

Ischemia with no obstructive coronary artery disease (INOCA): A patient self-report quality of life survey from INOCA international

Martha Gulati^{a,*}, Najah Khan^b, Maria George^c, Colin Berry^d, Alaide Chieffo^e, Paolo G. Camici^f, Filippo Crea^g, Juan-Carlos Kaski^h, Mario Marzilliⁱ, C. Noel Bairey Merz^a

^a Barbra Streisand Women's Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, USA

^b Houston Methodist Hospital, Houston, TX, USA

^c INOCA International, Glasgow, UK

^d British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

^e San Raffaele Hospital, Milan, Italy

^f San Raffaele Hospital and Vita-Salute University, Milan, Italy

^g Catholic University of the Sacred Heart, Rome, Italy

^h Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK

ⁱ University of Pisa, Pisa, Italy

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ABSTRACT

Background: There is limited information available regarding evidence of ischemia with no obstructive coronary arteries (INOCA) and quality of life.

Purpose: To determine associations between INOCA and self-reported physical, social, and mental health.

Methods: We conducted a survey of all members (n = 1579) of the INOCA International patient support group. Current self-reported diagnosis and health measures were collected. Functional capacity was retrospectively estimated using the Duke Activity Status Index (DASI), assessing levels of activities performed prior and after symptom onset.

Results: A total of 297 (20.8% response rate, 91% women) reported symptoms of chest pain, pressure, or discomfort in 92.9%. Overall, 34.4% were living with symptoms for ≥ 3 years before an INOCA diagnosis, and 77.8% were told their symptoms were not cardiac. Estimated functional capacity was higher prior to compared to after symptom onset (8.6 ± 1.8 METs vs 5.6 ± 1.8 METs; $P < 0.0001$). Most respondents reported an adverse impact of symptoms on their home life (80.5%), social life (80.1%), mental health (70.4%), outlook on life (69.7%), sex life (55.9%), and their partner/spouse relationship (53.9%), while approximately three-quarters reduced their work hours or stopped work completely, 47.5% retired early, and 38.4% applied for disability.

Conclusions: INOCA symptoms are associated with adverse physical, mental and social health quality of life. Increased patient awareness, physician recognition and diagnosis, and clinical trials are needed to develop evidence-based guidelines for this increasingly recognized cardiovascular disorder.

1. Introduction

The diagnosis of coronary artery disease (CAD) has traditionally focused on the presence of obstructive CAD. Nonetheless, it is estimated that at least 2 in every 5 patients with angina referred for elective angiography have nonobstructive coronary arteries, with rates even higher in women.[1,2] Ischemia does not require the presence of

obstructive coronary arteries,[3] and this is recognized in the recent American Heart Association/American College of Cardiology chest pain guidelines expanding the definition of CAD to include both obstructive and nonobstructive CAD.[4] These same guidelines included a diagnostic pathway for evaluation of chest pain for those with evidence of myocardial ischemia but no obstructive coronary arteries (INOCA).[4]

Patients with INOCA pose both a diagnostic and therapeutic

Abbreviations: CAD, coronary artery disease; DASI, Duke Activity Status Index; INOCA, ischemia with no obstructive coronary arteries; METs, metabolic equivalents.

* Corresponding author at: 127 S. san Vicente Blvd, Suite A3600, Los Angeles, CA 90048, USA.

E-mail address: Martha.Gulati@cshs.org (M. Gulati).

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challenge. Most patients with INOCA struggle for years to have an accurate diagnosis made, due to lack of physician awareness and limited availability of diagnostic testing and expertise in INOCA.[5] In addition, the optimal medical management for INOCA is not well-defined, given that medical therapy should be directed based on the diagnosis of the underlying cause of ischemia, which is best defined by invasive vaso-reactive testing but this is not routinely performed.[6] As a result, patients with INOCA often live with protracted symptoms, undergo repeated diagnostic evaluations, and remain inadequately treated and inadequately diagnosed.[2]

To date, there is limited literature available on INOCA and quality of life. We sought to determine relations between INOCA symptoms and self-reported physical, social, and mental health. We hypothesized that all aspects of life could be adversely associated with INOCA symptoms.

2. Methods

The survey was provided to all members of the patient support group from the United Kingdom (UK)-Based INOCA International, which is an international organization for persons living with INOCA. Awareness of the survey was released by a newsletter, as well as on Twitter and Facebook but only members of the patient support group could access the platform to receive a link for the survey. Participants could fill the survey only once from a single IP address. The survey collection began on October 27, 2021 and was closed on December 27, 2021. The survey questions are included in Appendix 1. All data collected was anonymized and answered directly through SurveyMonkey[®]. Approval for this survey was received from the Cedars-Sinai institutional review board.

Assessment of functional capacity was measured using the Duke Activity Status Index (DASI), previously validated in women with suspected INOCA.[7] The survey assessed prior to and after the onset of symptoms. Functional capacity was calculated for each participant by converting the sum of DASI questionnaire scores to metabolic equivalents (METs) using the following formula: METs = 0.43 x DASI + 9.6 / 3.5, as previously described.[8]

The statistical analysis included descriptive and frequency distributions, with chi-squared statistics for categorical variable comparisons, and t-tests for continuous variable comparisons. Simple linear regression was performed to determine the association of days lost due to poor physical and mental health, and inability to perform recreational activities per month, related to functional capacity change after onset of symptoms. All statistical analyses were conducted via STATA (College Station, TX) statistical software.

3. Results

Three hundred and twenty-eight respondents completed the survey. Given that the established membership of the patient support group of INOCA International is 1579, this represented a response rate of 20.8%. Thirty-one respondents reported not having INOCA, and by default could not answer any further questions in this survey and were excluded. Two hundred and ninety-seven respondents were finally included.

3.1. Characteristics of survey respondents

Most respondents were women (91.2%), which is slightly higher than the gender representation of the patient support group (83.3% women). The most common forms of diagnosis of INOCA in the responders were coronary microvascular dysfunction (64.3%) and coronary artery spasm (50.5%). Almost two-thirds were diagnosed between the ages of 40 to 60 years. A history of myocardial infarction was reported in 22.6%. A medical history of migraines was common (46.5%), as was a history of any adverse pregnancy outcomes (47.1%), with 25.2% having at least one miscarriage. (Table 1).

