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The international prevalence and variability of nonadherence to the nonpharmacologic treatment regimen after heart transplantation: findings from the cross-sectional BRIGHT study

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Abstract

Introduction. Heart transplant (HTx) recipients need to follow a complex therapeutic regimen. We assessed the international prevalence and variability in nonadherence to six nonpharmacologic treatment components (physical activity, sun protection, diet, alcohol use, nonsmoking, and outpatient follow-up visits).

Methods. We used self-report data of 1397 adult HTx recipients from the 36-HTx-center, 11-country, 4-continent, cross-sectional BRIGHT study (ClinicalTrials.gov ID: NCT01608477). The nonadherence definitions used were as follows: Physical activity: <3 times/wk 20 minutes' vigorous activity, <5 times/wk 30 minutes' moderate activity, or <5 times/wk a combination of either intensity; Sun protection: not "always" applying any sun protection; Diet: not "often" or "always" following recommended diet(s); Alcohol use: >1 alcoholic drink/d (women) or >2 drinks/d (men); Smoking: current smokers or stopped <1 year before; Follow-up visits: missing ≥1 of the last 5 outpatient follow-up visits. Overall prevalence figures were adjusted to avoid over- or underrepresentation of countries. Between-country variability was assessed within each treatment component via chi-square testing.

Results. The adjusted study-wide nonadherence prevalence figures were as follows: 47.8% for physical activity (95% CI [45.2-50.5]), 39.9% for sun protection (95% CI [37.3-42.5]), 38.2% for diet recommendations (95% CI [35.1-41.3]), 22.9% for alcohol consumption (95% CI [20.8-25.1]), 7.4% for smoking cessation (95% CI [6.1-8.7]), and 5.7% for follow-up visits (95% CI [4.6-6.9]). Significant variability was observed between countries in all treatment components except follow-up visits.

Conclusion. Nonadherence to the post-HTx nonpharmacologic treatment regimen is prevalent and shows significant variability internationally, suggesting a need for tailored adherence-enhancing interventions.

Keywords

Adherence; Compliance; Health behaviors; Heart transplantation; Nonpharmacologic treatment

1 INTRODUCTION

Evidence shows that long-term graft attrition rates after adult heart transplantation (HTx) have not changed markedly over time and that reduced mortality rates are almost exclusively attributable to survival gains in the early post-HTx phase.[1,2] Improving long-term survival is therefore a priority in research and clinical practice. Nevertheless, immunosuppressant intake might hamper long-term survival.[3] Indeed, long-term immunosuppressant intake may trigger systemic and metabolic complications and elevate the risk of cancer, augmenting the risk of graft injury and all-cause mortality. According to the most recent registry data,[4] at 5 years post-HTx, 51.1% of HTx recipients have renal dysfunction, 35.5% have diabetes, 29.3% have cardiac allograft vasculopathy, and 15.9% have malignancy (all types combined).

To prevent or delay the incidence of these comorbidities, post-HTx care guidelines[5] recommend lifelong follow-up to monitor graft function and lifestyle modifications including weight control, physical activity, diet (eg, low fat and sodium intake), abstinence from smoking or heavy alcohol intake, and use of sun protection. It remains unclear, however, to what extent HTx recipients are able to follow this complex therapeutic regimen. The bulk of evidence on post-HTx behavior focuses on medication adherence; robust evidence on the prevalence of nonadherence to the post-HTx nonpharmacologic therapeutic regimen is scarce.

A 2007 meta-analysis[6] showed nonadherence rates of 33.7 cases per 100 patient-years for physical activity, 28.1 cases for following a diet, 8.5 cases for attending clinic appointments, 4.9 cases for alcohol use, and 3.2 cases for tobacco use in HTx recipients. However, these estimates were based on a small number of available studies. Moreover, although meta-analyses pool and summarize evidence, nonadherence prevalence rates for each behavior might vary widely across studies due to methodological issues, for example, nonstandard measurement methods or sampling strategies. Since that 2007 meta-analysis, the few related studies published have most commonly used small samples or focused on a single behavior. Larger studies investigating multiple behaviors enrolled patients from one center only,[6, 7] providing no evidence on variations in HTx recipients' health behaviors between centers or countries. Physical inactivity in the general population, for instance, is far more prevalent in Belgium, Spain, and the UK than in the Netherlands, Germany, or France,[8] and tobacco smoking is more prevalent in Europe than in the Americas.[9] Generating and comparing regional nonadherence rates could help HTx centers prioritize lifestyle interventions and plan resources to remedy problems specific to their local populations. Therefore, the international HTx community would benefit from a single large study using a homogeneous methodological approach to investigate the prevalence of nonadherence to all post-HTx nonpharmacologic treatment components.

