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Factors impacting medication adherence in a birth cohort at higher risk for Hepatitis C infection

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Abstract

Due to the high prevalence of Hepatitis C virus (HCV) infection among individuals born between 1945 and 1965, in 2012 the Centers for Disease Control and Prevention began recommending HCV screening for this birth cohort. As adherence to HCV treatment is essential for sustained virologic response, identifying factors influencing medication adherence is important. The validated Adherence to Refills and Medications Scale (ARMS) is used to study recent medication adherence in those with chronic disease. This cross-sectional pilot study assesses factors associated with reduced adherence, indicated by higher ARMS scores, among individuals in this birth cohort. To elucidate factors associated with medication adherence, measured by the ARMS score, among a birth cohort at higher risk for HCV to guide future treatment and improve adherence. Patients born between 1945 and 1965, accessing care at an academic family medicine clinic, were recruited between April and June 2019. Demographics, prior HCV diagnosis, HCV risk factors (prior imprisonment, tattoos, and intravenous drug use), depression assessment (Patient Health Questionnaire-9), adverse childhood experiences (ACEs), and ARMS scores were collected. Mean ARMS scores were compared using *t* tests and analysis of variance ($\alpha = 0.05$), while multiple variable models were performed using linear regression. Women comprised 58% of participants (n = 76), 52% reported depression and 37% 4 or more ACEs. The mean ARMS score was 16.3 (SD = 3.43) and 10% reported prior diagnosis of HCV. In the final multiple variable model, ARMS scores were 2.3 points higher in those with mild depression (95% CI: 0.63, 4.04), 2.0 in those with at least 4 ACEs (95% CI: 0.55, 3.49), and 1.8 in those with tattoos (95% CI: 0.30, 3.28). ACEs and food insecurity were identified as confounding variables in those with moderate to severe depression. This study found medication adherence was related to depression, ACEs, tattoos, and food insecurity among patients in this birth cohort at higher risk for HCV.

Abbreviations: ACEs = adverse childhood experiences, ARMS = Adherence to Refills and Medications Scale, CDC = Centers for Disease Control and Prevention, DAAs = direct acting antivirals, HCV = Hepatitis C Virus, IVDU = intravenous drug use, PHQ-9 = patient health questionnaire-9.

Keywords: adverse childhood experiences, depression, food insecurity, Hepatitis C, medication adherence

1. Introduction

Before COVID-19, Hepatitis C virus (HCV) infection was the leading cause of death among 60 notifiable infectious diseases in the United States and HCV incidence increased almost 3-fold from 2011 to 2018.[1,2] Additionally, the majority of HCV infections are asymptomatic, but more than half progress to chronic infection and can cause significant morbidities, such as chronic liver disease, cirrhosis, and hepatocellular carcinoma.[3–5] HCV prevalence is higher among those born during 1945 to 1965 at 3%, which is 6 times higher than any other age group,[6] and multiple studies have reported 75% of HCV infected individuals were in this birth cohort.[6–8] Thus, in 2012 the Centers for Disease Control and Prevention (CDC) started recommending HCV screening for individuals born between 1945 and 1965 due to the high prevalence in this age group, lack of testing, and the improvement of therapies, such as direct acting antivirals (DAAs).[8] Although in 2020, the CDC expanded its recommendation to screen all adults for HCV,[2] the prevalence remains highest in this birth cohort.[9] Previous studies have found DAAs are effective in treating HCV with sustained viral response rates up to 97% for certain Hepatitis C virus genotypes.[10,11] Despite treatment success of DAAs, failure to complete treatment limits the effectiveness of the DAA, which is more common in treatment-naïve patients.[12] Therefore, identifying factors associated with medication adherence in this birth cohort at risk for HCV may inform targeted strategies to improve adherence and reduce treatment failure.[13]

Previous studies have found associations between poor medication adherence and social determinants of health.[14,15]