Table 1
Participant Characteristics

	Respondents (N= 297)
Men	26 (8.8)
Established Diagnoses	
CMD	191 (64.3)
Coronary Artery Spasm	150 (50.5)
Nonobstructive atherosclerosis	18 (6.1)
Heart Failure with Preserved Ejection Fraction	13 (4.4)
Takotsubo Cardiomyopathy/Stress Cardiomyopathy	13 (4.4)
Not given any diagnosis aside from INOCA	24 (8.1)
Unknown	13 (4.4)
MINOCA	67 (22.6)
Age at Diagnosis of INOCA	
<30 Years	8 (2.7)
30–40	29 (9.8)
40–50 Years	77 (25.9)
50–60 Years	115 (38.7)
>60 Years	54 (18.2)
Comorbidities	
Migraines/ frequent headaches	138 (46.5)
Raynaud's	64 (21.5)
Thyroid disorder	64 (21.5)
Rheumatoid Arthritis	16 (5.5)
Lupus/ systemic lupus erythematosus	4 (1.3)
Other autoimmune disorder	64 (21.5)
History of stroke	10 (3.3)
Kidney disease	15 (5.1)
None	76 (25.6)
Adverse Pregnancy Outcomes	140 (47.1)
Hypertension During pregnancy	55 (18.5)
Preeclampsia or Eclampsia	38 (12.8)
Gestational Diabetes	24 (8.1)
Preterm Delivery	36 (12.1)
Miscarriage	75 (25.2)
Does Not Apply To Me/I have Never Been Pregnant	139 (46.8)

Legend: INOCA -Ischemia with No Obstructive Coronary Arteries. MINOCA-Myocardial Infarction with No Obstructive Coronary Arteries.

3.2. Medical evaluation for INOCA symptoms

Most respondents (40.4%) had experienced INOCA symptoms for at least 1 to 5 years, with almost half of them experiencing symptoms for anywhere between 1 and 10 years before the diagnosis of INOCA was made, and 77.8% who had been told their symptoms were not cardiac. The symptoms the respondents experienced were numerous, but 92.9% reported symptoms of chest pain, chest pressure, or chest discomfort, and 80.6% reported shortness of breath. Only 8.4% felt the ambulance crew understood the diagnosis of INOCA and 15.3% would not call the ambulance for their INOCA symptoms because they felt their symptoms were not taken seriously. The most common triggers of INOCA reported were stress (79.8%), exercise/exertion (73.4%), and excitement/high emotional state (69%). For the women who had undergone menopause, 37.5% reported that their symptoms changed with menopause. The majority (50.2%) had seen 3 or more cardiologists for the treatment of INOCA. Additionally, 31.6% had been referred to a psychiatrist for their symptoms and 42.1% had been prescribed an anti-depressant. Most respondents (53.9%) had been told their symptoms were due to gastroesophageal reflux disease, with 32% having undergone upper endoscopy for further evaluation. The majority of those surveyed reported that they were told that although their symptoms of INOCA may be unpleasant, they could not die from INOCA or have a heart attack (66.4%). Of the respondents who attended the emergency department for their symptoms, 69.4% were discharged without any treatment. (Table 2).

A minority (6.4%) were diagnosed with INOCA at the first consultation for the onset of symptoms. The majority (93.6%) reported multiple consultations before the diagnosis of INOCA was made. The majority (50.2%) also had consulted 3 or more cardiologists for the treatment of INOCA. All respondents underwent some diagnostic testing with non-invasive imaging performed in 93.3%, and 72.7% underwent

Table 2
INOCA Symptoms, Trigger, Referral Patterns & Evaluation

	Respondents (N= 297)
Years With INOCA Symptoms	
<1 Year	34 (11.4)
1–5 Years	120 (40.4)
5–10 Years	62 (20.9)
10–20 Years	46 (15.5)
>20 Years	21 (7.1)
Time From Symptom Onset to Diagnosis of INOCA	
<1 Month	26 (8.8)
1 Month-1 Year	92 (31.0)
1–3 Years	67 (22.6)
3–10 Years	73 (24.6)
>10 Years	29 (9.8)
Clinical Assessment of Symptoms	
Told that Symptoms were Not Cardiac	224 (77.8)
Seen in ED for Symptoms+ Discharged without Treatment	200 (69.4)
Told that although symptoms of INCOA are unpleasant, you cannot die from it or have a heart attack	188 (66.4)
Had ever called an ambulance for symptoms	166 (58.7)
Knew when to call an ambulance or go to the hospital for INOCA symptoms	184 (65.5)
Ambulance Response to INOCA Symptoms	
Taken to hospital+ ECG+ Monitor	147 (49.4)
No ambulance dispatched	9 (3.2)
Assessed by ambulance crew but not taken to hospital	39 (13.8)
Taken to hospital but no ECG or cardiac monitor performed	23 (8.2)
Ambulance crew understood the diagnosis of INOCA	25 (8.4)
Ambulance crew did not understand the diagnosis of INOCA	75 (27.0)
I never had to call an ambulance	97 (34.4)
I do not call the ambulance because they do not take my symptoms seriously	43 (15.3)
Symptoms	
General: Fatigue/exhaustion, Sweats	260 (87.5)
Cardiovascular	
Chest pain/chest pressure/chest discomfort	276 (92.9)
Palpitations	181 (60.9)
Shortness of breath	239 (80.5)
Back, shoulder, arm, neck, jaw pain	242 (81.5)
Neurologic: Confusion, brain fog, vision changes, light headedness, dizziness	230 (77.4)
Gastrointestinal: Nausea, reflux-like symptoms	146 (49.2)
Other	45 (15.2)
Triggers	
Stress	237 (79.8)
Exercise/Exertion	218 (73.4)
Excitement or High Emotional State/Anger	205 (69.0)
Cold Weather	178 (59.9)
Change in Temperature or Weather Change	145 (48.8)
Triggered during Menstruation	49 (16.5)
Other	70 (23.6)
No Known Triggers	18 (6.1)
Did Symptoms Change at Menopause?	
Yes	75 (25.3)
No	45 (15.2)
Unsure	80 (26.9)
Have Not Undergone Menopause	53 (17.8)
Male- Does Not Apply	26 (8.8)
No Response	18 (6.1)
Prior to the Diagnosis of INOCA:	
Told Symptoms Were Due to GERD	160 (53.9)
Underwent Endoscopy to Assess for GERD	96 (32.3)
Told Symptoms Were Not Cardiac	223 (75.1)
Referred to a Psychiatrist for Symptoms	94 (31.6)
Recommended to Start Antidepressant/Antianxiety Medication for Symptoms	125 (42.1)
Seen in the ED For Symptoms of INOCA & Discharged Without Treatment	200 (67.3)
Total Consults Seen Prior to INOCA Diagnosis	
Diagnosed Right Away	19 (6.4)
1–2 Additional Consults	86 (28.9)
3–5 Additional Consults	105 (35.4)
>5 Additional Consults	75 (25.3)
Non-invasive Imaging	277 (93.3)
ECG	261 (87.9)

