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Self-Reported Questionnaire Detects Family History of Cancer in a Pancreatic Cancer Screening Program

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer death; approximately 5–10% of PDAC is hereditary. Self-administered health history questionnaires (HHQs) may provide a low-cost method to detail family history (FH) of malignancy. Pancreas Center patients were asked to enroll in a registry; 149 with PDAC completed a HHQ which included FH data. Patients with FH of PDAC, or concern for inherited PDAC syndrome, were separately evaluated in a Prevention Program and additionally met with a genetic counselor (GC) to assess PDAC risk (n=61). FH obtained through GC and HHQ were compared using Wilcoxon signed-rank sum and generalized linear mixed models with Poisson distribution. Agreement between GC and HHQ risk-assessment was assessed using kappa (κ) statistic. In the Prevention Program, HHQ was as precise in detecting FH of cancer as the GC (all $p>0.05$). GC and HHQ demonstrated substantial agreement in risk-stratification of the Prevention Program cohort ($\kappa = 0.73$, 95% CI 0.59–0.87.)

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Conflict of Interest: Author Lucas, Author Tarlecki, Author Van Beck, Author Lipton, Author Levinson, Author Kumar, Author Chung, Author Frucht and Author Genkinger declare that they have no conflict of interest.

The sensitivity of the HHQ to detect a patient at elevated risk (i.e., moderate- or high-risk) of PDAC, compared to GC, was 82.9% (95% CI 67.3%–92.3%) with a specificity of 95% (95% CI 73.1%–99.7%). However, seven patients who were classified as average-risk by the HHQ were found to be at an elevated-risk of PDAC by the GC. In the PDAC cohort, 30/149 (20.1%) reported at least one first-degree relative (FDR) with PDAC. The limited sensitivity of the HHQ to detect patients at elevated risk of PDAC in the Prevention Program cohort suggests that a GC adds value in risk-assessment in this population. The HHQ may offer an opportunity to identify high-risk patients in a PDAC population.

Keywords

genetic counselor; health history questionnaire; pancreatic cancer; pancreatic ductal adenocarcinoma; hereditary pancreatic cance

BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of death from cancer in the United States, with 53,070 new diagnoses and 41,780 deaths in 2016(“American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016.,”). Surgical resection offers the only opportunity for cure, yet only 20% of patients are eligible for resection at the time of diagnosis. (Spanknebel & Conlon, 2001) Overall 5-year survival is a dismal 6%, but those with localized disease have 5-year survival of 24%.(Siegel, Ma, Zou, & Jemal, 2014) Furthermore, patients with small (<1 cm), asymptomatic, lymph node negative PDACs have 5-year survival rates of 58–69%.(Egawa et al., 2004; Ishikawa et al., 1999) The lifetime incidence of PDAC in the general population is approximately 1.5% (1 in 67). (Siegel et al., 2014) While tobacco,(Iodice, Gandini, Maisonneuve, & Lowenfels, 2008) obesity,(Arslan et al., 2010) heavy alcohol use,(Lucenteforte et al., 2012; Michaud et al., 2010) and diabetes(Ben et al., 2011) have been identified as contributors to development of PDAC, modeling PDAC risk in the average-risk population is not sufficiently discriminative to inform clinical prediction models.(Klein et al., 2013)

However, approximately 5–10% of PDAC has a hereditary component.(Klein, Hruban, Brune, Petersen, & Goggins, 2001; Shi, Hruban, & Klein, 2009) Certain patient populations are at higher risk of PDAC, including those with the breast-ovarian cancer syndrome (*BRCA1*/*2* mutations),(Couch et al., 2007; Hahn et al., 2003; Lucas et al., 2014; Lucas et al., 2013; Murphy et al., 2002; Thompson & Easton, 2002) hereditary pancreatitis (HP), (Applebaum-Shapiro et al., 2001; Howes et al., 2004) Peutz-Jeghers syndrome (PJS), (Giardiello et al., 2000) familial atypical multiple mole melanoma (FAMMM),(Goldstein, 2004; Lynch, Fusaro, Lynch, & Brand, 2008; Vinarsky et al., 2009) and Lynch Syndrome. (Kastrinos et al., 2009; Umar et al., 2004) The remainder of familial PDAC (FPC) may be due to yet unidentified genetic risk factors, shared environmental exposures, or other non-genetic causes, and thus the mainstay of assessing PDAC risk remains family history (FH). (Canto, Harinck, et al., 2012) High-risk individuals (HRIs) are those with ≥ 2 family members with PDAC, (Klein et al., 2004) or gene mutations associated with PDAC, and are at considerable risk for disease. (Axilbund & Wiley, 2012; Becker, Hernandez, Frucht, &

