumption, AD or MCI may be concomitant diseases with diabetes in the elderly. Our analysis shows that diabetic subjects had higher risk for incidence of AD or MCI than non-diabetics. Diabetes not only shares the same mechanism with AD or MCI in aetiology, but also seems to play an important role in the onset of AD or MCI. Subjects with diabetes, regardless of APOE ε4 status, are at higher risk for AD than those without diabetes, and APOE ε4 significantly increased the risk for AD in diabetic subjects.[35] These results show that diabetes increases the risk for AD independently of APOE ε4, although subjects with both diabetes and APOE ε4 had the highest risk for AD.

Vascular disease is a definite and essential aetiological factor of VD. Diabetes is a well-known risk factor for lacunar infarction and stroke, therefore its association with VD is not surprising. Interestingly, diabetes is a risk factor for AD or MCI, thus diabetes causes onset of VD, although both vascular and non-vascular factors. In the present study, the relative risk for VD was higher than that for AD or MCI, and can be explained by the important role of vascular factors in the onset of VD.

In the present study, we assessed the relative risk in diabetic subjects for each type of dementia and MCI. In the meta-analysis for AD, VD and any dementia, all included studies were assessed to be of high quality. The relative risks were 2.48 and 1.46 for VD and AD, respectively, and for any dementia was 1.51 (between those for VD and AD); the subjects with any dementia enrolled in the meta-analysis might mainly include VD and AD, which were the two main types of dementia. However, there were few data for the other types of dementia (e.g. Parkinson's disease, Lewy body dementia, alcohol-related dementia and Pick disease). Further study on these types of dementia should be conducted. Meanwhile, the data for the association of diabetes with onset of MCI were available in only two studies. Pooling these two studies constituted only 392 diabetic participants, and the increased risk for MCI in diabetes was of borderline statistical significance. So our results on the association of diabetes with MCI should be viewed cautiously, and this field should be further studied.

Our results suggested that it may be important to prevent dementia or MCI in diabetic patients. Dementia or MCI significantly reduces quality of life and shortens life expectancy. Considering both the social burden of dementia or MCI and the higher risk for dementia or MCI in diabetic patients, it is as important to prevent dementia or MCI as to treat diabetes. However, there is not sufficient evidence on the most effective methods to prevent dementia or MCI in the treatments of diabetes. Therefore, this should be further studied.

Although we attempted to adhere to the guidelines for reporting meta-analyses of observational studies (Stroup *et al*.[22]), this review did have limitations. We did not hand search journals nor did we attempt to identify unpublished studies. We only included studies in MEDLINE and EMBASE; other databases, such as the Cumulative Index to Nursing and Allied Health Literature and PsycINFO, were not included. Moreover, the search was limited to articles published in English and Chinese. Therefore, some studies may have been missed.

Conclusion

Overall, the results from this meta-analysis showed that the risk of dementia or MCI is higher among people with diabetes than in the general population. Diabetic patients are at more than double the risk of developing VD, and also have higher risk of developing AD, any

dementia, and MCI. However, the high risk of developing MCI should be further confirmed by using larger high-quality studies. Our results suggest that diabetic treatments, which may decrease the risk of dementia or MCI, should be chosen, or that subjects with diabetes should be given special prevention strategies for dementia or MCI.

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ORIGINAL ARTICLES

Barriers faced by migrants in accessing healthcare for viral hepatitis infection

M. Guirgis,[1] F. Nusair,[2] Y. M. Bu,[1] K. Yan[1] and A. T. Zekry[1,2]

[1]Gastroenterology and Hepatology Department, St George Hospital, and [2]Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia

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Correspondence
Marianne Guirgis, Department of Gastroenterology, St George Hospital, Gray Street, Kogarah, Sydney, NSW 2017, Australia.
Email: marianne.guirgis@gmail.com

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Abstract

Background: The morbidity and mortality of hepatitis B virus- and hepatitis C virus-related complications are disproportionately higher in the culturally and linguistically diverse population (CALD) when compared with Australian-born individuals.
Aim: This project aims to elucidate the barriers faced by the CALD population in accessing viral hepatitis management.
Method: CALD outpatients attending a viral hepatitis clinic in a tertiary teaching hospital were invited to participate in interviews. Questions pertained to: reason for screening for viral hepatitis, barriers to healthcare, perceived community view of viral hepatitis, main source of information of viral hepatitis and suggestions to engage members of CALD to seek healthcare.
Results: The total number of participants was 60. The two major countries of birth included China (40%) and Egypt (17%). In 40% of the cohort, viral hepatitis was identified through screening programmes. Importantly, 37% were diagnosed as a result of complications of hepatitis infection, presenting late in the stage of disease. Forty-five per cent of participants perceived language to be a chief barrier. twenty-two per cent reported cultural barriers to accessing healthcare. Of these, 53% reported fear of discrimination/stigma. The lack of knowledge of available treatments/options was stated as a major obstacle in 40%. The two prevailing recommendations were greater education and awareness (85%) and changes in the health system itself (11%).
Conclusion: Substantial hurdles identified by participants include cultural differences, language difficulties, cultural beliefs, stigma and misinformation. These data demonstrate the need for the greater dissemination of information in culturally and linguistically appropriate mediums to raise awareness about viral hepatitis, pathogenesis and available treatments.