Table 2 (continued)

	Respondents (N= 297)
Echocardiogram	242 (81.5)
Exercise Stress Test	201 (67.7)
Stress Echocardiogram	145 (48.8)
CT Angiogram	134 (45.1)
Cardiac MRI	138 (46.5)
PET Scan	31 (10.4)
Invasive Imaging	216 (72.7)
Cardiac Catheterization	185 (62.3)
Cardiac Catheterization with Acetylcholine Testing	97 (32.7)
Number of Cardiologists Consulted for Treatment of INOCA	
1	60 (20.2)
2	76 (25.6)
≥3	149 (50.2)
Finding An INOCA Specialist	
Self-Referred	106 (35.7)
Referred by Cardiologist	45 (15.2)
Referred by Family Doctor or Other Doctor	18 (6.1)
Never Under the Care of an INOCA Specialist	114 (38.4)
Currently Under the Care of an INOCA Specialist	146 (49.2)

Legend: CT computed tomography; ECG electrocardiogram; GERD Gastroesophageal Reflux Disease; INOCA Ischemia with No Obstructive Coronary Arteries, MRI magnetic resonance imaging; PET positron emission tomography.

invasive imaging but only 32.7% underwent cardiac catheterization with acetylcholine testing. Self-referral to a cardiology specialist familiar with INOCA was reported by 35.7% of individuals, and 38.4% reported never being under the care of an INOCA specialist. Of the respondents, 49.2% were currently under the care of a INOCA specialist (Table 2).

3.3. Associations with health quality of life

General Health: At the time of the survey, most of the respondents living with INOCA reported their health as being fair (32.7%) or poor (19.2%). (Table 3).

Physical Health: Prior to the onset of INOCA symptoms, the mean functional capacity for those surveyed was 8.6 ± 1.8 METs, with 69.7% able to perform >8 METs. Following the onset of symptoms, the reported functional capacity was 5.6 ± 1.8 METs, with only 11.4% able to perform >8 METs. (Table 3, Table 4). Those who reported poorer health had a lower functional capacity (data not shown). Those with a prior myocardial infarction had lower post-diagnosis functional capacity when compared with those without a myocardial infarction (5.5 ± 1.8 METs vs 8.5 ± 1.9 METs, respectively; $p < 0.0001$). Those with self-reported kidney disease had lower symptom onset functional capacity compared with those without kidney disease (4.6 ± 1.0 METs vs. 5.7 ± 1.9 METs; $p = 0.031$), and those with any co-morbidities had a lower post-symptom onset functional capacity than those with no co-morbidities. (6.1 ± 1.9 METs vs. 5.4 ± 1.8 METs; $p = 0.0027$).

Social and Mental Health: While living with INOCA, most of the respondents reported an adverse impact on their home life (80.5%), social life (80.1%), mental health (70.4%), outlook on life (69.7%), sex life (55.9%), and their partner/spouse relationship (53.9%). (Table 3) Those who reported an adverse impact of INOCA on specific aspects of their social and mental health had a significantly lower functional capacity compared to those who did not report any adverse impact of INOCA on those factors (Fig. 1). Those who reported that their sex life was adversely affected the mean functional capacity level was lower than for those whose sex life was not adversely affected (5.1 ± 1.5 METs vs. 6.9 ± 1.9 METs; $p < 0.0001$).

Work and Disability: Most respondents (69.0%) felt that there was an adverse impact on their work life while living with INOCA; and those who reported an adverse impact on their work life had a significantly lower mean functional capacity than those did not report any adverse impact on their work life (5.3 ± 1.5 METs vs. 7.6 ± 2.2 METs,

Table 3
Health Status and Quality of Life

	Total Respondents (N= 297)
Overall Health After Onset of Symptoms	
Excellent	6 (2.0)
Very Good	48 (16.3)
Good	87 (29.5)
Fair	97 (32.7)
Poor	57 (19.2)
Did not answer	2 (0.7)
Functional Capacity Level by DASI (METs) Prior to Onset of INOCA Symptoms	
<5 METs	15 (5.1)
5-8METs	63 (21.2)
>8 METs	207 (69.7)
Estimated Exercise Capacity (METs)	8.6±1.8
Functional Capacity Level by DASI (METs) After Onset of Symptoms	
<5 METs	123 (41.4)
5-8METs	128 (43.1)
>8 METs	34 (11.4)
Estimated Exercise Capacity (METs)	5.6±1.8
Mental Health After Onset of Symptoms	
INOCA Adversely affected your Mental Health	209 (70.4)
INOCA Negatively affected your Outlook on Life	207 (69.7)
Social Health After Onset of Symptoms	
INOCA Adversely affected Home Life	239 (80.5)
INOCA Adversely affected your Relationship with Partner/ Spouse	160 (53.9)
INOCA Adversely affected your Social Life	238 (80.1)
INOCA Adversely affected your Sex Life	166 (55.9)
Work & Disability After Onset of Symptoms	
INOCA Adversely affecting Work Life	205 (69.0)
Reduced Work Hours due to INOCA symptoms	167 (56.2)
Retired Early because of INOCA	141 (47.5)
Changed Job/Roles for less stressful Position due to INOCA symptoms	111 (37.4)
Changed Job/Roles resulting in Lower Pay due to INOCA symptoms	97 (32.7)
Applied for Disability because of INOCA symptoms	114 (38.4)
Successful Application for Disability Benefits	88 (77.2)

Legend: DASI Duke Activity Status Index; INOCA Ischemia with No Obstructive Coronary Arteries; METs metabolic equivalents.

Table 4
Estimated functional capacity prior and following symptom onset stratified by diagnosis.

