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REVIEW
Social-psychological factors

Mental health status and quality of life after an acute myocardial infarction with non-obstructive coronary arteries or takotsubo syndrome: a systematic review

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Aims Myocardial infarction with non-obstructive coronary arteries (MINOCA) and takotsubo syndrome (TS) are both characterized by lack of significant coronary artery stenoses and a higher prevalence of mental health disorders preceding the event. Currently, little is known about their pathological aetiologies and subsequent treatment plans, giving cause for concern among those affected. The objective of this review is to provide a comprehensive overview of mental health status and quality of life (QoL) in MINOCA and TS patients after the acute event, compared with both cardiac and non-cardiac populations, and over time.

Methods and results A systematic search was conducted via Cochrane Library, CINAHL, PsycINFO, PubMed, ASSIA, Web of Science, Scopus, and Embase from inception to May 2024. The review was registered in PROSPERO and methods, and results were reported in accordance with the PRISMA guidelines. Quality assessment and risk of bias were evaluated using the Newcastle–Ottawa Scale for cross-sectional and cohort studies. Sample sizes ranged from 13 to 5322 participants. The risk of bias was high in 18/28, medium in 7/28, and low in 3/28 studies. Across the symptoms assessed, MINOCA and TS patients reported worse mental health status or QoL than non-cardiac groups in 10/13 studies and cardiac groups in 10/20 studies. Investigating change over time, 1/5 studies found deteriorating mental health status, 3/5 reported improved mental health status or QoL, and 1/5 reported no change in MINOCA and TS patients.

Conclusion Patients with MINOCA or TS seem to have worse mental health status and QoL after the acute event than non-cardiac individuals, but it is yet difficult to conclude whether mental distress and QoL are equal or worse compared with coronary heart disease patients. There is no convincing evidence that mental health status or QoL of MINOCA and TS patients naturally improve over time after the acute event. Among the studies evaluated, risk of bias was high. More high-quality studies are needed, investigating mental health status and QoL among MINOCA and TS patients.

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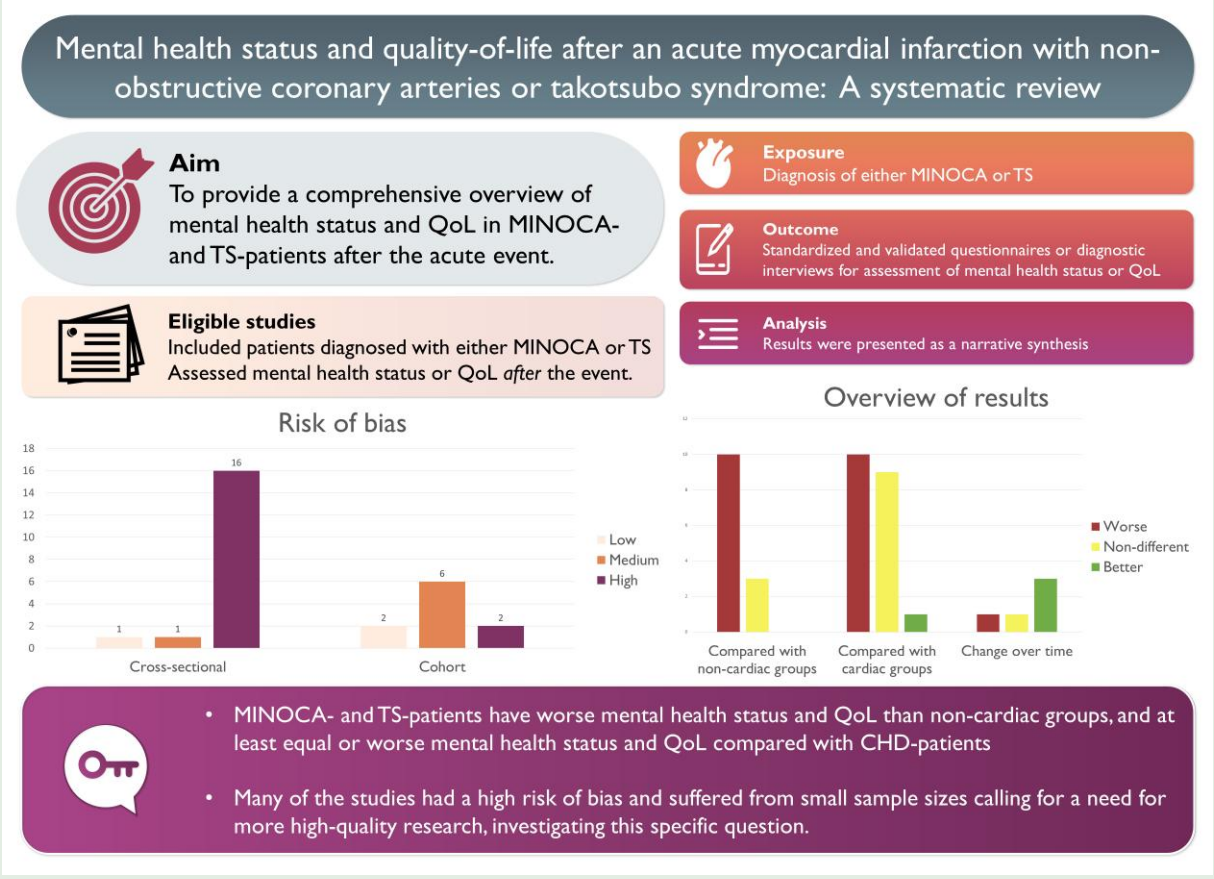
Lay summary