Therefore, this study has two aims: (i) to describe the prevalence of nonadherence to the post-HTx nonpharmacologic treatment regimen (ie, physical activity, sun protection, diet recommendations, limiting alcohol use, smoking abstinence, and appointment keeping); and (ii) to describe between-country variability in nonadherence rates regarding these health behaviors and test its significance in a large sample of adult HTx recipients from various countries.

2 PATIENTS AND METHODS

This study used data from the Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (BRIGHT) study[10,11] (ClinicalTrials.gov ID: NCT01608477), a cross-sectional study assessing healthcare providers' practice patterns and the prevalence and variability of nonadherence to the post-HTx treatment regimen in 36 HTx centers from 11 countries in Asia, Europe, North America, and South America.

2.1 Sampling and data collection

The BRIGHT study used a multistage sampling approach. Countries and HTx centers were included via convenience sampling, enrolling at least 2 centers per country. HTx centers were eligible to participate in the study if they met all of the following criteria:

1. Performance of at least 50 HTx over the 60 months prior to inclusion.
2. Location in Europe, North America, South America, or Australia.
3. Willingness to provide formal study support through the center's HTx director and responsible administrator.
4.

Using a stratified random sampling approach based on center size,[10] HTx recipients were eligible to participate if they:

1. Were adults (≥18 years at time of enrollment);
2. Were transplanted and followed up for routine care at a participating HTx center;
3. Received their HTx as a single-organ transplant;
4. Underwent a first-time HTx (no retransplantation);
5. Were 1-5 years post-HTx;
6. Were able to read and understand one of the study languages; and
7. Were willing to provide written informed consent.

HTx recipients were excluded if they had participated in adherence intervention research or drug trials during the 6 months prior to inclusion or if they had received professional support for medication intake. Detailed information on the methodology of the BRIGHT study is reported elsewhere.[10,11]

The data were collected (once for each HTx recipient) between March 2012 and October 2015 after obtaining ethical approval from each participating center's institutional review board (IRB) or ethics committee.

2.2 Variables and measurement

To describe the sample, sociodemographic characteristics were collected via patient interviews during a scheduled clinic visit (ie, age, gender, marital status, ethnicity, educational level, and employment status). Clinical data (date of HTx and heart failure etiology) were captured based on chart reviews.

Nonadherence to 6 components of the nonpharmacologic treatment regimen (ie, physical activity, nonsmoking status, limited alcohol use, use of sun protection measures, following of diet recommendations, and the keeping of follow-up appointments) was assessed by a self-report questionnaire during a scheduled outpatient clinic visit.[12-16] Table 1 describes how each component was measured and scored.

Table 1. Self-report instruments used to measure the investigated health behaviors

Variable	Instrument	• Number of items • Recall period • Response options • Nonadherence definitions	Validity/Reliability
Physical activity (PA)	Brief Physical Activity Assessment tool (12)	• 2 items • Average week • No. times/wk 20 min of vigorous PA: <1 time/wk/1-2 times/wk/ ≥3 times/wk and No. times/wk 30 min of moderate PA: <1 time/wk/1-2 times/wk/3-4 times/wk/ ≥5 time/wk • Nonadherence: <3 times/wk vigorous PA OR <5 times/wk moderate PA OR <5 times/wk a combination of either PA intensities	Assessed against an accelerometer-Criterion validity (10) (κ = 0.40, 95% CI = 0.12-0.69) -Inter-rater reliability (10) (κ = 0.53, 95% CI = 0.33-0.72)
Smoking status	1 item from the Swiss Health Survey (13)	• 1 item • 1 y • Currently smoking/Stopped smoking less than a year before/Stopped smoking more than a year before/Never smoked • Nonadherent: currently smoking or stopped less than a year before	No available information on psychometric properties
Alcohol use	Investigator developed (14)	• 3 items • Average week • Yes/No • No. shots or glasses/wk (1.5 oz. = 45 mL); • No. pints of beer/wk (1 pint = 12 oz. = 355 mL); • No. glasses of wine/wk (1 glass = 5 oz. = 148 mL) • No. times drinking/wk: Daily/3-4 times/wk/1-2 times/mo/<1 time/mo/Never • Nonadherent = heavy drinker: >1 drink/d (women); >2 drinks/d (men)	No available information on psychometric properties
Sun protection	Swiss study on health of people with cancer, leukemia, and tumor in childhood (15) and Cambridge University Hospitals' perception of skin cancer in transplant recipients scale (16)	• 4 items • Current situation • Using sunscreen, wearing protective clothing, staying in the shade, being sensitive to the time of the day: 5-point Likert scale ranging from "1 = never" to "5 = always" • Nonadherent: not always using at least 1 of these sun protection methods	Unidimensional scale, having a Cronbach's alpha of 0.59
Diet recommendations	Investigator developed	• 5 items • 1 y • Yes/No for advice to follow a specific diet (low salt, low calorie, low saturated fats, low sugar, or other diets) and, correspondingly, a 5-point Likert scale ranging from "1 = never" to "5 = always" to evaluate adherence to each recommended diet • Nonadherent: score 1-3 on any of the 5 diets recommended by the transplant team	No available information on psychometric properties
Follow-up appointment keeping	Investigator developed	• 1 item • Previous 5 scheduled clinic appointments • No. appointments missed: 6-point scale ranging from "none" to "6 = all 5 appointments" • Nonadherent: missed ≥ 1 appointment	No available information on psychometric properties

[a] 352 HTx recipients reported not having been recommended any diet.