INOCA Forms	Functional Capacity Prior to Symptoms Onset (METs±SD)	Functional Capacity Post Symptom Onset (METs±SD)	P-Value
ALL INOCA (N=297)	8.6 ±1.8	5.6 ±1.8	<0.0001
CMD (N=191)	8.5 ±1.9	5.3 ±1.7	<0.0001
Coronary artery spasm (N=150)	8.7 ±1.9	5.6 ±1.8	<0.0001
Nonobstructive atherosclerosis (N=18)	8.3 ±2.2	5.4 ±1.9	<0.0001
HFpEF (N=13)	8.3 ±2.1	4.5 ±0.9	<0.0001
Takutsubo Cardiomyopathy (N=13)	8.3 ±1.7	4.7 ±0.8	<0.0001
I don't know/I wasn't diagnosed (N=37)	8.6 ±1.6	6.1 ±2.0	<0.0001

Legend: CMD coronary microvascular dysfunction; HFpEF heart failure with preserved ejection fraction; INOCA Ischemia with No Obstructive Coronary Arteries; METs metabolic equivalents; SD standard deviation.

respectively; $p < 0.0001$). After experiencing INOCA symptoms, approximately 3 of every 4 respondents had either reduced their work hours or had stopped work completely, 47.5% retired early, and 38.4% applied for disability (Table 3). Of those who applied for disability,

22.8% were unsuccessful at receiving disability benefits, with those who were successful having a lower functional capacity than those who were not (4.8 ± 1.4 METs vs. 5.9 ± 2.1 METs, respectively; $p < 0.0001$). Those who applied for disability, retired early or reduced working hours had a significantly lower functional capacity than those who did not (Fig. 2).

Living with INOCA Symptoms and Days of Declining Health: After onset of symptoms, the respondents reported that for every 1 MET decrease in functional capacity, there was a loss of 3.0 ± 0.6 days of physical health per month, 1.8 ± 0.6 days of mental health per month, and 2.9 ± 0.7 days of inability to perform recreational activities per month ($p < 0.0001$) (Fig. 3).

4. Discussion

This study depicts adverse associations with many aspects of quality of life in INOCA patients. Patients reported that their physical, mental and social health were adversely impacted by INOCA symptoms indicative of reduced overall quality of life. Additionally, when compared to prior to the onset of INOCA symptoms, living with INOCA was associated with a significant reduction of approximately 3 METs of functional capacity, comparable to losing the ability to do light housework, activities of daily living (dressing, bathing, use the toilet independently), or being able to walk 1 block on level ground. Those who reported an adverse impact of INOCA on specific aspects of life had a relatively greater reduction in functional capacity, when compared with those who do not. These findings are unique, as there has been very limited data relating the patient experience of living with INOCA.

For the respondents of this survey, functional capacity was significantly reduced while living with INOCA when compared to prior to the onset of INOCA symptoms. Functional capacity is an established independent predictor of mortality,[9] particularly when functional capacity falls below 5 METs,[10] which in this surveyed population was the case for 5.1% prior to the onset of symptoms, but increased to 41.4% post-symptom onset. In the Women's Ischemia Syndrome Evaluation (WISE) study, poor functional capacity in women with INOCA was associated with an adverse prognosis.[11] A prior evaluation of registry studies demonstrated that patients with INOCA have relatively greater physical limitations and anginal frequency than patients with stable obstructive coronary artery disease and acute myocardial infarction survivors.[12] This conflicts with findings from the WISE study, where functional capacity was demonstrated to be slightly greater in those women with nonobstructive CAD, when compared with obstructive CAD, using the DASI (5.0 METs ± 4.3 vs 5.6 ± 4.7 METs, respectively; $p = 0.01$).[13] In this current INOCA survey, following symptom onset functional capacity was similar to what was seen in WISE (5.6 ± 1.8 METs).[13] Further, the survey demonstrates for the first time a decline in functional capacity associated with worsened aspects of physical, mental, and social health. Specifically, for every 1 MET reduction in functional capacity once experiencing INOCA symptoms, there was a self-reported 3-day loss in in physical health and ability to perform recreational physical activities per month, and 2 days per month with suboptimal mental health. The implication of poor functional capacity is important in understanding the impact of this disease and appreciating that the prognosis of INOCA is not benign.

Mental health was adversely impacted in 70.4% of those surveyed, with almost the same number reporting that INOCA had negatively affected their outlook on life. Psychological stress, which includes anxiety, depression, anger and personality disturbances, can be quite common in patients with CAD,[14] including those with INOCA.[15] It is estimated that the prevalence of depression is 15–30% in those with coronary heart disease, and highest post MI and in women,[16] but it is unclear if these estimates included patients with nonobstructive CAD. The WISE study demonstrated that higher anxiety variables predicted more severe cardiac symptoms.[17] In a previously reported study of 66 patients with INOCA, cardiac anxiety levels as assessed using the

