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Prevalence and Predictors of Patient-Reported Long-Term Mental and Physical Health After Donation in the Adult to Adult Living Donor Liver Transplantation Cohort Study (A2ALL)

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Disclosures

The authors declare no conflicts of interest.

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Abstract

Background—Prospective and longitudinal studies have examined liver donors' medical outcomes beyond the first 1–2 years postdonation. There is no analogous longitudinal evidence on long-term psychosocial outcomes, including patient-reported clinically significant mental health problems and perceptions of physical well-being. We examined prevalence, descriptive characteristics, and predictors of diagnosable mental health conditions and self-reported physical health problems, including fatigue and pain, in the long-term years after liver donation.

Methods—Donors from 9 centers who initially completed telephone interviews at 3–10 years postdonation (M=5.8 years, SD=1.9) were reinterviewed annually for 2 years using validated measures. Outcomes were examined descriptively. Repeated measures regression analyses evaluated potential predictors and correlates of outcomes.

Results—Of 517 donors initially interviewed (66% of those eligible), 424 (82%) were reassessed at least once. Prevalence rates of major depression and clinically significant pain were like general population norms; average fatigue levels were better than norms. All donors showed little temporal change. Anxiety and alcohol use disorder rates exceeded normative rates at 1 or more assessments.

Longer postdonation hospitalization, female sex, higher body mass index (BMI), concerns about donation-related health effects, and burdensome donation-related financial costs were associated with increased risk for most outcomes ($p < .05$). Men were at higher risk for alcohol use disorder ($p < .001$).

Conclusions—Anxiety and alcohol use disorders were more common than would be expected; they may warrant increased research attention and clinical surveillance. Surveillance for long-term problems in the areas assessed may be optimized by targeting donors at higher risk based on identified predictors and correlates.

Introduction

Living organ donation is a 1-time event with the potential for lifelong impact on donors' medical and psychosocial status. Given growing emphasis in Western countries on increasing donations from living donors to offset the organ shortage,¹ it is critical that the impact of donation on the donor be understood not only in the first several years postdonation but also in the later-term years. However, in contrast to a number of longitudinal investigations of long-term outcomes in kidney donors,^{2–5} follow-up of liver donors has only recently extended beyond the first 1–2 years postdonation.⁶ In particular, a growing number of studies have begun to document long-term risks for mortality and medical complications after liver donation,⁶ including large-scale prospective and longitudinal studies of national cohorts.^{7,8} Such information is essential for potential liver donors to be fully informed about risks, and for transplant programs to plan surveillance efforts to monitor postdonation medical issues in their donors.

A less recognized long-term outcome area pertinent to both informed consent and surveillance plans concerns liver donors' psychosocial outcomes. Patient-reported outcomes are well-recognized as critical elements to include when delineating the impact of medical procedures, including living donation.^{9–11} Yet studies documenting liver donors' long-term psychosocial status, including both their mental health and their perceptions of physical well-being and health-related quality of life (HRQOL), have lagged behind the literature on medical outcomes in several important respects. First, studies of these long-term psychosocial outcomes have been predominantly cross-sectional^{12–22} and, as such, have been unable to examine trends over time. Second, most reports do not examine clinically significant difficulties in the psychosocial domains assessed, and instead focus on either nonspecific, generic HRQOL assessments^{13,21,23} or unvalidated, single-item assessments with unknown performance characteristics.^{12,15–20} Third, the clear majority of reports examine small single-site cohorts,^{12,13,15–20,22} resulting in findings of unknown, potentially limited, generalizability.

In the present study, we utilized data from the 9-site Adult to Adult Living Donor Liver Transplantation Cohort Study-2 (A2ALL-2), conducted in 2009–2014, to longitudinally chart the nature of clinically significant psychosocial difficulties in both donor-reported mental and physical health domains in the long-term years postdonation. We move beyond our previous examination of long-term psychosocial outcomes in our cohort, in which we considered generic HRQOL and general questions about emotional and physical reactions to

donation cross-sectionally among 517 individuals assessed at up to 10 years postdonation.¹⁴ Namely, herein we examined the prevalence and nature of change over time of diagnosable mental health conditions and specific areas of physical health problems in the cohort. We also examined patterns of cooccurrence among the conditions, since they are likely to be comorbid rather than occurring in isolation.^{24–26} We considered whether the prevalence of any such problems differs from normative levels in healthy community samples, and we examined whether sociodemographic factors, donation-related clinical factors, and donors' perceptions of the donation experience were associated with risk for mental and physical health problems.

Materials and Methods

Participants and Study Design

In the A2ALL-2 Consortium, we previously enrolled 517 liver donors in a cross-sectional investigation of their long-term postdonation psychosocial status.¹⁴ The Consortium was formed in 2009 with 1 Canadian and 8 US centers. At enrollment, eligible donors were aged 18 years, spoke English, and were 3–10 years postdonation (donation occurred between 2002–2009). Of eligible donors, 66% enrolled (71% of those located).¹⁴

In the current investigation, we followed this cohort for 2 years. They were assessed 3 times (at enrollment, and twice annually thereafter).

Procedure

The study was approved by the Institutional Review Boards and Privacy Boards of the University of Michigan Data Coordinating Center and each transplant center. Participants provided informed consent. Telephone interviews lasting 30–45 minutes were conducted at each time point by trained interviewers using computer-assisted interview methods to ensure that questions were asked in a standardized manner.^{14,27}

Trained research staff at each center extracted clinical information (described below) from donors' medical records.

Measures (Table 1)

Outcomes—We used validated, widely-used measures to assess current mental health (psychiatric disorders including major depression, nonpanic anxiety disorder [ie, generalized anxiety disorder], and alcohol use disorder; depression symptom severity; and general mental HRQOL) and current physical health (fatigue, pain severity, pain interference with daily activities, and general physical HRQOL).

Potential predictors and correlates of mental and physical health outcomes—We assessed variables in 3 areas: sociodemographic characteristics; clinical factors from donors' medical records; and donors' perceptions related to the donation experience (Table 1).