2.3 Statistical analysis

Frequencies and percentages (for categorical variables) or measures of central tendency and dispersion (for continuous variables) are used to describe the sample. The data were aggregated on the country level and the level of the entire sample as appropriate. The prevalence of nonadherence to each of the nonpharmacologic treatment components is presented as a percentage. To avoid over- or underrepresentation of any country's HTx recipient population, the overall nonadherence prevalence for each treatment component was calculated as a weighted average. This was accomplished by multiplying each country's nonadherence rate by a weighting factor that corresponds to the ratio of the HTx recipient population in the corresponding country to that of all included countries in the time period corresponding to that of the study's data collection in the country.

Standard deviations and ranges are used to describe between-country variability in nonadherence prevalence. Chi-square testing was used to determine the significance of this variability. After applying the Bonferroni correction to the significance level of $P < .05$ to account for multiple testing, the significance level was set at 0.008.

With one exception—alcohol use—missing data affected fewer than 10% of the cases involving the variables used to calculate nonadherence to the investigated health behaviors. Accordingly, patients with completely missing data on a health behavior of interest were excluded only from the corresponding analysis (available-case analysis). For alcohol use, missing data in the 2 variables, that is, number of drinks/week and weekly drinking frequency, were imputed using the R (version 3.4.2) programming language and the MICE (multivariate imputation by chained equations) package. For all other analyses, Stata® 15 (StataCorp LLC, College Station, TX, USA) was used.

3 RESULTS

3.1 Sample characteristics

At the 36 participating centers, of 2523 HTx recipients found eligible for inclusion, 1677 were randomly selected and invited to participate. Of this number, 244 declined and 36 died before enrollment, resulting in a final sample size of 1397 HTx recipients. Information on the sample size per country and health behavior is presented in Table 2.

Table 2. Number of heart transplant recipients with data on each of the investigated behaviors (per country and per health behavior)

	Appointment keeping	Smoking cessation	Alcohol use	Diet recommendations	Sun protection	Physical activity
Belgium (n = 74)	74	74	74	48	70	74
France (n = 160)	157	157	160	110	150	146
Germany (n = 67)	65	64	67	19	62	65
Italy (n = 111)	111	110	111	64	110	105
Spain (n = 227)	224	221	227	218	220	222
Switzerland (n = 47)	46	46	47	14	44	46
United Kingdom (n = 99)	99	99	98	28	98	96
Canada (n = 121)	116	115	120	88	116	116
USA (n = 340)	336	335	339	278	334	334
Australia (n = 51)	51	51	51	26	51	51
Brazil (n = 100)	97	97	100	71	94	85
Total sample (N = 1397)	1376	1369	1394	964[a]	1349	1340
Missing data	21	28	3	81	48	57

[a] 352 HTx recipients reported not having been recommended any diet.

Table 3 shows the main characteristics of the final HTx recipient sample, overall, and per country. Participants were 72.7% (1011) male, and on average 53.7 (SD: 13.2) years old and 3.4 (SD: 1.4) years post-HTx at time of enrollment.

Table 3. Sociodemographic and clinical characteristics of the participating heart transplant recipients