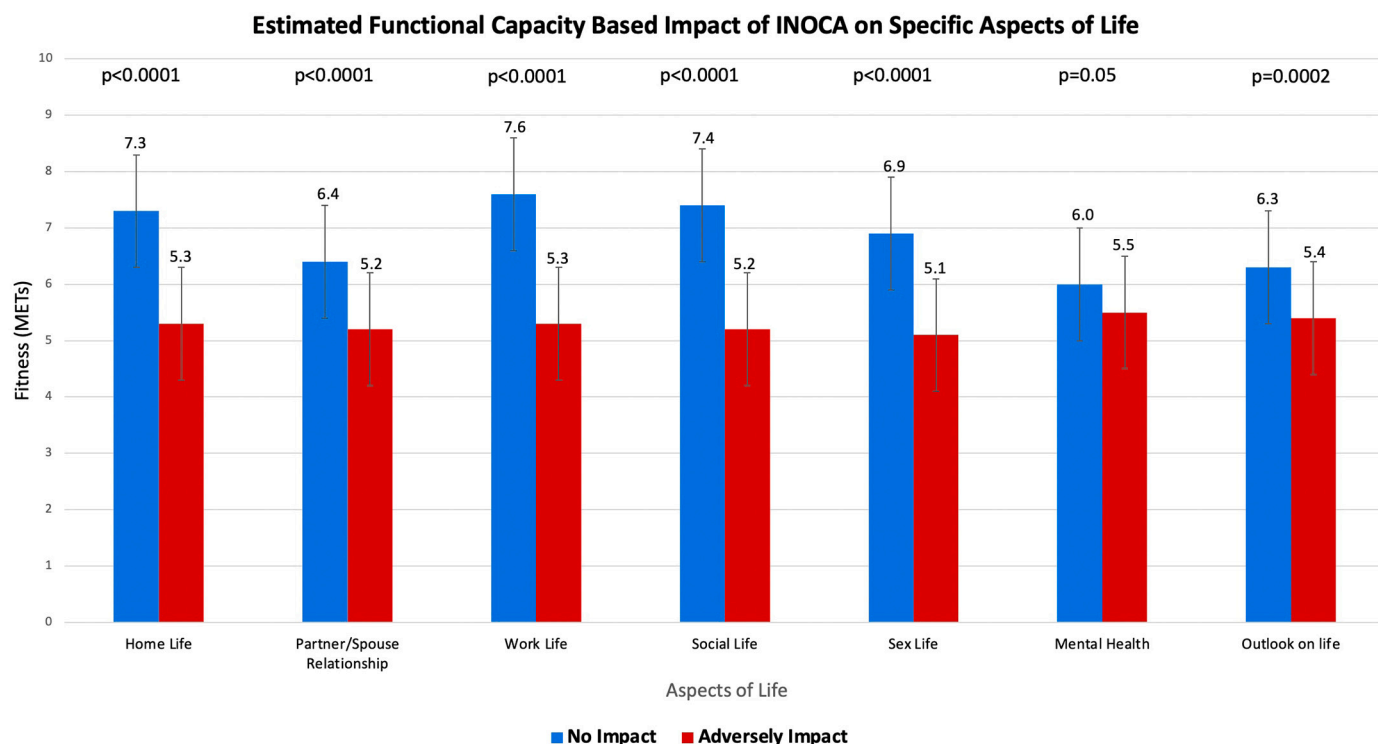


Fig. 1. Estimated Functional Capacity Based on Impact of INOCA on Specific Aspects of Life
 Functional capacity based on impact of INOCA on specific aspects of life.
 Legend: INOCA= Ischemia with No Obstructive Coronary Arteries; METs= metabolic equivalents.

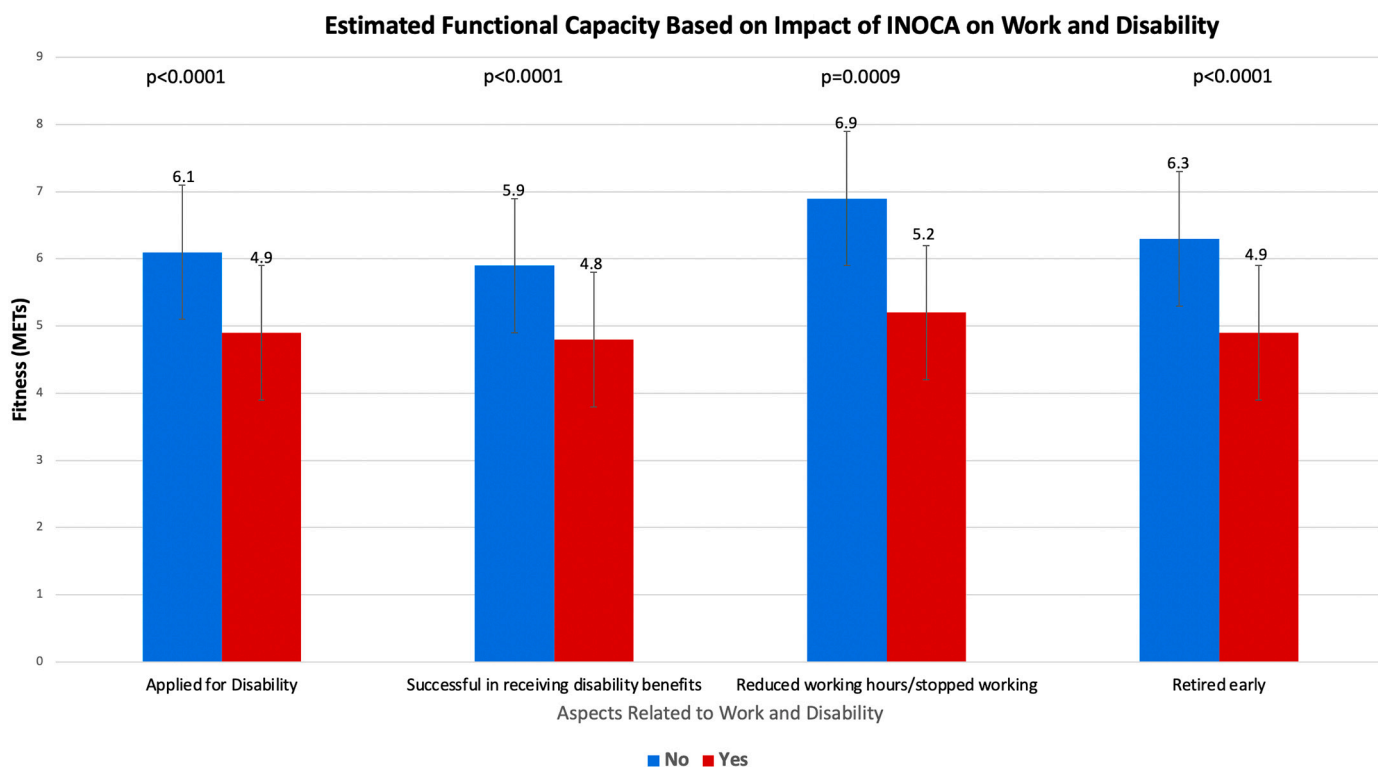


Fig. 2. Estimated Functional Capacity Based on Impact of Living with INOCA on Work and Disability
 Functional capacity in those living with INOCA based on specific aspects of work and application for disability.
 Legend: INOCA= Ischemia with No Obstructive Coronary Arteries; METs= metabolic equivalents.