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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These determinants have been linked to chronic diseases such as hypertension, cardiovascular disease, diabetes, stroke, and cancer.[15,16] Specifically, previous studies have found those with depression were less adherent to medication regimens.[17] Others have found food insecurity, the inability to access nutritional foods, was associated with poor medication adherence.[17–19] Similarly, adverse childhood experiences (ACEs), which include components of physical abuse, emotional abuse, and household substance use, were found to be associated with medication non-adherence to statin therapy in men.[20] Some HCV risk factors such as history of imprisonment,[21] intravenous drug use (IVDU),[22,23] and other factors, such health literacy,[22,24,25] may also affect medication adherence. One study also found reduced adherence to HIV antiretroviral therapy associated with alcohol and drug use, viral load, and social determinants, such as homelessness.[26]

While previous studies have elucidated some important risk factors associated with reduced adherence, research has not yet been conducted in the 1945 to 1965 birth cohort known to be at higher risk for HCV infection. This cohort is often inadequately tested for HCV and at higher risk for a variety of other chronic diseases.[7–9,27–29] Assessing the relationship between medication adherence and these factors could be the first step in identifying barriers to HCV treatment completion.

The Adherence to Refills and Medications Scale (ARMS) is a validated tool designed to assess medication adherence and has been used to measure recent adherence to medications among patients with chronic diseases.[30,31] It has also been used to study the effect of risk factors for cardiovascular disease and diabetes on medication adherence.[30,32,33] Applying the ARMS tool to this high-risk HCV birth cohort could provide valuable information on the relationship between recent medication adherence and HCV risk factors or social determinants of health for this cohort. This pilot study aimed to assess medication adherence, using the validated ARMS tool, among the 1945–1965 birth cohort at higher risk of HCV infection and how recent medication adherence is related to HCV risk factors and social determinants of health in this cohort.

2. Methods

This pilot study assessed medication adherence, measured by the ARMS score, among a birth cohort at high risk for HCV infection who accessed care at an academic ambulatory family medicine clinic. The associations between the ARMS score and HCV risk factors and social determinants of health were also assessed. This study was approved by the academic Institutional Review Board.

2.1. Population/recruitment

The target population of this pilot study was patients in the CDC-defined higher risk 1945–1965 birth cohort who accessed care at an urban academic family medicine clinic. The majority of this patient population was of lower socioeconomic status but insured by Medicaid and Medicare. A convenience sample of patients were recruited into this study during April and June 2019 during regularly scheduled clinic visits. Eligibility criteria included being born between 1945 and 1965 and ability to read English. The goal was to approach as many eligible patients as feasible by a research staff member available on days during the pilot months of the study. A nurse would provide patients an overview of the study, then the research staff would provide more details and invite them to participate. The research staff then engaged in an informed consent discussion with the patients. After informed consent was obtained, the patient completed the questionnaire. No incentives were offered.

2.2. Outcome

The primary outcome of this study was medication adherence, assessed by the ARMS questionnaire. The ARMS tool, developed by Kripalani et al (2009), is a 12-item questionnaire that has been previously used to assess recent medication adherence in those with chronic disease.[30,32,33] This tool is copyrighted by Emory University and is used in this study with permission. (Sunil Kripalani, MD, e-mail communication, September 2018) The ARMS questionnaire can be viewed in the original study by Kripalani et al[30] Each ARMS question begins with "how often do you" and ends with a statement describing failure to comply with an aspect of medication adherence or prescription refills.[30] Response options for each question are on a Likert scale ranging from none to all and is scored on a scale from 1 (none) to 4 (all).[30] The individual question response scores are summed for the total ARMS score, which ranges from 12 to 48. A lower ARMS score indicates better adherence, while a higher ARMS score indicates less self-reported adherence to current medication.

2.3. Independent variables

In addition to the ARMS questionnaire, the survey obtained self-reported information regarding cigarette smoking, alcohol use, and HCV risk factors to ascertain scores for ACEs, depression, food insecurity, and health literacy. Each of these variables and scales are defined below.

HCV risk factors assessed on the survey included prominent risk factors, such as IVDU, history of imprisonment, living with a person infected with HCV, and tattoos. The survey questions were designed to be easily understood by the target population, thus lay terminology was used, such as "shot up" and "body art" (see Table, Supplemental Digital Content, http://links.lww.com/MD/I161, which describes the questions and final response categories).