	Overall N = 1397	Europe n = 785							North America n = 461		Australia n = 51	South America n = 100
		Belgium n = 74	France n = 160	Germany n = 67	Italy n = 111	Spain n = 227	Switzerland n = 47	UK n = 99	Canada n = 121	USA n = 340	Australia n = 51	Brazil n = 100
Age, years (n)	1380	74	160	65	111	227	47	98	113	335	51	99
Mean (SD)	53.7 (13.2)	53.3 (12.6)	50.2 (13.0)	55.3 (10.3)	56.7 (12.5)	56.5 (11.7)	50.1 (14.6)	49.3 (14.8)	55 (13.4)	56.3 (12.8)	49.7 (14.2)	46.8 (13.3)
Gender (n)	1390	74	160	65	111	227	47	98	120	337	51	100
Male, n (%)	1011 (72.7%)	50 (67.6%)	121 (75.6%)	50 (76.9%)	93 (83.8%)	174 (76.7%)	32 (68.1%)	76 (77.6%)	87 (72.5%)	229 (68%)	31 (60.8%)	68 (68%)
Ethnicity (n)	1381	74	159	65	111	224	47	99	119	336	47	100
Caucasian, n (%)	1186 (85.9%)	73 (98.7%)	142 (89.3%)	65 (100%)	110 (99.1%)	205 (91.5%)	43 (91.5%)	93 (93.9%)	106 (89.1%)	251 (74.7%)	33 (70.2%)	65 (65%)
Education (n)	1377	73	158	65	111	220	47	99	119	339	50	96
Primary school, n (%)	187 (13.6%)	3 (4.1%)	10 (6.3%)	7 (10.8%)	37 (33.3%)	94 (42.7%)	5 (10.6%)	0	3 (2.4%)	3 (0.9%)	0	25 (26%)
Secondary school, n (%)	426 (30.9%)	42 (57.5%)	53 (33.5%)	6 (9.2%)	51 (46%)	60 (27.3%)	3 (6.4%)	45 (45.5%)	35 (29.4%)	71 (20.9%)	9 (18%)	51 (53.1%)
Further education, n (%)	294 (21.4%)	15 (20.6%)	64 (40.5%)	40 (61.5%)	2 (1.8%)	25 (11.4%)	32 (68.1%)	24 (24.2)	16 (13.5%)	59 (17.4%)	17 (34%)	0
University, n (%)	470 (34.1%)	13 (17.8%)	31 (19.6%)	12 (18.5%)	21 (18.9%)	41 (18.6%)	7 (14.9%)	30 (30.3%)	65 (54.6%)	206 (60.8%)	24 (48%)	20 (20.8%)
Employment status (n)	1391	74	160	65	111	226	47	99	119	339	51	100
Employed, n (%)	413 (29.7%)	18 (24.3%)	58 (36.3%)	17 (26.2%)	33 (29.7%)	27 (12%)	20 (42.6%)	37 (37.4%)	39 (32.8%)	117 (34.5%)	25 (49%)	22 (22%)
Marital status (n)	1387	74	159	65	110	227	47	97	120	337	51	100
Single, n (%)	242 (17.5%)	8(10.8%)	36 (22.6%)	8 (12.3%)	14 (12.7%)	26 (11.5%)	8 (17%)	26 (26.8%)	19 (15.8%)	60 (17.8%)	13 (25.5%)	24 (24%)
Married/cohabiting, n (%)	955 (68.9%)	56 (75.7%)	103 (64.8%)	49 (75.4%)	83 (75.5%)	158 (69.6%)	32 (68.1%)	59 (60.8%)	82 (68.3%)	234 (69.4%)	34 (66.7%)	65 (65%)

Table 3. Sociodemographic and clinical characteristics of the participating heart transplant recipients

	Overall N = 1397	Europe n = 785							North America n = 461		Australia n = 51	South America n = 100
		Belgium n = 74	France n = 160	Germany n = 67	Italy n = 111	Spain n = 227	Switzerland n = 47	UK n = 99	Canada n = 121	USA n = 340	Australia n = 51	Brazil n = 100
Divorced/separated, n (%)	149 (10.7%)	8 (10.8%)	19 (12%)	6 (9.2%)	11 (10%)	33 (14.5%)	6 (12.8%)	10 (10.3%)	11 (9.2%)	30 (8.9%)	4 (7.8%)	11 (11%)
Widowed, n (%)	41 (3%)	2 (2.7%)	1 (0.6%)	2 (3.1%)	2 (1.8%)	10 (4.4%)	1 (2.1%)	2 (2.1%)	8 (6.7%)	13 (3.9%)	0	0
Time post-HTx (n)	1395	74	160	67	111	227	47	99	121	340	49	100
Years, Mean (SD)	3.4 (1.4)	3.4 (1.2)	3.6 (1.3)	3.4 (1.4)	3.2 (1.3)	3.6 (1.3)	3.5 (1.2)	3.5 (1.2)	3.7 (1.4)	3 (1.3)	4.2 (1.3)	2.8 (1.5)
Heart failure etiology (n)	1362	74	159	65	111	226	47	93	118	328	48	93
Idiopathic	714 (52.4%)	33 (44.6%)	88 (55.4%)	33 (50.8%)	69 (62.2%)	130 (57.5%)	31 (66%)	55 (59.1%)	68 (57.6%)	144 (43.9%)	31 (64.6%)	32 (34.4%)
Ischemic	401 (29.4%)	28 (37.8%)	44 (27.7%)	23 (35.4%)	31 (27.9%)	64 (28.3%)	8 (17%)	18 (19.4%)	35 (29.7%)	128 (39%)	11 (22.9%)	11 (11.8%)
Valvular	44 (3.2%)	2 (2.7%)	10 (6.3%)	0	3 (2.7%)	15 (6.6%)	3 (6.4%)	1 (1.1%)	1 (0.9%)	4 (1.2%)	1 (2.1%)	4 (4.3%)
Congenital	45 (3.3%)	2 (2.7%)	5 (3.1%)	1 (1.5%)	3 (2.7%)	6 (2.7%)	2 (4.3%)	14 (15.1%)	5 (4.2%)	4 (1.2%)	2 (4.2%)	1 (1.1%)
Other	158 (11.6%)	9 (12.2%)	12 (7.6%)	8 (12.3%)	5 (4.5%)	11 (4.9%)	3 (6.4%)	5 (5.4%)	9 (7.7%)	48 (14.6%)	3 (6.3%)	45 (48.4%)