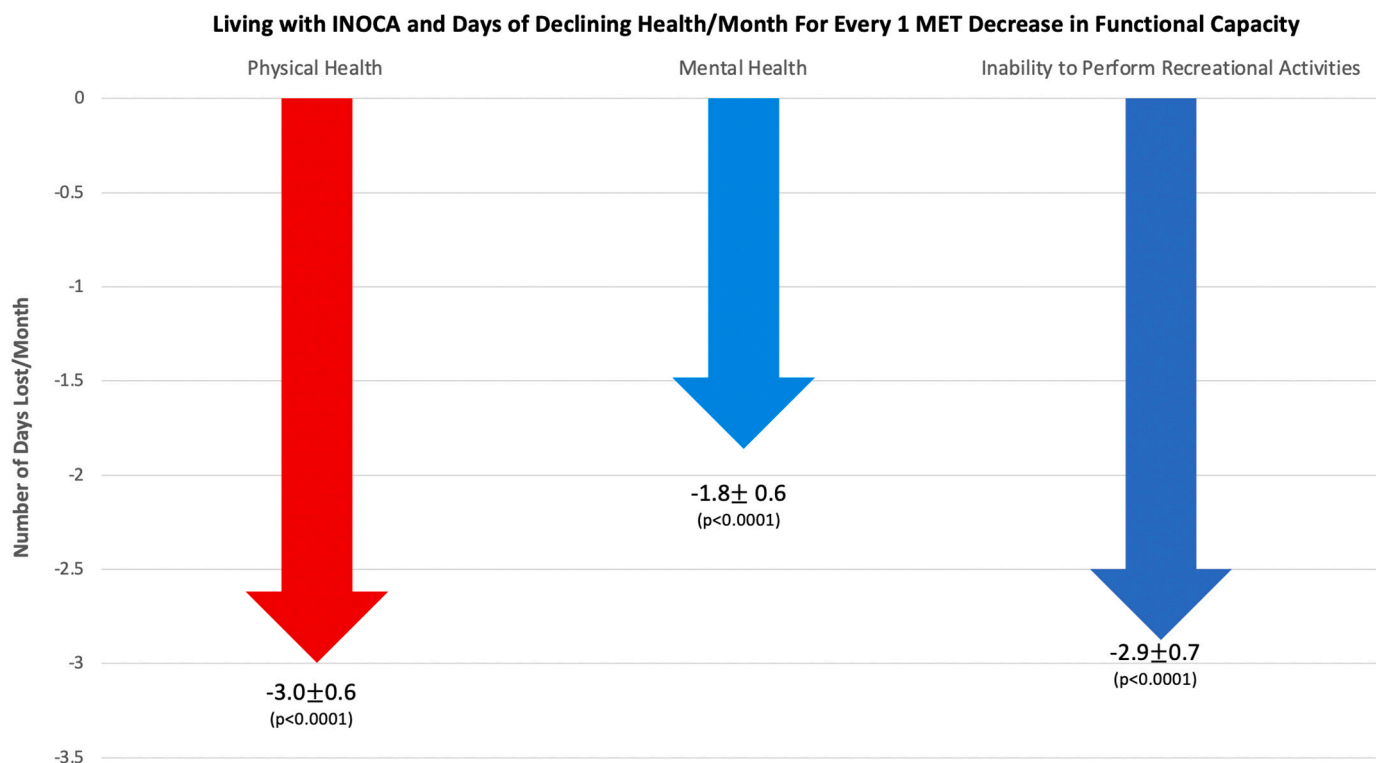


Fig. 3. Living with INOCA and Days of Declining Health Per Month For Every 1 MET Decrease in Functional Capacity
Number of days per month of declining physical and mental health, and ability to perform recreational activities, for every unit (MET) of decline in functional capacity for those living with INOCA (\pm Standard Deviation).

Legend: INOCA= Ischemia with No Obstructive Coronary Arteries; METs= metabolic equivalents.

Cardiac Anxiety Questionnaire were significantly higher in INOCA patients when compared with prior assessments in patients with sudden cardiac death, and quite similar to those documented in patients with hypertrophic cardiomyopathy.[12] Psychological stress can induce endothelial dysfunction and be an underlying cause of INOCA, particularly coronary microvascular dysfunction and vasospasm.[18–20]

The social health of patients was adversely impacted in those living with INOCA symptoms, with at least 4 of every 5 respondents reporting that their symptoms adversely affected their home life and social life. Sexual activity may often decrease after a myocardial infarction due to fears of inducing another myocardial infarction or anginal symptoms, as was demonstrated in a study of myocardial infarction survivors, where 47% of patient abstained or reduced their sexual activity after their myocardial infarction.[21] This is comparable to the current survey results, where 1 in 2 patients reported that following onset of INOCA symptoms, their relationship with their partner/spouse and their sex life was adversely impacted. Providing counselling to patients regarding sexual activity after an acute myocardial infarction is far too infrequent, [22] but for those with INOCA or myocardial infarction with no obstructive coronary arteries (MINOCA), it remains unknown what counselling is provided, if any. Based on the 2021 AHA Scientific Statement on sexual activity and CVD, “sexual activity is reasonable for patients who can exercise ≥ 3 –5 METs without any angina, without angina, excessive dyspnea, ischemic ST-segment changes, cyanosis, hypotension, or arrhythmia.”[23] In the current survey, 41.4% of the INOCA patients reported a functional capacity was < 5 METs after onset of symptoms, and those who reported that their sex life was adversely impacted had a significantly lower functional capacity, compared with those whose sex life was not adversely affected.

We observed a significant association of living with INOCA symptoms on the ability to work, with almost 7 out of every 10 patients reporting that INOCA adversely affected their work life, resulting in

more than half reducing their work hours or even retiring earlier than expected. Approximately one third of those surveyed changed their job or roles resulting in lower pay. Application for disability was also quite common in those living with INOCA. Our findings are consistent with a study of 66 patients where INOCA was assessed using cardiac magnetic resonance and demonstrated that patients with INOCA frequently missed work (1.1 ± 2.2 full workdays missed in last 2 weeks) and had work limitations, suggestive of a substantial economic impact by work productivity loss.[12] Nonetheless, this study did not address disability or changes in job or roles that also result in lower pay directly for the patient. A study from Denmark examined patients referred for coronary angiography for symptoms of stable angina, and demonstrated no difference in premature exit from the workforce or being on disability in those with obstructive and nonobstructive CAD.[24] The national register from Sweden demonstrated that persons of working ages with ischemic heart disease took 83.9 days per year of disability leave in the first post-event year after adjusting for age, sex and education (~ 6.9 days per month).[25] This was six-fold greater than the national average of disability days. Nonetheless, this prior study did not distinguish between those with obstructive versus nonobstructive CAD. Additionally, disability days leveled off within the second year similar to the pre-event year.[25]