Statistical analysis

We compared individuals who continued versus dropped out during the study on initial assessment characteristics using χ^2 tests and t tests. The sample's distribution on each mental and physical health outcome variable was examined at each assessment. Change across time for each outcome was evaluated with a mixed effects model, with time as a fixed effect and random intercepts to account for repeated measures within donors. This approach allowed us to include all available data, regardless of whether donors completed all assessments. We also used descriptive statistics to examine: (a) the percentage of donors with clinically significant problems on a given outcome (eg, presence of psychiatric disorder; elevated fatigue or pain levels) at >1 time points; and (b) comorbidity patterns among the outcomes.

Donors' scores on the outcomes were compared with normative data from population-based healthy community samples, when available, using 1-sample χ^2 tests and t tests. Because each outcome was compared with normative data at 3 time points, we adjusted for multiple comparisons (3 per variable) using Hochberg's modified Bonferroni method.⁴⁷

To identify potential predictors and correlates of outcomes, repeated measures regression models were fit. We used generalized estimating equation models where dependence among observations from a given donor over time was taken into account when determining the impact of predictors/correlates. A separate model was fit for each outcome. Variables were entered into the model in 2 sequential stages, to reflect their temporal ordering of occurrence.⁴⁸ First, sociodemographic and clinical characteristics were entered to evaluate their effects. Then, variables related to donors' long-term perceptions of the donation experience were added to determine their contribution to the outcome beyond the sociodemographic/clinical variables' impact. At each modeling stage, the final, most parsimonious model was chosen based on best subset selection guidelines.⁴⁹ Missing data on the predictors were multiply imputed using Rubin's procedure⁵⁰ and IVEware.⁵¹ The extent of missing data is reported in Table 2 (footnote a). Predictors were retained in models if p values from overall tests were <0.05.

We examined whether outcomes differed across centers and whether adjusting for centers affected other predictors' impact. Thus, we compared model results before and after controlling for centers in sensitivity analyses.

Results

Sample description

We previously described the cohort of 517 donors, who averaged almost 6 years postdonation at enrollment¹⁴ (see also Table 2, first column). In the present study, 93 donors (18.0%) were lost over the 2-year follow-up: 46 completed only the initial assessment, and 47 completed the first 2 but not the third assessment. Among these 93 donors, 5 could not be located, 45 were located but did not respond to phone or mailed requests, and 43 were recontacted but refused additional interviews. We compared the 93 donors with the remaining 424 donors (Table 2). These groups were similar, except that donors who dropped out had lower education levels.

Description of mental and physical health outcomes across assessments

Table 3 shows the sample's distribution on each measure in the 2 outcome domains at each assessment time point. Prevalence rates or mean scores on most variables were stable across the study period. The exceptions were that anxiety disorder prevalence changed significantly across assessments, with the highest rate at the first assessment, and the rate for having any 1 of the 3 psychiatric disorders showed a similar pattern.

For each outcome, we examined whether donors met criteria for a psychiatric disorder or scored in the clinically significant range on a measure at only 1 time point or at multiple time points. As shown in Table 4, 7% to 23% met criteria for the psychiatric disorders at >1-time point. Overall, 22 of the 96 donors who had assessed psychiatric disorders during the study had them at multiple time points. Almost half of donors with depressive symptoms reported such symptoms at multiple assessments, and 1/3 or more of donors with poor MCS scores, PCS scores, fatigue or pain at any assessment were likely to show these problems at multiple assessments.

Finally, we characterized the outcome variables' patterns of cooccurrence. First, we examined whether each donor experienced 1 psychiatric disorder during the 2-year study period, regardless of whether the disorders overlapped in time. Figure 1 displays these patterns for the 96 donors who had any disorder during the study period. For example, 46 donors had only alcohol use disorder, 4 had both anxiety and alcohol use disorders, and so on. Overall, alcohol use disorder most often occurred alone ie, donors never met criteria for another disorder: only 19% (11/57) of those with alcohol use disorder also had anxiety and/or major depressive disorders. Comorbidity rates were higher for anxiety and major depressive disorders: 53% (21/39) of those with anxiety disorder met criteria for another assessed disorder, as did 60% (17/28) of those with major depressive disorder.

We examined whether individuals with multiple disorders had episodes of disorders that overlapped at a given assessment time point. Of the 21 cases in Figure 1 with 1 disorder, 81% (ie, all but 4 cases: 2 with alcohol use and anxiety, 2 with anxiety and major depression) had multiple disorders that overlapped at 1 or more time points.

We also examined cooccurrence of clinically significant fatigue and pain during the 2-year period. Of 178 donors with either problem, 31% reported both, 43% reported only pain, and 26% reported only fatigue. Among those reporting both (n=56), 86% (all but 8 cases) had the conditions together at 1 or more time points.

Cases are too sparse to examine comorbidities of all combinations of specific mental and physical problems. However, of 218 donors who met caseness criteria for either psychiatric disorder or clinically significant pain or fatigue over the 2 years, 56 (26%) met criteria in both mental and physical domains, 40 (18%) had only mental disorders, and 122 (56%) had only pain or fatigue.

Comparison of mental and physical health outcome levels to normative data—

We compared the sample to normative data, where available (Table 3, rightmost column). Donors' anxiety disorder rate was significantly higher than the normative rate at the first

assessment but not thereafter. Their alcohol use disorder rate was significantly higher than the normative rate at 2 of the 3 assessments. The sample's mean SF-36 MCS scores were significantly poorer than the normative mean at all time points. Donors had significantly less fatigue than normative levels at all time points, based on both mean scores and percentage with clinically significant fatigue.

Predictors and correlates of mental and physical health outcomes

Regression results for the mental and physical health outcomes are shown in Tables 5 and 6, respectively. Because (a) <5% of the sample had major depressive disorder and <5% had anxiety disorder at any given time point; and (b) these disorders were highly comorbid, as discussed above, we created a composite reflecting whether individuals had either disorder to use in the regression analysis. For this composite variable, time of assessment was significant (Table 5): consistent with the patterns in Table 3, the likelihood of having a disorder was significantly lower after the initial assessment. Men were at greater risk for alcohol use disorder and lesser risk for depressive symptomatology. Relative to respective referent groups, obese donors and unrelated donors were at higher risk for depressive symptoms. A longer postdonation hospitalization increased the risks for depressive symptoms and poor MCS scores.

Table 5 shows that long-term perceptions of donation were also related to the mental health outcomes. Higher posttraumatic growth was associated with lower alcohol use disorder risk. Greater concern about health due to donation was associated with all 4 mental health outcomes. Donors who had incurred burdensome financial costs were at higher risk for the major depression/anxiety disorder composite, depressive symptoms, and poor MCS scores.