Lucas, 2014) Several institutions have initiated research screening programs for HRIs for PDAC, and have demonstrated the ability to detect early stage cancers and premalignant pancreatic lesions that are amenable to curative surgical therapy.(Brentnall, Bronner, Byrd, Haggitt, & Kimmey, 1999; Canto, Hruban, et al., 2012; Verna et al., 2010) Consensus-based guidelines recommend screening certain HRIs for PDAC in conjunction with a research protocol(Canto, Harinck, et al., 2012), and recent modeling studies have suggested that this approach may be cost-effective in certain patient populations with an elevated risk of PDAC. (Pandharipande et al., 2015)

Self-administered health history questionnaires (HHQs) may provide a low-cost method to obtain detailed personal and FH of medical problems, including malignancy. Prior to genetic testing, patients often meet with a genetic counselor (GC) to construct a detailed pedigree to conduct risk assessment and determine appropriateness of genetic testing to modify that risk. This type of detailed pedigree analysis remains costly and labor intensive, and is likely not cost-effective to screen all patients regardless of risk stratification.(Buchanan et al., 2015; Trepanier & Allain, 2014) We sought to determine if there was agreement between the HHQs and pedigrees obtained by the GC in a cohort of patients felt to be at high-risk of developing PDAC, and further if these HHQs could be used to select patients with a familial predisposition in both the high-risk population and the PDAC population.

METHODS

Study Participants

The Pancreas Center is a multi-disciplinary center that focuses on pancreatic diseases, including PDAC. At the Pancreas Center, patients diagnosed with disease such as PDAC are evaluated for surgical resection and medical treatment. Additionally, healthy asymptomatic patients with 1) a FH of PDAC or 2) a gene mutation that predisposes to PDAC are also seen at the Pancreas Center in the Pancreatic Cancer Genetics and Prevention Program (“Prevention Program”). Patients are either self-referred to the Prevention Program because they have a family member with PDAC or a gene mutation associated with PDAC, or they are referred from other local providers. When all patients present to the Pancreas Center for evaluation, they are asked to enroll in an Institutional Review Board-approved registry which was designed to study risk for and outcomes from pancreatic diseases. All PDAC and Prevention Program patients who presented to the Pancreas Center between January 2006 and January 2012 and completed a health history questionnaire (HHQ) were eligible for inclusion in the study. The only exclusions were patient refusal to provide informed consent. and non-PDAC diagnoses in surgical patients (e.g., pancreatic cysts.)

Study Procedures

PDAC patients and Prevention Program patients who enrolled were asked to complete a HHQ as part of the registry. This HHQ included detailed demographic and medical information including gender, age, race, religion, history of smoking, alcohol consumption, height, weight, and medical history (e.g., history of diabetes, history of pancreatitis). The patients also filled out the history of cancer of their first-, second- and third-degree relatives, noting the type of cancer and the age of onset on the FH of cancer section of the HHQ. The

HHQ requests detailed information for all parents, grandparents, children and siblings regardless of cancer history in these relatives. For aunts, uncles, cousins, grandchildren and other second- or third-degree relatives with a history of cancer, the questionnaire asks individuals to describe the relationship (e.g., cousin), type of cancer, and age at diagnosis. The total number of unaffected aunts, uncles, cousins, grandchildren and other second- or third-degree relatives was not obtained through the HHQ.