The current results suggest that patients with INOCA often initially live with diagnostic uncertainty despite the presence of symptoms that adversely impact their lives. Most patients reported living with their symptoms for at least 1 year before a diagnosis was made, with almost half experiencing symptoms of INOCA for 1 to 10 years before diagnosis. More than half had seen three or more consultants before their diagnosis of INOCA was made, and three or more cardiologists for the treatment of INOCA. Many reported undergoing endoscopy or psychiatric evaluation of their symptoms. Even for these patients with a diagnosis of INOCA, less than a third had undergone cardiac catheterization with coronary

flow reserve testing to determine optimal medical therapies, given that there are many different forms of INOCA. This on top of a lack of understanding of INOCA even within the cardiology community, results in the signs and symptoms of INOCA often being downplayed, dismissed and often untreated and undiagnosed.[26]

5. Study limitations

There are several limitations in this study. Although most respondents were female, limiting implications somewhat to men, however INOCA is a condition that predominantly affects women. This survey was limited to the patient support group of INOCA International. Accordingly, the survey reflects: (1) participants had an established diagnosis or suspicion of INOCA; (2) they had undergone some evaluation for this diagnosis; (3) they had had time to join a patient-focused support group; and (4) they may have sought out such an organization because of issues related to getting a diagnosis or living with active symptoms of INOCA, and thus may not represent all INOCA patients. A survey-based study will always be limited to a higher literacy audience and may unintentionally exclude those INOCA patients with lower levels of literacy. Because the survey was administered online, there was no interviewer to probe the respondents and ensure understanding of the intention of the questions. There is survival bias in this study, and it remains unknown how large the population of INOCA patient is, but it is likely patients remain undiagnosed and untreated and would not be represented in this study. Reports of applications for disability and successful approval differ from one country to another, and although we do not know where these participants live, this is a UK-based organization. In addition, the survey did not distinguish between short-term or long-term disability. Certainly, recall bias can limit the self-interpretation of quality of life and functional capacity prior to INOCA symptoms. Functional capacity was estimated using the DASI questionnaire, but this has been validated in populations living with ischemic heart disease including those with INOCA from the WISE study.

Appendix 1 Survey

INOCA Survey

We are interested in how living with INOCA (Ischemia with No Obstructive Coronary Arteries) has impacted your medical care, health and life. Your responses will remain anonymous. Thank you for your time in responding to our questions.

Question 1

Do you have Ischemia with No Obstructive Coronary Arteries (INOCA)?

Yes

No

(if No, no further questions)

Question 2

Would you say that your general health is:

Excellent

Very Good

Good

Fair

Poor

Question 3

Which of the following forms of INOCA were you diagnosed with? (Check all that apply)

Coronary Microvascular Dysfunction

Coronary Artery Spasm

Nonobstructive Atherosclerosis

Heart Failure with Preserved Ejection Fraction (HFpEF)

Takotsubo's Syndrome (also known as Stress Cardiomyopathy/"Broken Heart" Syndrome)

I was not given a diagnosis aside from INOCA

I don't know

Question 4

How long did it take from the onset of your symptoms to getting a diagnosis of INOCA?

Less than 1 months

1-12 months

1-3 years

3-5 years

5-10 years

[7,8,11,27,28] Information on pharmacological and non-pharmacology therapy was not collected, so we are unable to assess how treatment may influence any of the self-reported measures. Lastly, we have included respondents with a diagnosis of INOCA who also reported being diagnosed with Takotsubo Cardiomyopathy, given that a prevailing hypothesis is that the underlying pathophysiologic process may be due to underlying coronary microvascular ischemia.[29]

6. Conclusions

INOCA symptoms are associated with adverse physical, mental and social health quality of life, comparable to patients with symptoms of obstructive CAD. Additionally, functional capacity declines are evident following onset of INOCA symptoms. Increased patient awareness, physician recognition and diagnosis, and clinical trials are needed to develop evidence-based guidelines for this increasingly recognized cardiovascular disorder.

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 >10 years

Question 5

Prior to your diagnosis of INOCA were you ever told your symptoms were due to Reflux or GERD (gastroesophageal reflux disease)?

 Yes No

Question 6

Prior to your diagnosis of INOCA did you undergo an endoscopy to assess for reflux/GERD based on your symptoms?

 Yes No

Question 7

Prior to your diagnosis of INOCA were you ever told your symptoms were not cardiac?

 Yes No

Question 8

Prior to your diagnosis of INOCA were you seen in the Emergency Room/A&E for your symptoms of INOCA and discharged without any treatment?

 Yes No

Question 9

Prior to your onset of symptoms of INOCA, which of the following could you previously do? (Check All That Apply)

 Take Care of Yourself (ie. dress, eat, bathe, use toilet) Walking Indoors Walk 200 yards (182 meters) on level ground Climb a flight of stairs or walk up a hill Run a Short Distance Do light work around the house (ie. dusting, washing dishes) Do moderate work around the house (ie. vacuuming, sweeping floors, carrying groceries) Do heavy work around the house (ie. scrubbing floors, lifting or moving heavy furniture) Do yardwork (ie. raking leaves, weeding, pushing a lawn mower) Have Sexual Relations Participate in Moderate Recreational Activities (ie. golf, bowling, doubles tennis, throwing baseball, kicking football) Participate in Strenuous Sports (ie. swimming, singles tennis, football, basketball, skiing)

Question 10

With your diagnosis of INOCA, which of the following can you currently do? (Check All That Apply)

 Take Care of Yourself (ie. dress, eat, bathe, use toilet) Walking Indoors Climb a flight of stairs or walk up a hill Run a Short Distance Do light work around the house (ie. dusting, washing dishes) Do moderate work around the house (ie. vacuuming, sweeping floors, carrying groceries) Do heavy work around the house (ie. scrubbing floors, lifting or moving heavy furniture) Do yardwork (ie. raking leaves, weeding, pushing a lawn mower) Have Sexual Relations Participate in Moderate Recreational Activities (ie. golf, bowling, doubles tennis, throwing baseball, kicking football) Participate in Strenuous Sports (ie. swimming, singles tennis, football, basketball, skiing)

Question 11

How many consultants/specialists/doctors did you see prior to your diagnosis of INOCA?

 0 (meaning diagnosed right away) 1-2 3-5 >5

Question 12

How many cardiologists have you consulted for treatment of your INOCA?

 1 2 3-5 >5

Question 13

Prior to your diagnosis of INOCA were you ever referred to a psychiatrist for your symptoms or was such a referral suggested to you by your doctor?

 Yes No

Question 14

Have you ever been started on, or been recommended to start, an antidepressant or anti-anxiety medication for your INOCA symptoms?

 Yes No

Question 15

Are you under the care of a specialist in INOCA?