Among physical health outcomes, men were at lower risk for clinically significant fatigue, pain, and poor PCS scores (Table 6). Obese donors were at higher risk for fatigue, pain interference, and poor PCS scores. Unrelated donors were more likely to have clinically significant fatigue, and a longer postdonation hospitalization increased the risk for all 4 physical health outcomes. Concerning long-term perceptions of donation, the most consistently potent factors—associated with increased risk of all 4 outcomes—were reporting donation-related health concerns, and incurring burdensome donation-related financial costs. Greater posttraumatic growth was associated with lower risk of clinically significant fatigue, while feeling that 1 was a better person for having donated was associated with higher risk of pain interference. Experiencing problems with health/life insurance was associated with higher likelihood of a poor PCS score.

Results in Tables 5 and 6 were unchanged when controlling for transplant center. There were significant between-center differences only for clinically significant pain (overall $p=.038$). Using the center with the most donors as the referent, donors at 2 centers were at increased risk to report pain; remaining centers did not differ significantly from the referent (Table S1). The distributions of donors across centers were too sparse for additional analyses.

Discussion

To our knowledge, ours is the first study to examine the prevalence, course of change, and cooccurrence of clinically significant patient-reported mental and physical health problems in the long-term years after living liver donation, using standardized, validated measures and a large, multisite cohort. We also could explore comorbidity patterns for these outcomes, and consider potential predictors and correlates of patients' reports of their health.

Several key findings emerged. Donors' average scores on the physical health measures that we examined—including generic physical-related HRQOL (PCS) scores, pain severity and fatigue—were generally either like or even better (in the case of fatigue) than normative levels for healthy community residents at every assessment. However, this was not the case for the mental health outcomes. Donors showed higher rates of anxiety and alcohol use disorders than normative samples at 1 or more study assessments. Their mental health-related HRQOL (MCS) scores were also poorer than the normative mean at all assessments, although the difference was small. While major depressive disorder and depression symptom severity were also temporally stable, their prevalence and average severity (respectively) were similar to those in normative samples; this is consistent with findings for donors assessed within 1–2 years postdonation.^{65–68} Although norms were not available for pain interference with daily activities, this outcome appeared to be relatively rare, as has been found for liver donors at 1-year postdonation.⁶⁹ Overall, these results may suggest that depression, pain, and any decrements in general physical HRQOL are not unduly prominent in the long-term after liver donation. Alternatively, because donors are highly screened before donation and thus likely to be healthier than general community normative samples (even when those samples are limited to individuals without self-reported chronic diseases), the donors' outcomes might be expected to be better rather than like normative rates.^{6,70} Thus, their depression, pain, and any impairments in physical HRQOL in the long-term postdonation may not be inconsequential.

Moreover, if it is expected that donor outcomes should be better than norms, our findings of elevated anxiety and alcohol use disorder rates are worrisome. Unfortunately, there are no other long-term studies of these conditions after liver donation. Anxiety disorder rates in our sample declined and did not exceed the normative rate by the third assessment; the low rates at 2 of the 3 assessments are consistent with rates and symptom burden found in studies focused on the early years postdonation.^{65–68} However, the elevated alcohol use disorder rates showed no reliable change across assessments. It is well-known that the propensity for alcohol abuse runs in families,⁷¹ and most of our donors were family members of their recipients. Alcoholic liver disease (ALD) is a prominent indication for transplantation in Western countries, and the prevalence of alcohol use disorder in our sample might have been driven by donors at risk for alcohol problems by virtue of their family linkage to a transplant recipient who had ALD. We only have information on recipients' indications for transplantation for a small subset of the donors in our cohort ($n=137$, who had participated in the A2ALL-1 Consortium, which existed before the 2009 formulation of A2ALL-2, and which collected this recipient information). Among these 137 individuals, there was a weak, nonsignificant association between recipient ALD diagnosis and whether donors had alcohol use disorder during the present study (Fisher's exact $p=0.421$, effect size, ϕ [correlation

between variables]=0.07). Similarly, in a separate A2ALL-2 cohort studied during the first 2 years postdonation, we also found little relationship between donor alcohol abuse and recipient ALD diagnosis.⁶⁵ Given that alcohol abuse was observed in up to 5% of donors at any given assessment in this previous study—like rates reported herein—we suggest monitoring for alcohol use in donors might be important not only in the short-term postdonation,^{65,72} but also in the longer-term years.

Our examination of mental disorders' comorbidity patterns suggests that some donors were burdened with multiple mental health problems, and that these problems usually cooccurred in time. A similar pattern of temporal cooccurrence was noted for fatigue and pain. From a clinical perspective, this suggests that if 1 area of difficulty is uncovered, more detailed probing may be needed in order to understand the full constellation of problems the donor may be experiencing.²⁶

The identification of risk factors and correlates for the mental and physical health problems that we studied may also help transplant center teams to better target or refine detection efforts. Among sociodemographic and clinical predictors, sex, predonation BMI, and length of hospitalization postdonation were the most robust predictors, emerging as important for most outcomes. A longer hospitalization—likely reflecting a more difficult recovery—increased donors' risk for all physical outcomes, and 2 of 4 mental health outcomes. Sex and BMI were important for most physical outcomes—with women and obese donors at heightened risk for most these outcomes. The impact of BMI is consistent with evidence indicating its importance for kidney donors' long-term outcomes.⁷³ Female sex and BMI also increased our donors' risk for depressive symptomatology. Consistent with known risk factors for alcohol abuse,⁷¹ men were at increased risk for this problem. Length of hospital stay, sex, and BMI are easy to ascertain and could thus be useful to transplant programs aiming to proactively identify liver donors most likely to have mental and/or physical health problems in the long-term years.

Donors' perceptions of the donation experience, assessed at our first long-term time point, also proved relevant for their health outcomes. The most prominent factor was donation-related health concerns. Donors acknowledging any concerns were at elevated risk for every outcome. The experience of burdensome postdonation financial costs was also important for all outcomes except depressive symptomatology. This reinforces and extends the range of critical concerns noted in the transplant community regarding donor financial issues and costs associated with donation.^{3,46,74–76} Our data suggest that such burden may have impacts that diffuse across multiple areas of well-being, and may remain salient even years postdonation.