3.2 Overall prevalence of nonadherence to the nonpharmacologic treatment regimen

Figure 1 shows the overall unadjusted and adjusted prevalence of nonadherence to the different nonpharmacologic treatment components. Based on the adjusted values, the highest prevalence of nonadherence was observed for physical activity: 47.8% (95% CI [45.2-50.5]) of the sample were insufficiently physically active. Sun protection followed, with 39.9% (95% CI [37.3-42.5]) not always protecting themselves as recommended. Of those who were advised to follow specific diets, 38.2% (95% CI [35.1-41.3]) did not always or often follow recommendations. Heavy alcohol use was reported by 22.9% (95% CI [20.8-25.1]); 7.4% (95% CI [6.1-8.7]) were still smokers or had stopped less than 1 year prior to data collection. Appointment keeping had the lowest nonadherence prevalence, with 5.7% (95% CI [4.6-6.9]) missing at least one of their prior five outpatient clinic appointments.

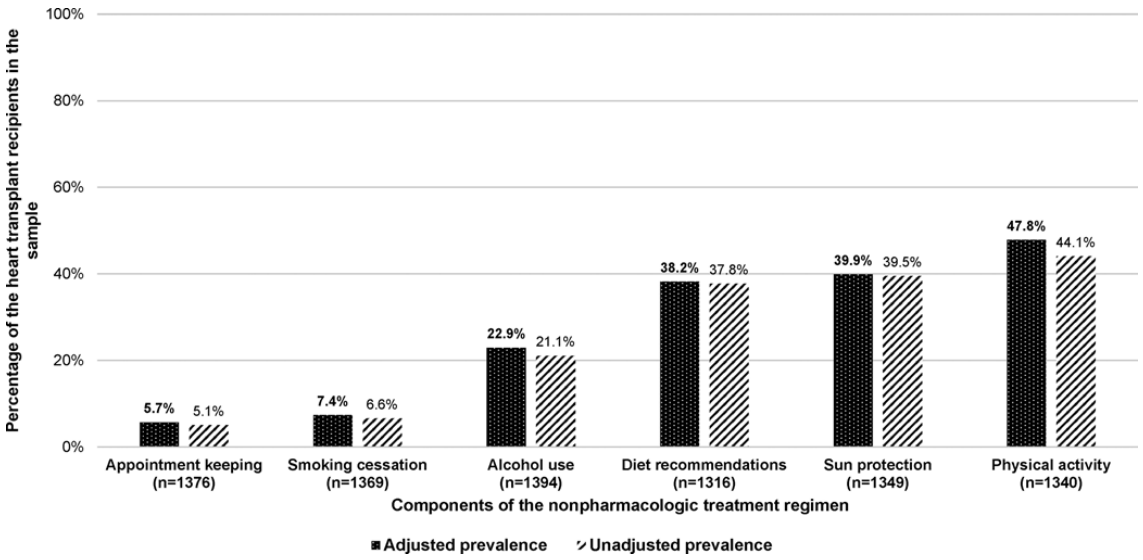

Figure 1 The adjusted and unadjusted overall prevalence of nonadherence to the nonpharmacologic treatment regimen

3.3 Between-country variability in nonadherence prevalence

Figure 2 shows the between-country variability in the prevalence of nonadherence to each of the investigated health behaviors. The largest variability (SD: 13.6%) was observed in heavy alcohol use, which ranged from 2% in Brazil to 42.9% in the UK. This was followed by variability in nonadherence to sun protection (SD: 9.5%): 24.1% of Spanish HTx recipients did not always use sun protection as opposed to 51.4% in Belgium, which had the highest prevalence. Variability in insufficient physical activity (SD: 8.5%) came third, with Spain's participants having the lowest rate (32%) and France's the highest (59.6%). Diet nonadherence came fourth (SD: 7.1%), varying from 26.6% (Spain) to 48.2% (USA). In Australia, no HTx recipients reported nonadherence to smoking cessation, while this number was 12.7% in France, with relatively low variability between countries (SD: 4%). Nonadherence to appointment keeping had the lowest variability (SD: 2.9%) ranging from 3% (UK) to 11.8% (Australia).