Patients referred to the "Prevention Program" who were enrolled in the registry additionally met with a clinician and GC to assess PDAC risk. During this session, a detailed FH is collected by the GC. A three-generation pedigree was created that included gender, age, ethnicity, and tobacco history. The GC documented the history and type of cancer as well as the age of diagnosis for the patient as well as all their relatives. Family history of cancer was self-reported. These data were extracted from the pedigrees and entered into the dataset in de-identified fashion. Genetic testing was ordered by the GC and the clinician provider at their discretion. Clinical *BRCA1/2* testing included testing for the 3 Ashkenazi Jewish founder mutations or comprehensive sequencing of both *BRCA1* and *BRCA2* with the *BRCA1* 5-site rearrangement panel performed for non-Ashkenazi Jewish patients. Genetic testing for Lynch syndrome, Peutz-Jeghers syndrome, HP and FAMMM was performed at the discretion of the clinician and GC. Genetic testing for partner and localizer of *BRCA2* (*PALB2*), ataxia telangiectasia (*ATM*), and multi-gene panel testing were not clinically available during the study period.

Patients who were initially evaluated in the Prevention Program were risk-stratified into average-, moderate- and high-risk of pancreatic cancer based on their personal and FH obtained by the GC according to institutional protocol.(Verna et al., 2010) Genetic testing results, if available, were incorporated into the risk-stratification. Average-risk patients were defined as 1) patients with only one family member with PDAC over the age of 55 years, or 2) patients without a FH of PDAC or genetic mutation predisposing to PDAC. Moderate-risk subjects included those with 1) at least two first-, second-, or third-degree relatives with PDAC, 2) patients with one first-degree relative (FDR) with PDAC at an age younger than 55, or 3) not otherwise meeting criteria for high-risk. High-risk patients included those with 1) two or more FDRs with PDAC, 2) at least three first-, second-, or third-degree relatives with PDAC, 3) one FDR and a second-degree relative with PDAC if one PDAC occurred at age <55, or 4) those who had a genetic mutation that was known to be associated with PDAC during the study period (e.g., *BRCA1*, *BRCA2*, FAMMM, Lynch syndrome, and Peutz-Jeghers syndrome.) If the age at PDAC diagnosis in a family member was unknown, we took a conservative approach and assumed the age to be >55 years.

Data Analysis

Means and frequencies were calculated for demographic and clinical data, as appropriate. In the Prevention Program, we assessed the differences in number of relatives documented and number of relatives with cancers between GC and HHQ using the Wilcoxon signed rank-sum test and generalized linear mixed models with Poisson distribution. (Brown & Prescott, 2015) Agreement between GC and HHQ risk assessment (e.g., average-, moderate- or high-risk for PDAC) was assessed using kappa (κ) statistic and weighted κ statistic. κ statistics

were rated according to Landis and Koch, with a κ value as over .81 is almost perfect agreement, .61 to .80 as substantial agreement, and .41-.60 as moderate agreement.(Landis & Koch, 1977) Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) for the HHQ were calculated using the GC pedigree as the reference. Statistical analyses were performed using SAS 9.3 (Cary, North Carolina). (“ SAS Institute Inc. 2011. SAS® 9.3 System Options: Reference, Second Edition. Cary, NC: SAS Institute Inc.,”) This study was approved by the Columbia University Institutional Review Board.

RESULTS

Prevention Program

A total of 61 patients evaluated in the Prevention Program had both a HHQ and GC pedigree available for analysis (Table 1). Thirty two (52.46%) patients were female, 59 (96.72%) were Non-Hispanic White, and the mean age was 54.9 years with a range of 26 to 79 years. In the Prevention Program cohort, no significant differences were found for the number of affected first-, second-, or third-degree relatives when ascertained by the GC compared to the HHQ (p-value for Wilcoxon signed-rank sum >.05 and p-value for generalized linear mixed model >.05) (Table 2). Compared to the HHQ, the GC documented a greater number of total second- and third-degree relatives, as well as a greater number of unaffected second- and third-degree relatives (p-value for Wilcoxon signed-rank sum <0.001 and p-value for generalized linear mixed model <.001).