Our findings are also notable in that a critical transplant outcome, namely the death of the donor's recipient, did not emerge as an important predictor of any outcome, including conditions such as major depression. As we and others have reported previously, both clinical experience and qualitative studies show that donors are deeply affected by recipient death.^{77–80} Nevertheless, bereaved donors almost universally state that they take comfort in having done all they could and they have no regrets about having donated.^{13,14,20,77,78} Additionally, we previously reported very low average levels of perceived guilt or

responsibility for the recipient's death in our cohort,¹⁴ and other liver donor follow-up studies have not found recipient death to increase risk for adverse long-term general HRQOL.^{18,20,21} Moreover, the experience of grief following bereavement does not necessarily mean that an individual will meet criteria for a psychiatric disorder, including the conditions we assessed; in fact, a large empirical literature shows that the vast majority of bereaved individuals do not develop any psychiatric disorder.^{81,82} It is also noteworthy that most of our donors who lost their recipient experienced this event multiple years before any of our interviews.

Major study limitations are that we did not enroll donors before donation and follow them prospectively, and we did not assess nondonor comparison groups. Indeed, we are unaware of any long-term follow-up study in living donors that has examined outcomes relative to an important comparison group: eligible donor candidates who did not donate.⁸³ Nevertheless, given the dearth of evidence on clinically significant psychosocial difficulties in the long-term postdonation and the lack of information on how these difficulties may trend over time, our study provides important new information. Moreover, we put our results into perspective by comparing them to normative data from U.S. population-based cohorts of individuals without self-reported major chronic diseases and who were similar in age range, education range, and BMI range as our sample. Further, our strategy of making comparisons to normative data is a strategy that has been employed to facilitate interpretation in large, multicenter long-term psychosocial follow-up studies of living kidney donors (eg, Gross et al⁷³) where it would not have been economically or practically feasible to collect prospective data over periods of many years since donation. Comparisons to normative data are well-recognized as providing valuable information for the interpretation of results obtained in each sample and for determining the clinical significance of those results.^{84–88}

Additional study limitations include the fact that some A2ALL-2 centers were small, restricting our ability to detect center differences. We did find center differences in rates of donor-reported pain. We previously reported that, in a separate cohort of A2ALL-2 donors who donated more recently than the current cohort, centers varied in some elements of perioperative pain management.⁸⁹ However, we have no information on centers' pain management practices for our cohort, and it is not clear that any such differences would affect pain perceptions many years later. Regarding other potential predictors, we had no information on donors' predonation history of the mental and physical health problems. Thus, our findings cannot speak to issues of whether donor selection practices should change. However, previous studies have not consistently found that lifetime psychiatric history, or predonation fatigue or pain predicted postdonation outcomes in these areas, at least in the first few years postdonation.^{68,69} There may also have been intervening factors between donation and time of our assessments, including life events unrelated to donation, that increased risk for our outcomes but that we could not assess. Nevertheless, the existence of such factors would not necessarily obviate the importance of the predictors that we did identify. Another limitation is that we do not have information on other variables relevant to our outcomes, including any interventions received for them. Finally, our donor cohort is relatively well-educated and predominantly nonHispanic White, potentially limiting generalizability, and precluding examination of differences between specific ethnic

minorities. However, like our cohort, the clear majority of U.S. living liver donors are nonHispanic Whites.⁹⁰ (Living donor ethnicity information is not available for Canada.⁹¹)

Beyond these limitations, our study serves to heighten awareness that, while most donors may not experience difficulties in the mental and physical health areas we examined, a subset of donors are at risk for such problems. Among these problems, anxiety and alcohol use may warrant more attention in both research and clinical surveillance efforts. Robust risk factors for our outcomes appear relatively straightforward to assess and, therefore, may be important for transplant programs to consider to identify at-risk donors. Some factors, such as predonation obesity and postdonation burdensome financial costs, are well-recognized as important (but challenging) targets for intervention in their own right. If they can be ameliorated, risk for long-term mental and physical health problems may be lessened. This remains an important issue for future research, given that our study was observational and did not establish cause-effect relationships. Nevertheless, our findings suggest that the monitoring of donor well-being beyond the first few years postdonation should include patient-reported mental and physical health outcomes, and may be most efficiently performed by targeting surveillance efforts to donors at highest risk for such difficulties.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

A2ALL	Adult to Adult Living Donor Liver Transplantation Cohort Study
ALD	alcoholic liver disease
BMI	body mass index
BPI	Brief Pain Inventory
CI	confidence interval
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy Fatigue Scale
HRQOL	health-related quality of life
M	mean
MCS	Mental Component Summary

NRS	Numeric Rating Scale
OR	odds ratio
PCS	Physical Component Summary
PHQ-9	Patient Health Questionnaire-9
PRIME-MD-PHQ	Primary Care Evaluation of Mental Disorders, Patient Health Questionnaire version
REF	referent
SD	standard deviation
SF-36	Short Form-36

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*Percentages reflect cases out of the total of 96 who had each pattern of comorbid conditions.

Figure 1.

Comorbidity of psychiatric disorders during study period in 96 donors who met criteria for at least 1 disorder.

Table 1

Measures used to assess study outcomes and potential predictors and correlates of outcomes.