Cigarette smoking was defined as those who have smoked 100 cigarettes in their lifetime and currently smoke cigarettes either daily or non-daily.[34]

Alcohol use was assessed with the validated Alcohol Use Disorders Indication Test (AUDIT-C).[35] This test creates a score ranging from 0 to 12, with a positive screening result for alcohol abuse of 4 or more for men and 3 or more for women.[35,36]

ACEs were assessed using the standard ACEs 10-item questionnaire that is scored with 1 point for each yes response for a total range between 0 and 10.[37,38] This survey was developed to identify traumatic events experienced in childhood, and the questionnaire includes components of physical abuse, emotional abuse, and household substance use.[37] Previous evidence indicates 4 or more ACEs are associated with an increased risk for cardiovascular disease, alcoholism, drug abuse, depression, and suicide attempts compared to those with 3 or less ACEs.[38,39] Thus, ACE scores for this study were collapsed into groups with 3 levels: no ACEs, 1 to 3 ACEs, and 4 or more ACEs, as well as 2 levels: 4 or more ACEs and less than 4 ACEs.

Depression was assessed using the standard Patient Health Questionnaire-9 (PHQ-9) questionnaire. Each of the nine PHQ-9 questions is assigned a score ranging from 0 to 3, depending on the frequency of each event, for a final score ranging from 0 to 27.[40] The PHQ-9 has been validated with scores over ten indicating major depression with 88% sensitivity and 88% specificity and cut points at 5, 10, 15, and 20 for mild, moderate, moderately severe, and severe depression.[40] Due to small frequencies in the moderate to severe categories for the analyses the PHQ-9 scores were collapsed into 3 categories: minimal (PHQ-9 = 0–4), mild (PHQ-9 = 5–9), and moderate to severe (PHQ-9 = 10–27).

Food insecurity was assessed using the standard adult 10-item USDA Food Security Survey.[41] The lowest response to each question was assigned a raw score of 0, with 1 point for each increasing

response as designed in the USDA scoring system.[42] Raw scores were categorized into 2 final groups, according to the USDA's scale, including those experiencing food insecurity (scores: 2–10) and those reporting scores reflecting food security (scores: 0–1).[42]

Health literacy was measured by a single standardized question, "How comfortable are you in filling out medical forms by yourself" with responses of extremely, quite a bit, somewhat, a little bit, and not at all.[43] Previous studies have shown that this question is a feasible and effective way to screen for health literacy in a clinic setting.[43,44] For the analysis, the response options were categorized into 2 groups "extremely to quite a bit" and "somewhat to no" health literacy.[43]

2.4. Statistical methods

Distribution of continuous variables were assessed for normality. Mean ARMS scores were compared between groups using independent *t* tests and analysis of variance, as appropriate. Variables with more than 2 levels were further collapsed if the mean ARMS scores did not differ in 2 or more groups. Linear regression models were used to assess the relationship between the ARMS scores and independent variables. Variables that were significantly associated with the ARMS outcome in univariate models were included in bivariate models and assessed for interaction and then for confounding. Confounding was defined by at least a 20% change in the parameter estimate from the univariate model upon adjusting for the potential confounder. A final multiple variable linear regression model included all significant main effects, interactions, and confounding variables.

An available case analysis was conducted, such that participants were included for whom relevant information was available, which varied between univariate and multivariate models. All statistical analyses used an alpha level of 0.05 and were performed in SAS, version 9.4.

3. Results

3.1. Participants

A total of 83 patients were recruited during the study period, of which 76 were included in univariate models and 65 were included in multiple variable analyses (see Figure, Supplemental Digital Content, http://links.lww.com/MD/I162, which describes participant inclusion). Seven participants did not complete the ARMS outcome information and eleven participants did not complete key covariate information.

The demographic characteristics and covariates of study participants completing the ARMS questionnaire are summarized in Table 1. There were slightly more women (58%) than men (42%) and the mean age was 63 (SD = 5.67). About half (52%) reported at least mild depression (PHQ-9 = 5+) and over 1-third (37%) reported 4 or more ACEs. Of 79 participants who reported HCV diagnosis information, 8 reported ever receiving a diagnosis of HCV (10.13%). The mean ARMS score in the study sample with complete outcome information (n = 76) was 16.3 (SD = 3.43). The mean ARMS scores did not differ significantly for those completing all multiple variable model information (n = 65) compared to the group missing information used in multiple variable models (n = 11) (16.3 vs 17.4; $P = .36$).