Pedigrees obtained by the GC in the Prevention Program cohort revealed 20 (32.8%) average-risk, 19 (31.2%) moderate-risk, and 22 (36.1%) high-risk subjects. The HHQs classified 26 (42.6%) at average risk of PDAC, 17 (27.9%) at moderate-risk, and 18 (29.5%) subjects at high-risk of PDAC (Table 3). Using the GC as the gold standard, the sensitivity of the HHQ to detect a subject at elevated risk (i.e., moderate- or high-risk) of PDAC was 82.9% (95% CI, 67.3%–92.3%), with a specificity of 95.0% (95% CI, 73.1%–99.7%), PPV of 97.1% (95% CI, 83.3%–100.0%), and NPV of 73.1% (95% CI, 51.9%–87.6%). Seven patients who were classified as average-risk by the HHQ were found to be at an elevated-risk (i.e., moderate- or high-risk) of PDAC by the GC (Table 3.) Substantial agreement was demonstrated between GC and HHQ risk-level assessment of pedigrees (κ 0.73 [95% CI 0.59–0.87], weighted κ 0.71 [95% CI 0.54–0.87).

PDAC Cohort

A total of 149 PDAC patients completed HHQs. In this cohort, 57 (38.3%) were female, 140 (94.0%) were Non-Hispanic White, and the mean age was 65.6 years with a range of 37 to 87 years (Table 1).Three PDAC subjects reported a personal history of breast cancer, 6 had a personal history of prostate cancer, and 4 had a personal history of colorectal cancer on the HHQ. Supplemental Table 1 details FH of cancer reported by HHQ in PDAC subjects. No PDAC patients were found to be at high-risk of PDAC prior to their own diagnosis based on their HHQ pedigree, 13 patients (8.7%) were identified at moderate-risk of PDAC through the use of an HHQ, and 17 (11.4%) patients had a FDR with PDAC over the age of 55 based on the HHQ pedigree.

DISCUSSION

Practice Implications

To our knowledge, this is the first study to demonstrate the reliability of self-reported HHQ to detect a FH of cancer in a PDAC Prevention Program. No differences were observed for the number of affected first-, second-, or third-degree relatives when ascertained by the GC compared to the HHQ. Significant differences were reported in total number of second- and third-degree relatives and the number of second- and third-degree relatives without of cancer, which is expected because GCs typically document more second- and third-degree relatives compared with HHQ.

Since approximately 90% of PDACs are sporadic(Klein et al., 2001) and the cost of GC assessment of all PDAC patients is prohibitive, it is important to find a valid and accurate measure of family history to adequately identify those at risk and provide the appropriate screening protocols(Canto, Harinck, et al., 2012; Lucas et al., 2014). In the PDAC cohort, 13 patients (8.7%) were stratified as moderate-risk of PDAC and an additional 17 patients (11.4%) were noted to have a FDR with PDAC at age >55, which is consistent with previous studies suggesting that up to 16% of PDAC patients have a FH of the disease. (Klein et al., 2001) Even though in the Prevention Program the GC had superior sensitivity for detecting increased risk of PDAC, the HHQ may provide an opportunity to select PDAC patients for GC referral. Family members of these PDAC patients (30/149, or 20.1% of the cohort) may also be eligible for PDAC screening under current guidelines. (Canto, Harinck, et al., 2012; Lucas et al., 2014; Verna et al., 2010)

At our center during the study period, average-risk patients were not offered PDAC screening. Moderate-risk patients were offered either Endoscopic Ultrasound (EUS) or Magnetic Resonance Imaging (MRI), and high-risk patients were offered both examinations to image the pancreas according to protocol.(Verna et al., 2010) It is important to note that screening and surveillance practices at other institutions may differ from the protocol described in this manuscript(Brentnall et al., 1999; Canto, Harinck, et al., 2012; Canto, Hruban, et al., 2012; Vasen et al., 2016). The low prevalence of moderate- and high-risk subjects in the surgical cohort does not warrant use of a GC in all PDAC diagnoses. However, those identified by HHQ with family histories suggestive of a genetic or inherited predisposition may benefit by assessment with a GC and Prevention Program clinician. (Lucas et al., 2014) Further analyses of this cohort, including a possible intervention for high-risk family members of these PDAC patients, are warranted.