Measure	Instrument and description	Instrument scoring	Cronbach's α , current sample
Mental health outcomes			
Psychiatric disorders (major depressive disorder, anxiety disorder, alcohol use disorder)	<ul style="list-style-type: none"> • Patient Health Questionnaire (self-report version of Primary Care Evaluation of Mental Disorders [PRIME-MD-PHQ]).²⁸ • Validated for outpatient and community populations.^{28–33} • Because it does not involve clinician administration, conditions identified are considered probable rather than definitive diagnoses.²⁸ However, they correspondence closely with clinician-made diagnoses.^{28,29} 	<ul style="list-style-type: none"> • Published algorithm for determining presence of a diagnosis at time of interview. 	n/a
Depressive symptom severity	<ul style="list-style-type: none"> • Patient Health Questionnaire-9 (PHQ-9)^{29,34} • 9-item symptom rating scale included in PRIME-MD-PHQ and validated in outpatient and community populations.^{29,34} 	<ul style="list-style-type: none"> • Sum of items (range, 0–27); sum is categorized in 5 severity levels (none/normal=scores of 0–4; mild=5–9; moderate=10–14; moderately severe=15–19; severe=20–27). 	0.84
General mental health-related quality of life	<ul style="list-style-type: none"> • Mental Component Summary (MSC) score from the Short Form-36 (SF-36), version 2.³⁵ • Composite focuses on SF-36 items pertaining to mental health, role limitations due to emotional health, social functioning, and vitality. 	<ul style="list-style-type: none"> • Published scoring algorithm (range, 0 [poor] - 100 [excellent]); scores are t scores (standardized, M=50, SD=10). • Poor scores defined as >0.5 SD of t score distribution (ie, 5 points) below M=50, per standard recommendations.³⁶ 	n/a
Physical health outcomes			
Fatigue	<ul style="list-style-type: none"> • Fatigue Scale from Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue).³⁷ Its 13 items assess fatigue severity. • Validated in healthy and chronic illness populations.^{37,38} 	<ul style="list-style-type: none"> • Sum of items (score range 0 [high] - 52 [low fatigue]). • Clinically significant fatigue defined as >0.5 SD below the normative mean in the general population.³⁹ 	0.93
Pain severity and pain interference	<ul style="list-style-type: none"> • Brief Pain Inventory (BPI).³⁹ • Includes single-item Numeric Rating Scale for pain severity;⁴⁰ used to 	<ul style="list-style-type: none"> • Severity item rated 0=no pain - 10=pain as bad as you can imagine. • Interference scale is item average (range 0 [no 	0.96

Measure	Instrument and description	Instrument scoring	Cronbach's α , current sample
	capture any abdominal or back pain in the past 24 hours.	pain/no interference]-10 [pain completely interferes]).	
	<ul style="list-style-type: none"> Includes 7-item Pain Interference Scale, assessing degree to which any pain has interfered with activities of daily living.³⁹ Validated in acute and chronic pain populations.³⁹ 	<ul style="list-style-type: none"> Scores 4 on severity and interference measures indicate pain of at least moderate severity and interference, respectively.^{41,42} 	
General physical health-related quality of life	<ul style="list-style-type: none"> Physical Component Summary (MSC) score from the SF-36, version 2.³⁵ Composite focuses on SF-36 items pertaining to physical functioning, role limitations due to physical functioning, pain, and general health. 	<ul style="list-style-type: none"> Published scoring algorithm (range, 0 [poor] - 100 [excellent]), scores are t scores (standardized, M=50, SD=10). Poor scores defined as >0.5 SD of t score distribution (ie, 5 points) below M=50.³⁶ 	n/a
Potential predictors and correlates of outcomes			
Sociodemographic characteristics	<ul style="list-style-type: none"> Standard items for characteristics such as age, sex, education; items also included to indicate relationship to transplant recipient and recipient vital status 	<ul style="list-style-type: none"> Categories for each variable are reported in Table 2 	n/a
Clinical characteristics	<ul style="list-style-type: none"> BMI at predonation medical evaluation, donation date, length of postoperative hospitalization, medical complications and related rehospitalizations during the first year postdonation, from donor medical record 	<ul style="list-style-type: none"> Categories and coding for each variable are reported in Table 2 	n/a
Donors' perceptions related to the donation experience	<ul style="list-style-type: none"> All measures have been used in prior living donor studies; multiitem scales have established psychometric properties 		
a. Psychological response to donation	<ul style="list-style-type: none"> Posttraumatic Growth Inventory-Short Form⁴³ (assessing whether donors felt they had personally grown due to donation) 	<ul style="list-style-type: none"> Sum of 10 items (range, 0 [low] -50 [high degree of growth]) 	0.91
	<ul style="list-style-type: none"> Better Person Scale⁴⁴ (assessing whether donors felt they had become a better person by donating) 	<ul style="list-style-type: none"> Sum of 10 items (range, 0 [low] -10 [high;stronger feeling of becoming a better person]) 	0.74
b. Worry/concern about current health due to donation	<ul style="list-style-type: none"> Items from Simmons Worries and Health measures^{14,44,45} related to physical health effects of donation 	<ul style="list-style-type: none"> Determination of whether any of 4 items were endorsed as present 	n/a

Measure	Instrument and description		Instrument scoring	Cronbach's α , current sample
c. Postdonation socioeconomic burdens	•	Items adapted from Holtzman's work ⁴⁶ on whether donors had incurred donation-related costs, been burdened by any costs, and experienced problems getting/keeping health or life insurance due to donation	• Each scored as yes v. no	n/a

M, mean; SD, standard deviation

Table 2

Demographic, clinical, and psychosocial characteristics of donors enrolled and approached for follow-up.

Characteristic at initial assessment ^{a,b}	Total cohort (N=517)	Completed follow-up (n=424)	Dropped out (n=93)	Comparison test ^c	p
Demographic					
Age at donation, years, % (n)				4.08	.253
19–30	23.0 (119)	21.9 (93)	28.0 (26)		
>30–40	26.7 (138)	25.7 (109)	31.2 (29)		
>40–50	30.0 (155)	31.1 (132)	24.7 (23)		
>50–61	20.3 (105)	21.2 (90)	16.1 (15)		
Current age, years, % (n)				6.84	.077
23–30	9.1 (47)	8.3 (35)	12.9 (12)		
>30–40	24.6 (127)	22.9 (97)	32.3 (30)		
>40–50	27.9 (144)	28.8 (122)	23.7 (22)		
>50–68	38.5 (199)	40.1 (170)	31.2 (29)		
Years since donation, M (SD, range)	5.8 (1.9, 3–10)	5.8 (1.9, 3–10)	5.8 (1.8, 3–10)	0.20	.843
Female sex, % (n)	53.2 (275)	54.5 (231)	47.3 (44)	1.57	.210
Race/ethnicity, % (n)				1.47 ^d	.225
White/European	87.6 (453)	88.4 (375)	83.9 (78)		
Hispanic/white	4.6 (24)	3.8 (16)	8.6 (8)		
Black/African	2.1 (11)	1.9 (8)	3.2 (3)		
Asian	2.3 (12)	2.4 (10)	2.2 (2)		
Other	3.3 (17)	3.5 (15)	2.2 (2)		
Education, % (n)				13.48	.004
high school	20.9 (108)	19.3 (82)	28.3 (26)		
Vocational or some college	22.9 (118)	20.8 (88)	32.6 (30)		
College graduate	36.2 (187)	38.9 (165)	23.9 (22)		
Postgraduate	20.0 (103)	21.0 (89)	15.2 (14)		
Married or had significant other, % (n)	70.5 (364)	71.4 (302)	66.7 (62)	0.82	.365
Employment status, % (n)				0.03	.998
Employed full-time	76.8 (395)	76.8 (325)	76.9 (70)		