Although mean ARMS scores were higher among those reporting 4 or more ACEs (M = 18.0), it was not different between those who experienced no ACEs compared to those who experienced 1 to 3 ACEs (14.8 vs 15.4; $P = .6$). Thus, the dichotomous form of ACEs (4 or more vs less than 4) was used in the modeling.

Table 1

Participant characteristics & Descriptive Statistics among those born between 1945 and 1965 in an Ambulatory Family Medicine Clinic.

Covariate		n	Mean ± SD	
ARMS scores		76	16.3 ± 3.43	
Age (years)		76	62.5 ± 5.67	
			ARMS Score by Covariate	
	Group		Frequency (%)	Mean ± S.D.	*P*-value
Gender	Female	44	57.9	16.1 ± 3.60	0.63
	Male	32	42.1	16.5 ± 3.33	
ACEs* (3-levels)	0	20	29.4	14.9 ± 3.24	**0.0019**
	1–3	23	33.8	15.4 ± 2.41	
	4+	25	38.4	18.0 ± 3.43	
ACEs* (2-levels)	0–3	43	63.2	15.2 ± 2.80	**0.0004**
	4+	25	36.7	18.0 ± 3.43	
PHQ-9	0–4	36	48	14.8 ± 2.55	**0.0006**
	5–9	19	25.3	17.9 ± 3.96	
	10–27	20	26.7	17.4 ± 3.08	
Tattoos	No	52	69.3	15.8 ± 3.00	**0.028**
	Yes	23	30.1	17.7 ± 4.06	
Food insecurity*	Food secure	39	57.4	15.5 ± 3.31	**0.031**
	Food insecure	29	42.6	17.2 ± 3.03	
History of Imprisonment	No	56	73.7	15.9 ± 3.17	0.075
	Yes	20	26.3	17.5 ± 3.91	
IVDU*	No	65	92.9	16.2 ± 3.15	0.5
	Yes	6	7.1	18.0 ± 5.52	
Smoking status	Nonsmoker	51	68.9	16.0 ± 3.12	0.19
	Current Smoker	23	31.1	17.2 ± 4.05	
Alcohol use	Negative	69	92	16.2 ± 3.44	0.14
	Positive	6	8	18.3 ± 3.08	
Health Literacy*	Extremely to quite a bit	57	81.4	16.2 ± 3.31	0.88
	Somewhat to no	13	18.6	16.1 ± 3.25	

ACEs = adverse childhood experiences, ARMS = adherence to refills and medications scale, IVDU = intravenous drug use, PHQ-9 = patient health questionnaire-9.

Bold indicates $P < .05$.

* Indicates missing 5 or more.

In univariate models, mean ARMS scores differed by categories of ACEs, depression, food insecurity, and tattoos (Table 2). Mean ARMS scores were 2.8 points (95% CI: 1.31, 4.37) higher for those reporting at least 4 ACEs compared to those with 3 or less. Mean ARMS scores were 3.1 points (95% CI: 1.39, 4.89) higher among those with mild depression and 2.7 points (95% CI: 0.93, 4.37) higher among those with moderate to severe depression than those with minimal depression. Mean ARMS scores were 1.9 points (95% CI: 0.21, 3.56) higher among those reporting having tattoos than those not reporting tattoos, and the mean ARMS scores were 1.7 points (95% CI: 0.17, 3.29) higher among those experiencing food insecurity compared to food secure individuals. Gender, IVDU, smoking status, alcohol drinking, health literacy, and history of imprisonment were not significantly associated with ARMS scores in univariate models (Table 2); hence these variables were not included in the multiple variable model.

No interaction was found between variables. In bivariate models, both ACEs and food insecurity reduced the association between moderate to severe depression and ARMS, indicating significant confounding. The difference in mean ARMS scores for those with moderate to severe depression compared to those with minimal depression decreased from 2.7 points to 1.8 when controlling for ACEs and from 2.7 points to 1.6 when controlling for food insecurity.