 Yes No Awaiting Initial Appointment I Don't Know

Question 16

(continued on next page)

(continued)

If you under the care of a specialist in INOCA, how did you get to them?

- Self-Referred (I found the specialist myself)
- My Family Doctor/GP referred me to the INOCA specialist
- Another cardiologists referred me to the INOCA Specialist
- Another doctor referred me to the INOCA Specialist
- AI have never been under the care of an INOCA Specialist

Question 17

How many years have you had symptoms of INOCA for?

- Less than 1 year
- 1-5 years
- 5-10 years
- 10-20 years
- >20 years

Question 17

At What Age were you Diagnosed with INOCA?

- Less than 30
- 30-40
- 40-50
- 50-60
- 60-70
- >70 years

Question 18

Have you ever had a Heart Attack?

- Yes
- No
- Unsure

Question 19

Have you ever been told that although your symptoms of INOCA may be unpleasant, you cannot die from it and cannot have a heart attack?

- Yes
- No

Question 20

Have you ever had to call an Ambulance for your symptoms of INOCA?

- Yes
- No

Question 21

When you have called an Ambulance for your symptoms of INOCA, have you experienced any of the following? (choose all that apply)

- Taken to the Hospital and Cardiac Monitor Attached and ECG performed
- No Ambulance dispatched
- Assessed by Ambulance Crew but not taken to the hospital
- Taken to the Hospital but No Cardiac Monitor or ECG performed despite symptoms
- Ambulance Crew Understood the Diagnosis of INOCA
- Ambulance Crew DID NOT Understand the Diagnosis of INOCA
- I have never had to call an Ambulance
- I do not call the Ambulance because they do not take my symptoms seriously

Question 22

As a patient living with INOCA, do you know when to call for an ambulance or go to the hospital for your INOCA symptoms?

- Yes
- No

Question 23

Which diagnostic tests have you had related to your INOCA symptoms? (Check all that apply)

- ECG
- Echocardiogram (also called Echo)
- Exercise Stress Test
- Stress Echocardiogram (Also called Stress Echo)
- CT Angiogram
- Cardiac MRI
- PET Scan
- Cardiac Catheterization (Also called Angiogram)
- Cardiac Catheterization (Also called Angiogram) with Acetylcholine Testing
- None of the Above

Question 24

Which symptoms do you experience related to INOCA? (Check all that apply)

- Chest Pain/Chest Pressure/Chest Discomfort
- Fatigue/Exhaustion
- Shortness of Breath
- Back Pain
- Shoulder or Arm Pain or Pressure
- Neck/Jaw Pain
- Palpitations/Racing of the heart
- Sweats
- Lightheadedness, Dizziness
- Nausea, reflux-like symptoms
- Confusion, Brain Fog

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(continued)

-
- Vision Changes
 Other
- Question 25
 Have You Ever Left any Doctor's Appointment and come away thinking they did not understand INOCA?
 All the Time
 Often
 Occasionally
 Never
- Question 26
 Have You Ever Had to Stop Working because of INOCA?
 Yes
 No
- Question 27
 Did You Had to Retire Early because of INOCA?
 Yes
 No
- Question 28
 Have You Ever Had to Reduce Working Hours because of INOCA?
 Yes
 No
- Question 29
 Have You Ever Had to Change Jobs or Roles for a Less Stressful Position because of your symptoms from INOCA?
 Yes
 No
- Question 30
 Have You Ever Had to Change Jobs or Roles that Resulted in Lower Pay Because of your Symptoms with INOCA?
 Yes
 No
- Question 31
 Have You Ever Had to Apply for Disability Benefits because of your symptoms with INOCA?
 Yes
 No
- Question 32
 If You Had to Apply for Disability Benefits because of your symptoms with INOCA, was your application successful?
 Yes
 No
 I have never applied for disability benefits
- Question 33
 Do You Ever Worry about being home alone?
 Yes
 No
- Question 34
 Do You Ever Worry about going out alone?
 Yes
 No
- Question 35
 Do You Drive?
 Yes,
 No, stopped due to INOCA symptoms
 Never Drove
- Question 36
 Did you have any of the following conditions during pregnancy? (check all that apply)
 Hypertension During pregnancy
 Preeclampsia or Eclampsia
 Gestational Diabetes
 Preterm Delivery
 Miscarriage
 Does Not Apply To Me, I have Never Been Pregnant
- Question 37
 Do you have any of the following conditions? (check all that apply)
 Migraines/ Frequent Headaches
 Raynaud's
 Thyroid Disorder
 Rheumatoid Arthritis
 Lupus/ Systemic Lupus Erythematosus
 Other Autoimmune Disorder
 History of Stroke
 Kidney Disease
 None
- Question 38
 Do You Have Any of the Following Triggers for Your Symptoms of INOCA?
 Stress
 Exercise/Exertion
 Excitement or High Emotional State/Anger
 Cold Weather
 Change in Temperature or Weather Change
 Triggered during Menstruation

(continued on next page)

(continued)

Other

No Known Triggers

Question 39

Did Your Symptoms Change at Menopause?

Yes

No

Unsure

Have not Undergone Menopause Yet

Male (Not Applicable)

Question 40

Has INOCA Adversely Affected Your Home Life?

Yes

No

Question 41

Has INOCA Adversely Affected Your Relationship with Your Partner/Spouse?

Yes

No

Not applicable

Question 42

Has INOCA Adversely Affected Your Work Life?

Yes

No

Question 43

Has INOCA Adversely Affected Your Social Life?

Yes

No

Question 44

Has INOCA Adversely Affected Your Sex Life?

Yes

No

Not applicable

Question 45

Has INOCA Adversely Affected Your Mental Health?

Yes

No

Question 46

Has INOCA Negatively Affected Your Outlook on Life?

Yes

No

Question 47

Thinking about your physical health, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good?

_ (no number >30 will be accepted)

Question 48

Thinking about your mental health, which includes stress, depression and problems with emotions, for how many days during the past 30 days was your mental health not good?

_ (no number >30 will be accepted)

Question 49

During the past 30 days, for how many days did poor physical health or mental health, keep you from doing your usual activities, such as self-care, work or recreation?

_ (no number >30 will be accepted)

IF YOU WOULD LIKE TO SHARE ANY OTHER COMMENTS WITH YOU ABOUT YOUR EXPERIENCE LIVING WITH INOCA, PLEASE FEEL FREE TO WRITE ANY COMMENTS HERE:

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2022.09.047>.

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