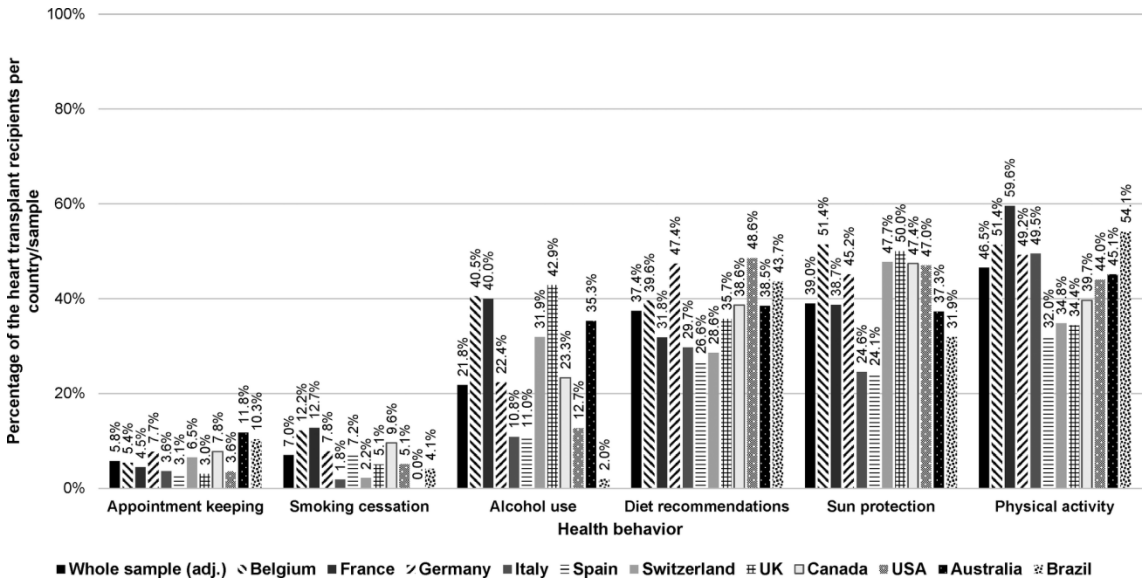

Figure 2 Behavior-wise investigation of the variability in nonadherence prevalence between countries

Table 4 shows that the observed variability was statistically significant for all behaviors except appointment keeping. Figure 3 depicts each behavior's nonadherence prevalence per country, indicating which behaviors are least and most problematic within each country.

Table 4. Chi-square test results for the between-country variability within each health behavior (showing nonadherence rates)

	Appointment keeping		Smoking cessation		Alcohol use		Diet recommendations		Sun protection		Physical activity	
	Adherent	Not adherent	Adherent	Not adherent	Adherent	Not adherent	Adherent	Not adherent	Adherent	Not adherent	Adherent	Not adherent
Belgium	70 (94.6%)	4 (5.4%)	65 (87.8%)	9 (12.2%)	44 (59.5%)	30 (40.5%)	29 (60.4%)	19 (39.6%)	34 (48.6%)	36 (51.4%)	36 (48.6%)	38 (51.4%)
France	150 (95.5%)	7 (4.5%)	137 (87.3%)	20 (12.7%)	96 (60%)	64 (40%)	75 (68.2%)	35 (31.8%)	92 (61.3%)	58 (38.7%)	59 (40.4%)	87 (59.6%)
Germany	60 (92.3%)	5 (7.7%)	59 (92.2%)	5 (7.8%)	52 (77.6%)	15 (22.4%)	10 (52.6%)	9 (47.4%)	34 (54.8%)	28 (45.2%)	33 (50.8%)	32 (49.2%)
Italy	107 (96.4%)	4 (3.6%)	108 (98.2%)	2 (1.8%)	99 (89.2%)	12 (10.8%)	45 (70.3%)	19 (29.7%)	83 (75.5%)	27 (24.5%)	53 (50.5%)	52 (49.5%)
Spain	217 (96.9%)	7 (3.1%)	205 (92.8%)	16 (7.2%)	202 (89%)	25 (11%)	160 (73.4%)	58 (26.6%)	167 (75.9%)	53 (24.1%)	151 (68%)	71 (32%)
Switzerland	43 (93.5%)	3 (6.5%)	45 (97.8%)	1 (2.2%)	32 (68.1%)	15 (31.9%)	10 (71.4%)	4 (28.6%)	23 (52.3%)	21 (47.7%)	30 (65.2%)	16 (34.8%)
United Kingdom	96 (97%)	3 (3%)	94 (94.9%)	5 (5.1%)	56 (57.1%)	42 (42.9%)	18 (64.3%)	10 (35.7%)	49 (50%)	49 (50%)	63 (65.6%)	33 (34.4%)
Canada	107 (92.2%)	9 (7.8%)	104 (90.4%)	11 (9.6%)	92 (76.7%)	28 (23.3%)	54 (61.4%)	34 (38.6%)	61 (52.6%)	55 (47.4%)	70 (60.3%)	46 (39.7%)
USA	324 (96.4%)	12 (3.6%)	318 (94.9%)	17 (5.1%)	296 (87.3%)	43 (12.7%)	143 (51.4%)	135 (48.6%)	177 (53%)	157 (47%)	187 (56%)	147 (44%)
Australia	45 (88.2%)	6 (11.8%)	51 (100%)	0 (0%)	33 (64.7%)	18 (35.3%)	16 (61.5%)	10 (38.5%)	32 (62.7%)	19 (37.3%)	28 (54.9%)	23 (45.1%)
Brazil	87 (89.7%)	10 (10.3%)	93 (95.9%)	4 (4.1%)	98 (98%)	2 (2%)	40 (56.3%)	31 (43.7%)	64 (68.1%)	30 (31.9%)	39 (45.9%)	46 (54.1%)
Chi-square test results	$\chi^2(10, N = 1376) = 17.91$, $P = .056$		$\chi^2(10, N = 1369) = 27.11$, $P = .003$		$\chi^2(10, N = 1394) = 146.21$, $P < .001$		$\chi^2(10, N = 964) = 31.22$, $P = .001$		$\chi^2(10, N = 1349) = 56.24$, $P < .001$		$\chi^2(10, N = 1340) = 40.67$, $P < .001$	