Multiple variable linear regression models are presented in Table 2. The R^2 of the covariates with the ARMS outcome in this model was 0.37. ACEs, depression, food insecurity, and history of tattoos were included in the final multiple variable linear regression model due to statistical significance in univariate models. ARMS scores were 2.0 points (95% CI: 0.55, 3.49) higher among those with 4 or more ACEs compared to those with 3 or less after adjusting for food insecurity, history of imprisonment, and other factors associated with the ARMS score. Similarly, ARMS scores were 2.3 points (95% CI: 0.63, 4.04) higher among those with mild depression compared to those with minimal depression in the adjusted model. However, after adjustment, ARMS scores for those with moderate to severe depression were no longer statistically different from those with minimal depression. Similarly, after controlling for other factors ARMS scores for those experiencing food insecurity was no longer higher than those not reporting food insecurity.

4. Discussion

To the authors' knowledge, this is the first study to assess medication adherence among a birth cohort at higher risk for HCV infection and to assess whether HCV risk factors and social determinants of health are associated with higher ARMS scores among patients in this birth. These results indicate that ACEs, mild depression, having tattoos, and food insecurity were related to lower medication adherence, which is consistent with previous research in other populations.[17–20,45–47] Similar to one previous study which found lower medication adherence to statin therapy was associated with higher ACE scores in men,[20] this study found ACEs were associated with increased ARMS scores across both genders in this birth cohort. Furthermore, the association between having 4 or more ACEs and lower medication adherence may be important for a wide range of chronic disease management in this birth cohort since previous literature has established that more ACEs are strongly associated with risk for chronic disease.[37,48,49]

Previous evidence also corroborates this study's findings that depression is associated with lower medication adherence[45,46,50] with one study reporting that patients were four times more likely to be non-adherent if they reported having depression.[50] Furthermore, prior studies have shown depression increased as ACE scores increased, in addition to those with childhood traumas having more physical symptoms and engaging in more health-risk behaviors.[49,51–53] This suggests an interrelation between ACEs and depression and a possible explanation for ACEs confounding the association of moderate to severe depression and ARMS scores in this study.[49,51–53] This combination of trauma, mental health maladaptation, and risky behaviors could play a larger role in understanding the deeper context of medication adherence.

Table 2

Covariate associations with ARMS by Linear Regression among those born between 1945 and 1965 in an Ambulatory Family Medicine Clinic.

	Univariate model		*Multivariate model*	
Covariate	Estimate	95% CI	Estimate	95% CI
ACEs				
4 + (vs 0–3)	**2.8**	**(1.31, 4.37)**	**2.0**	**(0.55, 3.49)**
PHQ-9				
5–9 (vs 0–4)	**3.1**	**(1.39, 4.89)**	**2.3**	**(0.63, 4.04)**
10–27 (vs 0–4)	**2.7**	**(0.93, 4.37)**	1.3	(–0.48, 3.01)
Tattoos				
Yes (vs No)	**1.9**	**(0.21, 3.56)**	**1.8**	**(0.30, 3.28)**
Food insecurity				
Food insecure (vs Food secure)	**1.7**	**(0.17, 3.29)**	1.0	(–0.41, 2.44)
History of Imprisonment				
Yes (vs No)	1.6	(–0.16, 3.34)		
Gender				
Male (vs Female)	0.4	(–1.19, 2.00)		
IVDU				
Yes (vs No)	1.9	(–1.25, 4.94)		
Smoking status				
Current smoker (vs Nonsmoker)	1.1	(–0.58, 2.85)		
Alcohol use				
Positive (vs Negative)	2.2	(–0.74, 5.06)		
Health literacy				
Extremely to quite a bit (vs Somewhat to no)	0.2	(–1.87, 2.18)		

ACEs = adverse childhood experiences, ARMS = adherence to refills and medications scale, IVDU = intravenous drug use, PHQ-9 = patient health questionnaire-9.
Bold indicates $P < .05$.

Additionally, the finding that those experiencing food insecurity had lower ARMS scores before adjusting for other factors is similar to a previous study which related food insecurity to lower adherence in HIV antiretroviral therapy.[19] The current study found food insecurity confounded the association between the ARMS score and those with moderate to severe depression (PHQ-9 10+). Previous studies have found an association between food insecurity and PHQ-9 scores greater or equal to 10 which could explain the reduction in the observed relationship between this level of depression and the ARMS scores, when controlling for food insecurity.[17,54] Thus, in those with higher levels of depression (PHQ-9 10+), food insecurity may play an influential role in medication adherence.