Characteristic at initial assessment ^{a,b}	Total cohort (N=517)	Completed follow-up (n=424)	Dropped out (n=93)	Comparison test ^c	p
Employed part-time	10.3 (53)	10.4 (44)	9.9 (9)		
Unemployed	9.7 (50)	9.7 (41)	9.9 (9)		
Retired	3.1 (16)	3.1 (13)	3.3 (3)		
Relation to transplant recipient, % (n), donor is:				4.79 ^d	.188
First-degree relative: Parent	3.7 (19)	3.3 (14)	5.4 (5)		
Adult child	31.3 (162)	29.7 (126)	38.7 (36)		
Sibling	23.4 (121)	23.8 (101)	21.5 (20)		
Spouse/partner	7.7 (40)	8.0 (34)	6.5 (6)		
Other relative: Biological relative	6.2 (32)	5.9 (25)	7.5 (7)		
Nonbiological relative	10.8 (56)	10.8 (46)	10.8 (10)		
Unrelated	16.8 (87)	18.4 (78)	9.7 (9)		
Clinical donation-related					
BMI at evaluation, % (n)				3.62	.164
17.9–24.9	39.5 (202)	40.6 (171)	34.4 (31)		
25.0–29.9 (overweight)	39.9 (204)	40.4 (170)	37.8 (34)		
30.0–42.6 (obese)	20.5 (105)	19.0 (80)	27.8 (25)		
Postdonation length of hospital stay, days, M (SD)	6.7 (2.2)	6.7 (2.3)	6.7 (1.8)	0.10	.919
Postoperative complications in first year postdonation, highest Clavien grade, % (n) ^e				2.02 ^d	.155
None	71.3 (263)	74.0 (225)	58.5 (38)		
Grade 1 (minor)	8.9 (33)	7.6 (23)	15.4 (10)		
Grade 2 (possibly life-threatening)	19.2 (71)	18.4 (56)	23.1 (15)		
Grade 3 (residual disability)	0.5 (2)	0.0 (0)	3.1 (2)		
Hospital readmission for complications in first year postdonation, % yes (n)	2.2 (8)	2.3 (7)	1.5 (1)	—	1.000
Recipient vital status (donor report), % deceased (n)	17.6 (91)	18.2 (77)	15.1 (14)	0.52	.471
Years postdonation that recipient death occurred, M (SD)	2.5 (2.3)	2.4 (2.2)	3.1 (2.7)	1.10	.275
Years before initial survey that recipient death occurred, M (SD) ^f	3.8 (2.1)	3.8 (2.0)	3.6 (2.5)	0.37	.710
Psychosocial					
Posttraumatic Growth Inventory (0=low, 50=high), M (SD)	25.8 (13.4)	25.6 (13.4)	26.5 (13.5)	0.58	.559
Better Person Scale (0=low, 10=high), M (SD)	5.1 (2.5)	5.0 (2.5)	5.4 (2.4)	1.29	.199

Characteristic at initial assessment ^{a,b}	Total cohort (N=517)	Completed follow-up (n=424)	Dropped out (n=93)	Comparison	
				test ^c	p
Health-related concerns and worries related to donation, % yes (n)	47.8 (247)	47.2 (200)	50.5 (47)	0.35	.556
Incurred donation-related financial costs, % yes (n)	60.5 (311)	61.4 (259)	56.5 (52)	0.74	.388
Donation-related costs were a burden, % yes (n)	15.1 (78)	14.2 (60)	19.6 (18)	1.70	.192
Had postdonation problems getting or keeping health/life insurance, % yes (n)	11.3 (58)	10.7 (45)	14.3 (13)	0.96	.326

BMI, body mass index; M, mean; SD, standard deviation

^aThe following variables had missing data (n): education, recipient vital status, marital status (1); Posttraumatic Growth Inventory, donation-related costs were a burden (2); employment, donation-related financial costs (3); insurance problems (5); BMI (6); postdonation length of hospital stay (10); postoperative complications and hospital readmissions (148). Concerning missing data on postoperative complications and readmissions, some donors did not return to centers for care through the complete first year postdonation. We previously reported that there was no statistically significant association between center and these variables.¹⁵ There were no differences in the distribution of missing data at initial assessment between donors who completed follow-up versus dropped out.

^bSmall sample sizes at individual centers do not permit separate analyses by center; centers (with n) were Columbia University (24), Lahey Clinic and Medical Center (108), University of Pennsylvania (11), Virginia Commonwealth University (24), University of Pittsburgh (115), Northwestern University (37), University of Toronto (151), University of Colorado (29), and University of California, San Francisco (18).

^c χ^2 test for proportions; t test for continuous variables, except for hospital readmissions for which a Fisher exact p is reported due to small cell sizes.

^dDue to small cell sizes, some categories were combined into 1 category for statistical testing. For race/ethnicity, categories of Hispanic, Black, Asian, and Other were combined. For relation to transplant recipient categories of parent, child and sibling were combined, and categories of other biologic relative and other nonbiologic relative were combined. For postoperative complications, none and Grade 1 were combined and were compared to a single category comprising Grades 2 and 3 (ie, none or minor complications vs. major complications).

^eDonor complications were graded with the Clavien classification⁵² using methods previously described.⁷

^fIn order to fully characterize this variable, we also provide the distribution in the 91 donors per specific time intervals: 5.5% (5 cases) experienced the recipient death from >3 to 6 months before the initial survey; 3.3% (3 cases) from >6 months to 1 year; 12.1% (11 cases) from >1 year to 2 years; 50.5% (46 cases) from >2 to 5 years, and 28.6% (26 cases) >5 years before survey. In addition to these 91 deaths before the initial survey, 17 donors' recipients died either before the second or third survey time points. Of these, 23.5% (4 cases) occurred within 3 months of survey; 35.3% (6 cases) from >3 to 6 months, and 41.2% (7 cases) >6 months before survey.