Even when presenting to the Prevention Program with an awareness of PDAC risk, some patients shifted risk classification based on assessment of FH cancer by a GC. Importantly, seven Prevention Program patients were misclassified as average-risk by the HHQ while the GC identified them as elevated-risk. In this high-risk population with a 57.1% (35/61) prevalence of increased-risk, the sensitivity of a HHQ to detect a FH of cancer is 82.9% with a NPV of 73.1%. The value of a GC in the Prevention Program cohort may be to detect non-pancreatic cancers which may place the patient at an elevated risk of PDAC due to a genetic syndrome, or suggest that genetic testing may be a useful adjunct to PDAC risk stratification.(Lucas et al., 2014)

Study Limitations

It is important to note that average-risk patients in the Prevention Program are not likely to be truly representative of an average-risk cohort. All average-risk patients in the Prevention Program had at least one family member with PDAC, albeit at an age over 55. Other environmental or lifestyle factors, such as tobacco or heavy alcohol use, may have contributed to the development of PDAC or other cancers in these family members(Genkinger et al., 2009; U.S. Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, 2014). These risk factors were not assessed in this analysis, and currently have limited clinical utility in predicting PDAC risk (Klein et al., 2013). It is also possible that some of these patients had an undefined inherited PDAC syndrome, yet were risk-stratified as average-risk because their family member with PDAC was diagnosed at an age over 55 years. The majority of patients in the Prevention Program have either been self-referred or referred by another clinician for specific evaluation of PDAC risk; this likely explains the near uniform agreement between GC and HHQ pedigrees for PDAC even to more distant blood relatives.

If a patient met with a GC before completing the HHQ, this may alter our findings. HHQs were mailed to patients prior to the office visit. However, if the HHQ was not completed prior to the office visit, the patients were allowed to take it home to complete, and return at a later date. We would expect that the HHQ is improved after a thorough review of the pedigree with the GC, which may bias our results toward the null, and demonstrate that the HHQ is similar to the GC assessment in detecting PDAC risk. Similarly, the sensitivity of a GC's pedigree may be improved if the patient has had time to think about their FH while completing the HHQ. Future studies may include varying whether the HHQ or GC pedigree was completed first, as well as assessment of the time and cost of each method, in order to better understand the cost-benefit relationship between these methods.

Conclusions

In summary, we demonstrate that HHQ can reliably identify FH of cancer in a PDAC Prevention Program when compared to GC assessment. While substantial agreement is described between GC and HHQ risk-stratification in a PDAC Prevention Program, the limited sensitivity and negative predictive value of a HHQ to detect patients at elevated risk of PDAC in this cohort suggests that a GC is valuable in risk-assessment of Prevention Program patients. Use of an HHQ in a PDAC cohort may offer an opportunity to identify high-risk patients and families.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Human Studies and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The study was approved by the Institutional Review Board of Columbia University.

Table 1

Demographic data for study population

	Prevention Program Patients n (%)		Surgical Patients n (%)
	HHQ	**GC**	**HHQ**
Gender			
Female	33 (54.1%)	33 (54.1%)	57 (38.3%)
Male	28 (45.9%)	28 (45.9%)	92 (61.7%)
Age			
Mean	54.9	54.4	65.6
Range	26–79	26–79	37–87
Median	56	55	66
SD	12.1	12.2	9.8
Race			
Non-Hispanic White	59 (96.7%)	56 (91.8%)	140 (94.0%)
Hispanic White	0 (0%)	1 (1.6%)	4 (2.9%)
Black	1 (1.6%)	1 (1.6%)	3 (2.0%)
Other	1 (1.6%)	2 (3.9%)	2 (1.3%)
Unknown	0 (0%)	1 (1.6%)	0 (0%)
Religion			
Ashkenazi Jewish	27 (44.3%)	34 (55.7%)	32 (21.5%)
Catholic	13 (21.3%)	2 (3.3%)	70 (47.0%)
Protestant	6 (9.8%)	0 (0%)	16 (10.7%)
Muslim	0 (0%)	0 (0%)	0 (0%)
Hindu	0 (0%)	0 (0%)	1 (0.7%)
Buddhist	2 (3.3%)	0 (0%)	1 (0.7%)
Other	13 (21.1%)	0 (0%)	29 (19.5%)
Unknown	0 (0%)	25 (41.0%)	0 (0%)
Smoking			
Current Smoker	2 (3.3%)	7 (11.5%)	13 (8.7%)
Former Smoker	32 (52.5%)	22 (36.1%)	75 (50.3%)
Non-Smoker	27 (44.3%)	32 (52.5%)	60 (40.3%)
Unknown	0 (0%)	0 (0%)	1 (0.7%)
Alcohol Consumption			
None	34 (55.7%)	14 (23.0%)	94 (63.1%)
0–2 Drinks/Day	26 (42.6%)	45 (73.8%)	49 (32.9%)
3–4/Day	1 (1.6%)	2 (3.3%)	3 (2.0%)
4+/Day	0 (0%)	0 (0%)	2 (1.3%)
Unknown	0 (0%)	0 (0%)	1 (0.7%)