Of the HCV risk factors assessed, this study's findings only indicate that having a tattoo was associated with higher ARMS scores which is consistent with one study which found high-risk behaviors, such as tattooing, are associated with medication non-adherence.[55] However, tattooing with contaminated equipment or while in prison may further increase risk of transmission of HCV and could be adversely related to adherence,[56,57] but this study was unable to explore this distinction. In contrast to other previous studies that found an association between prison history and IVDU with medication non-adherence,[22,23] this study did not find the same association. Previous studies have reported healthcare stigmatization as a significant risk factor for HCV infection in IV drug users.[58,59] Healthcare stigma surrounding IVDU may restrict healthcare access for these individuals.[58,59] Thus, a population of IV drug users may have medication adherence patterns that differ from those receiving regular healthcare.

Despite the lack of significance in univariate models, previous studies have identified an association between history of imprisonment and ARMS scores.[21,60] Therefore, additional multiple variable models were explored that included prison, but there was no evidence that history of imprisonment was associated with the outcome nor confounded any relationship in this population. Thus, history of imprisonment was excluded from the final model. Additionally, multiple variable models of ARMS scores were explored with the 3-level ACEs categorical variable and did not remain significant, which may be due to the smaller sample size and lower power to detect differences using the 3-level ACE categories.

Overall, these findings indicate depression, ACEs, and food insecurity may be important barriers to medication adherence among a low-income population born between 1945 and 1965. Specific combinations of these factors, such as ACEs and depression, appear to be interrelated. Screening for these factors could be performed with standardized questionnaires prior to the implementation of new medication regimens, particularly in HCV treatment with DAAs. However, these considerations could also uncover barriers prior to initiation of medication regimens for other chronic diseases relevant to this birth cohort such as hypertension, diabetes, and cardiovascular disease.[27–29] Screening for these factors could enable providers to address past trauma, depression, and food insecurity alongside treatment.

The strengths of this study include an exploration of the relationship between medication adherence and HCV risk factors and social determinants of health. These findings connect prior evidence that depression, ACEs, and food insecurity play a role in medication adherence to an important birth cohort.[17–20,45–47] The new data in the 1945 to 1965 birth cohort is particularly relevant since this group is at high risk for HCV, often inadequately tested, and at higher risk for other chronic diseases.[7–9,27–29] Understanding factors associated with lower medication adherence could inform chronic disease management in this population especially as chronic conditions become increasingly prevalent in an aging cohort.[27–29]

There were some limitations in this pilot study, including the limited sample size. This may have affected the ability to detect an association, if one exists, for some factors, such as history of imprisonment or IVDU. However, some significant associations were detected indicating strong relationships in this birth cohort. Additionally, a convenience sample of available patients may not include patients who lack regular outpatient healthcare, those who miss their appointment, or those with complex comorbidities or emergent situations because they are more likely to choose not to participate. Also, those who miss their clinic appointment may also be less likely to adhere to medication,[61] which means these findings may be biased toward the null and there may potentially be an even stronger association between ARMS scores and some of these factors. This convenience sample at an academic medicine clinic may also only be representative of lower income patients in this birth cohort, thus reducing generalizability outside of this group.

Additionally, 18 participants did not fully complete the survey, which may be due to limited clinic appointment time or patient fatigue from a high burden of healthcare paperwork. However, less than 10% of the total sample were missing outcome information and less than 15% were missing covariate information. Moreover, those missing covariate information had similar mean ARMS scores to those completing the entire survey, suggesting similar medication adherence in these groups.

5. Conclusions

These findings indicate among patients born between 1945 and 1965, those experiencing depression, childhood trauma, and food insecurity may have difficulty with medication adherence. Screening for these factors may provide valuable information about those in this birth cohort at higher risk for HCV, which may aid in identifying and addressing barriers to adherence leading to improved medication adherence and reduced treatment failure. Future prospective studies are needed in an expanded population to evaluate predictive adherence and intervention studies to explore whether addressing these factors improves HCV treatment and rates of cure.

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