Patient-reported mental and physical health at the 3 long-term follow-up assessments in living liver donors.^a

Table 3

Outcome ^b	First assessment (n=517) ^d	Second assessment (n=453) ^d	Third assessment (n=424) ^d	Change over time F test	p	Normative level ^c
<u>Mental health domain</u>						
Major depressive disorder, % (n)	3.1 (16)	1.8 (8)	1.4 (6)	1.70	.183	3.0
Anxiety disorder, % (n)	4.9 (25) *	2.0 (9)	2.6 (11)	3.36	.035	1.7
Alcohol use disorder, % (n)	5.6 (29) *	3.8 (17)	6.1 (26) *	1.43	.240	2.9
Any of the 3 disorders, % (n)	11.5 (59)	6.2 (28)	8.7 (37)	4.00	.019	—
Depression symptom severity, % (n)						
None, normal (0–4)	79.2 (408)	81.3 (366)	80.4 (340)	0.35	.708	81.5
Mild (5–9)	13.0 (67)	11.1 (50)	13.7 (58)	1.48	.228	12.7
Moderate (10–14)	5.6 (29)	6.0 (27)	4.5 (19)	0.71	.490	3.9
Moderately severe (15–19)	1.7 (9)	1.6 (7)	0.9 (4)			1.3
Severe (20–27)	0.4 (2)	0.0 (0)	0.5 (2)			0.6
SF-36 Mental Component Summary score						
M (SD)	52.5 (8.7) *	53.1 (8.5) *	52.9 (8.9) *	1.48	.228	54.3
% poor (n)	15.9 (82)	13.3 (60)	15.6 (66)	0.71	.490	
<u>Physical health domain</u>						
Fatigue severity						
M (SD)	44.4 (8.2) *	44.4 (8.9) *	44.5 (8.5) *	0.01	.994	40.4
Clinically significant fatigue, % (n)	11.4 (59) *	12.4 (56) *	12.8 (54) *	0.25	.778	22.1
Pain severity						
M (SD) ^d	1.2 (2.2)	1.1 (2.0)	1.2 (2.2)	0.71	.494	—
Clinically significant pain, % (n)	14.3 (74) *	12.9 (58)	14.2 (60)	0.19	.824	10.9
Pain interference						
M (SD) ^d	0.6 (1.6)	0.6 (1.5)	0.6 (1.5)	0.92	.398	—
Clinically significant interference, % (n)	5.4 (28)	5.8 (26)	6.1 (26)	0.22	.806	—
SF-36 Physical Component Summary score						

Outcome ^b	First assessment (n=517) ^a	Second assessment (n=453) ^a	Third assessment (n=424) ^a	Change over time F test	Normative level ^c p
M (SD)	54.6 (7.4)	54.4 (8.0)	54.3 (7.5)	1.99	.137
% poor (n)	8.1 (42)	11.1 (50)	10.6 (45)	1.47	.230

BMI, body mass index; M, mean; SD, standard deviation; SF-36, Short Form-36.

^aDescriptive information and test statistics were based on all available data from donors, no matter whether they completed all survey assessments. Analyses based on only those donors who completed all 3 assessments (n=406) yielded results indistinguishable from those presented in this table.

^bFor the sample available at each time point, the following variables had missing data: Major depressive disorder, anxiety disorder, substance use disorder, and PHQ-9 all had 2 cases, 3 cases, and 1 case missing at the first, second, and third assessments, respectively. FACIT Fatigue, NRS Pain Severity, BPI Pain Interference all had 1 case, 2 cases, and 1 case missing at the first, second, and third assessments, respectively. For the SF-36, 1 case each was missing at each assessment.

^cNormative data were drawn from North American population-based cohorts reported in the following sources:

Mental disorders (major depressive disorder, generalized anxiety disorder, alcohol use disorder): US Cohort, World Mental Health Initiative, 2001–2012^{53–57} (for the present analyses, limited to adults with the same upper age limit, the same education range and the same BMI range as A2ALL sample and without self-reported health conditions: coronary artery/heart disease, stroke, diabetes, arthritis, sleep disorders, respiratory disease);

Depression symptom severity, National Health and Nutrition Examination Survey 2011–2012⁵⁸ (for the present analyses, limited to adults with the same age range, the same education range and the same BMI range as A2ALL sample and without self-reported health conditions; see listed provided for mental disorders cohort above);

Fatigue severity, Patient-Reported Outcomes Measurement Information System, PROMIS 2006–2007 national normative sample^{59,60} (for the present analyses limited to adults with same upper age limit, and the same education and BMI range as A2ALL sample and without self-reported health conditions; see list provided for mental disorders cohort above)

Pain Severity, US Cohort, Global Burden of Disease 2010^{61–62} (for the present analyses limited to adults aged 25–69; based on US population);

SF-36 composite scores, United States National Health Measurement Study 2006^{63,64} (for the present analyses limited to adults with the same upper age limit, and the same education and BMI ranges as A2ALL sample and without self-reported health conditions (see listed provided for mental disorders cohort above).

^dLog transformed prior to analyses to better meet normality assumptions. Means and SDs are reported on the original scale to facilitate interpretation.

* p<.05 in comparison to normative data, using Hochberg’s modified Bonferroni method to adjust for performing 3 comparisons per variable.

Table 4

Percentage of donors who had each outcome at multiple assessments during the study period.

Outcome ^a	No. with outcome at any of 3 assessments	% (n) with outcome at >1 assessment
<u>Mental health domain</u>		
Major depressive disorder	28	7.1 (2)
Anxiety disorder	39	15.4 (6)
Alcohol use disorder	57	22.8 (13)
Any of the 3 disorders	96	22.9 (22)
PHQ-9 depression symptoms present (scores>4)	158	49.4 (78)
SF-36 Mental Component Summary score, poor	132	40.2 (53)
<u>Physical health domain</u>		
FACIT-Fatigue, clinically significant fatigue	102	44.1 (45)
NRS pain severity, clinically significant	132	32.6 (43)
BPI pain interference, clinically significant	53	35.8 (19)
SF-36 Physical Component Summary score, poor	85	42.4 (36)

BPI, Brief Pain Inventory; FACIT, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; NRS, Numeric Rating Scale; PHQ-9, Patient Health Questionnaire-9; SF-36, Short-Form-36.