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Table 2

Genetic Counselor (GC) compared with Health History Questionnaire (HHQ) assessment of family history by cancer type and relative degree for the 61 patients in Prevention Program.

			Wilcoxon Signed Rank-Sum	Generalized Linear Mixed Models	
Cancer Type	**GC**	**HHQ**	**p-value**	**i(β)**	**p-value**
First Degree Relative					
Total Relatives Documented	333	339	0.47	0.02	0.82
Pancreas	50	52	0.50	0.00	>0.99
Breast	12	12	>0.99	0.00	>0.99
Ovarian	5	4	>0.99	−0.22	0.74
Prostate	6	5	>0.99	−0.18	0.76
Colorectal	1	1	N/A[#]	N/A[#]	N/A[#]
Other	21	22	>0.99	0.11	0.68
No Cancer	228	238	0.55	0.04	0.64
Second Degree Relative					
Total Relatives Documented	847	581	<0.0001[@]	−0.38	<0.001[@]
Pancreas	21	22	>0.99	0.03	0.90
Breast	18	18	>0.99	−0.04	0.89
Ovarian	8	5	0.45	0.00	>0.99
Prostate	8	9	>0.99	0.12	0.81
Colorectal	11	11	>0.99	−0.08	0.84
Other	34	32	0.73	0.14	0.46
No Cancer	710	446	<0.0001[@]	−0.46	<0.001[@]
Third Degree Relative					
Total Relatives Documented	828	122	<.0001[@]	−1.61	<0.001[@]
Pancreas	8	3	0.50	−0.81	0.18
Breast	9	9	>0.99	−0.24	0.55
Ovarian	2	2	>0.99	0.00	>0.99
Prostate	2	3	>0.99	−0.51	0.49
Colorectal	9	3	0.13	−0.92	0.13

			Wilcoxon Signed Rank-Sum	Generalized Linear Mixed Models	
Cancer Type	**GC**	**HHQ**	**p-value**	**i(β)**	**p-value**
Other	15	14	>.99	0.23	0.45
No Cancer	766	71	<0.0001@	−2.04	<0.001@

@Significant values were reported, due to the observation that GCs typically document more second- and third-degree relatives compared with HHQ.

#Unable to assess

Table 3

Genetic Counselor and Health History Questionnaire Demonstrate Substantial Agreement in Risk Stratification of Prevention Program Patients.

Genetic Counselor	Health History Questionnaire		
	Average-Risk (n = 26)	**Moderate-Risk (n = 17)**	**High-Risk (n = 18)**
Average-Risk (n = 20)	19	1	0
Moderate-Risk (n = 19)	4	14	1
High-Risk (n = 22)	3	2	17

Seven patients were classified by Health History Questionnaire (HHQ) as Average-Risk, while the Genetic Counselor (GC) classified as Moderate-Risk (n = 4) or High-Risk (n= 3). Substantial agreement was demonstrated between GC and HHQ (κ = 0.73 [95% CI 0.59–0.87], weighted κ = 0.71 [95% CI 0.54–0.87]).