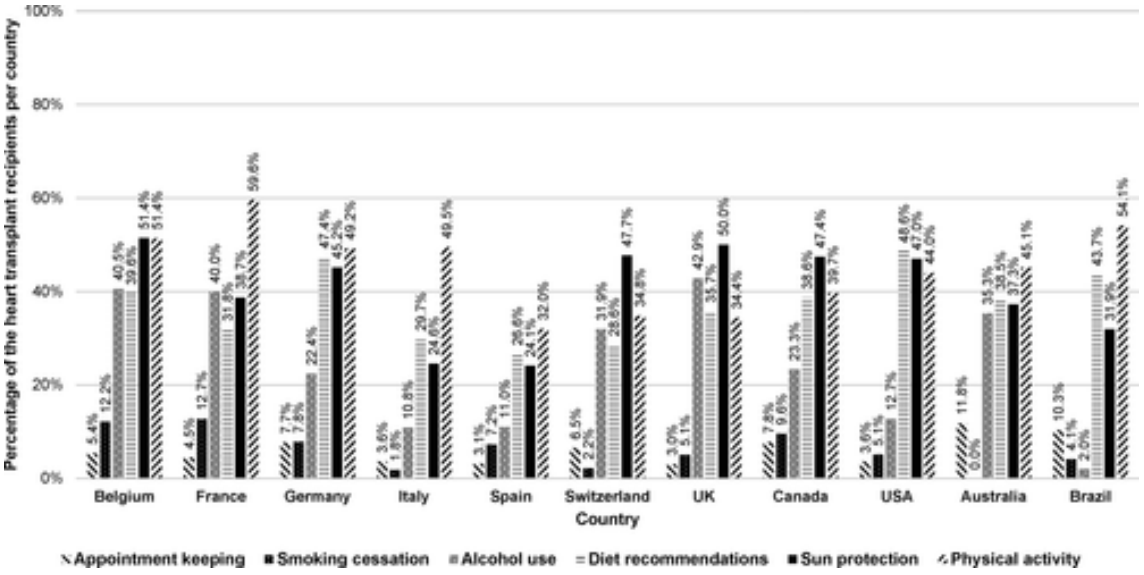

Figure 3 Country-wise investigation of nonadherence prevalence

4 DISCUSSION

This study is the largest ever to investigate the prevalence of nonadherence to various nonpharmacologic components of the post-HTx regimen in the same sample. Its multinational setup allows examination of intercountry variability in nonadherence prevalence.

The highest overall prevalence of nonadherence was noted for physical activity: 44.1% (observed/unadjusted rate)—more than double the prevalence in the general global adult population (23%).[17] As insufficient activity is a major risk factor for several chronic diseases,[17] including those that HTx recipients are at a higher risk of developing due to lifelong immunosuppressant intake, HTx recipients would benefit from interventions promoting physical activity. A meta-analysis[18] of 10 RCTs showed that cardiac rehabilitation programs could improve exercise capacity; however, most included studies focused on the immediate post-transplant period and did not investigate the programs' possible spin-off effects, for example, higher physical activity levels in daily life. That is, physical activity is a poorly investigated domain in HTx.

Next, 39.5% of our sample did not always apply sun protection when needed. As the prevalence of skin cancer in adult HTx recipients is 9.5% and 18.4% at 5 and 10 years post-HTx,[19] respectively, strategies that boost sun protection use may help to prevent skin cancer. Unfortunately, research on such interventions within transplantation is still in its infancy.