Table 5

Predictors of donors' mental health outcomes from repeated measures regression analysis.

Predictor ^a	Major depressive or anxiety disorder	Alcohol use disorder	PHQ depressive symptom severity >4	Poor HRQOL Mental Component Summary score
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Stage 1: Sociodemographic and clinical characteristics				
Assessment time point				
Time 1 (ref)	—			
Time 2	0.47 (0.25, 0.85)			
Time 3	0.56 (0.33, 0.95)			
Female sex		0.21 (0.11, 0.40)	1.59 (1.07, 2.32)	.019
BMI at donor evaluation				.004
17.0–24.9			—	—
25.0–29.9 (overweight)			1.14 (0.74, 1.78)	.546
30.0–42.6 (obese)			2.19 (1.35, 3.56)	.002
Relation to transplant recipient, donor is:				.006
First-degree relative (ref)			—	—
Spouse/partner			1.29 (0.66, 2.52)	.450
Other biological or nonbiological relative			0.74 (0.42, 1.32)	.308
Unrelated			2.02 (1.27, 3.19)	.003
Length of hospital stay after donation surgery (per 1 day increase)			1.11 (1.03, 1.21)	.011
				1.14 (1.05, 1.24)
				.001
Stage 2: Long-term perceptions of donation^b				
Post Traumatic Growth Inventory (0=low, 50=high) (per 5-point increase)		0.89 (0.80, 0.98)	.021	
Any health-related concerns related to donation	2.58 (1.31, 5.08)	2.88 (1.60, 5.16)	3.77 (2.52, 5.65)	<.001
Donation-related financial costs ^c				<.001
No (ref)	—		—	—
Yes but they were not a burden	0.91 (0.43, 1.94)		1.03 (0.67, 1.58)	.900
Yes and they were a burden	3.71 (1.74, 7.92)		2.63 (1.57, 4.41)	<.001
				3.07 (1.82, 5.20)
				<.001

BMI, body mass index; CI, confidence interval; HRQOL, health-related quality of life; OR, odds ratio; PHQ, patient health questionnaire; ref, referent.

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^g Other variables that were examined but did not meet criteria for inclusion in final models: race/ethnicity (nonHispanic White vs. all other groups), age at donation, education, postoperative complications (none or minor complications vs. major complications, as described in Table 2), years since donation, recipient death (no death, death within a year before assessment, death more than a year before assessment), Better Person Scale, and whether donors had trouble getting or keeping health/life insurance since donation. Hospital readmission was not included as a potential predictor because very few donors were rehospitalized and readmissions are included in the Clavien grading of complications.

^h For each outcome, the Stage 2 model adjusts for predictors entered at Stage 2.

^c Because incurring financial costs and experiencing costs as burdensome were highly correlated (costs could only be a burden if they were incurred), we created 1 composite variable that reflected both items.

Table 6

Predictors of donors' physical health outcomes from repeated measures regression analysis.

Predictor ^a	Clinically significant fatigue		Clinically significant pain		Clinically significant pain interference		Poor HRQOL Physical Component Summary score	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Stage 1: Sociodemographic and clinical characteristics								
Female sex	2.04 (2.16, 3.33)	.003	1.59 (1.07, 2.38)	.020			1.82 (1.09, 3.03)	.024
BMI at donor evaluation		.007				.034		.002
17.0–24.9	—	—	—	—	—	—	—	—
25.0–29.9 (overweight)	1.38 (0.81, 2.36)	.240			0.98 (0.47, 2.07)	.966	0.83 (0.45, 1.53)	.556
30.0–42.6 (obese)	2.53 (1.40, 4.57)	.002			2.32 (1.10, 4.89)	.027	2.34 (1.28, 4.27)	.006
Relation to transplant recipient, donor is:		.044						
First-degree relative (ref)	—	—						
Spouse/partner	1.34 (0.62, 2.93)	.459						
Other biological or nonbiological relative	0.80 (0.40, 1.60)	.528						
Unrelated	2.01 (1.16, 3.46)	.012						
Length of hospital stay after donation surgery (per 1 day increase)	1.20 (1.10, 1.32)	<.001	1.09 (1.01, 1.19)	.038	1.14 (1.02, 1.28)	.022	1.18 (1.07, 1.30)	.001
Stage 2: Long-term perceptions of donation^b								
Post Traumatic Growth Inventory (0=low, 50=high) (per 5-point increase)	0.90 (0.82, 0.97)	.010						
Better Person Scale (0=low, 10=high)					1.13 (1.01, 1.27)	.034		
Any health-related concerns related to donation	5.21 (3.10, 8.77)	<.001	2.60 (1.74, 3.89)	<.001	3.58 (1.79, 7.13)	<.001	3.42 (1.99, 5.88)	<.001
Had postdonation problems getting or keeping health/life insurance							1.93 (1.03, 3.61)	.041
Donation-related financial costs ^c		<.001		<.001		<.001		.002
No (ref)	—	—	—	—	—	—	—	—
Yes but they were not a burden	0.85 (0.50, 1.44)	.545	0.56 (0.36, 0.86)	.009	0.51 (0.23, 1.12)	.093	1.16 (0.65, 2.07)	.608
Yes and they were a burden	3.83 (2.18, 6.74)	<.001	2.32 (1.42, 3.77)	<.001	4.31 (2.22, 8.39)	<.001	2.89 (1.52, 5.48)	.001

BMI, body mass index; CI, confidence interval; HRQOL, health-related quality of life; OR, odds ratio; ref, referent.

^aOther variables that were examined but did not meet criteria for inclusion in final models: time/wave, race/ethnicity (nonHispanic White vs. all other groups), age at donation, education, postoperative complications (none or minor complications vs. major complications, as described in Table 2), years since donation, and recipient death (no death, death within a year before assessment, death more than a year before assessment). Hospital readmission was not included as a potential predictor because very few donors were rehospitalized, and readmissions are included in the Clavien grading of complications.

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For each outcome, the Stage 2 model adjusts for predictors entered at Stage 2.

Because incurring financial costs and experiencing costs as burdensome were highly correlated (costs could only be a burden if they were incurred), we created 1 composite variable that reflected both items.