The third highest nonadherence prevalence was for diet (37.8%). Poor dietary habits, for example, high caloric intake, can lead to overweight and obesity, which increase the burden of chronic illness in the general population[20] (eg, diabetes and hypertension). Yet, the question of whether overweight and obesity negatively impact post-HTx clinical outcomes also remains controversial. Most studies focusing on body mass index (BMI) at time of transplant have found an elevated risk for graft loss and mortality in HTx recipients with morbid obesity only (BMI > 35), but not in groups having a low BMI at transplantation.[21] Still, many patients gain weight post-HTx: one prospective registry study[22] reporting overweight and obesity in, respectively, 37% and 13.6% of patients at 3 years after HTx, which might ultimately elevate the risk for chronic disease. Unfortunately, few dietary interventions have been tested in transplant patients, leaving ample room for new evidence on how to effectively support healthy eating in HTx recipients.[23]

Fourth, heavy alcohol use was observed in 21.1% of the participants. One might argue that we used a very stringent definition; however, we followed CDC guidelines,[14] which state that exceeding the specified limit increases the risk for over 200 diseases and injuries, including liver disease, cardiovascular disease, and some forms of cancer.[24] Unfortunately, alcohol-related research in transplantation focuses predominantly on liver transplant patients: the HTx literature is sparse. It remains unclear whether heavy alcohol use after HTx will affect graft or patient survival.

Fifth, 6.6% of our sample smoked post-transplant. While in line with previously reported numbers,[7, 25] this prevalence is presumably underestimated, bearing in mind that we used self-report to document smoking.[26] Given that post-transplant smoking significantly reduces graft and patient survival,[27,28] we recommend that HTx programs regularly assess patients' smoking status via more objective means, for example, exhaled CO measurement, and should implement effective smoking cessation programs.[28]

Finally, appointment nonadherence was observed in 5.1% of the sample, which is similar to previously reported numbers.[7,29] Although the prevalence is relatively low, missing scheduled clinic visits after HTx is a risk factor for poor medication adherence, which elevates the risk for late acute rejections.[29] Therefore, transplant programs should do their best to reach out to HTx recipients who might miss or drop out of follow-up care.

In addition, we observed significant intercountry variability in nonadherence prevalence. The reasons behind this are open to speculation. For example, alcohol use at social occasions might be more common and acceptable in some countries. Likewise, patients might wrongfully assume that sun protection is less important in countries with cooler temperatures or fewer hours of sunshine. Summarizing the evidence on possible factors of nonadherence prevalence variability between countries for each studied behavior is beyond the scope of this paper. Based on these examples, however, it is clear that not only individual patient characteristics, but also factors related to the patients' communities, healthcare providers, healthcare settings or policies, or cultural aspects might contribute to the observed differences. Therefore, future studies should use a multilevel approach to understand variability,[11] incorporating all potentially relevant correlates of each relevant health behavior at the patient-, micro-, meso-, and macro-levels into a single model.

4.1 Limitations and strengths of the study

First, nonadherence was measured through self-report. Given the multitude of variables collected in the main study, the large sample size, and the multinational nature of the study, this was unavoidable. Second, the cutoff points used to categorize patients as adherent/nonadherent were chosen based on criteria that might not be clinically meaningful for the HTx recipient population. This was necessary in the absence of recommendations regarding appropriate levels of the investigated health behaviors for HTx recipients. Third, HTx recipients were recruited and data collected during follow-up clinic visits. This might have skewed certain results, for example, regarding appointment nonadherence, due to the possibility of including more adherent participants. Fourth, centers participated on a voluntary basis and could only participate if they performed at least 10 procedures, on average, per year. Smaller centers might organize follow-up care differently or might lack the experience or resources to monitor adherence or lifestyle factors, possibly resulting in higher nonadherence rates than those documented in the present paper. Finally, the design of the study was cross-sectional, giving a static rather than a dynamic picture of nonadherence over time.[30]

Strengths include our large multinational sample. Moreover, studying all nonpharmacologic components of the post-transplant regimen in the same patients is unique and allows a clear understanding of the corresponding adherence issues in HTx recipients. The use of random sampling at the patient level, applying the same nonadherence measures and operational definitions and our adjustment of prevalence rates to ensure appropriate representativeness of each country in relation to the entire sample (based on its HTx recipient population) further strengthens our belief that the numbers presented in this paper accurately depict the magnitude of the problem.

To summarize, HTx recipients' nonadherence to the nonpharmacologic components of the treatment regimen appears to be a major problem. By displaying the prevalence by behavior as well as by country, we hope our results will help clinicians prioritize their needs regarding tailored adherence-enhancing interventions.

CONFLICT OF INTEREST

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APPENDIX :

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