This is a systematic review of all papers reporting data on post-event mental health status and quality of life in individuals following either a MINOCA or takotsubo syndrome.

- Individuals who have suffered a MINOCA or takotsubo syndrome more often report worse mental health status and quality of life than healthy controls and at least as often or more often than other cardiac patients.
- Much of the available data had a high risk of bias, demonstrating a lack of high-quality investigation of the mental well-being of these patients, and more attention is warranted.

Graphical Abstract



Keywords MINOCA • Takotsubo syndrome • Mental health • Quality of life • Systematic Review • After event

Introduction

Cardiovascular disease (CVD), including myocardial infarction (MI), continues to be a leading cause of morbidity and mortality worldwide.[1] For those surviving an MI, it can be a highly disturbing event, and symptoms of psychological distress are common.[2] Eighty-five years ago, MI with non-obstructive coronary arteries (MINOCA) was first noted,[3,4] and over the last 20 years, it has been increasingly recognized by the frequent use of coronary angiography. However, the current understanding of MINOCA is limited, and the availability of evidence-based treatment is lacking.[5,6] While this may cause further psychological suffering, little is still known regarding these patients' mental health status and quality of life (QoL), after the acute event.

MINOCA is defined as a 'working diagnosis' and may be caused by several underlying pathological mechanisms, presenting unique diagnostic and therapeutic challenges.[7] One pathophysiological explanation that was long classified as a cause of MINOCA is takotsubo syndrome (TS).[7] While TS no longer is considered a type of MI,[8] MINOCA and TS still share common clinical features and aetiologies.[9] Compared with MI with obstructive coronary artery disease (MI-CAD), MINOCA and TS affect women to a greater extent, the patients are younger, and they have a higher prevalence of previous psychological distress or psychiatric illness.[5,6,10] Additionally, TS is often reported as triggered by intense physical or emotional stress.[5]

Around 5–6% of all MI cases are categorized as MINOCA,[6] and TS makes up around 2–3% of the cases presenting with a suspected acute coronary syndrome (ACS).[5] Comparing MINOCA and TS, one study found that TS patients more often were women and older than the MINOCA patients and had a higher prevalence of mental health disorders and more in-hospital complications, but with a better long-term

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prognosis.[9] Although lacking obstructive CAD, both patient groups have a worse prognosis and more functional impairment than the general population.[5,6]

Previous reviews have summarized somatic clinical features, mechanisms, treatments, and prognosis of MINOCA patients,[11–13] but as of yet, there is no review of the mental health status or QoL of MINOCA patients after the acute event. Takotsubo syndrome has been reviewed regarding psychological factors before the acute event,[14,15] but for mental health status after the acute event, there has only been a synthesis and review of case studies.[16] The aim of this review is therefore to fill this knowledge gap and provide a comprehensive overview of mental health status and QoL in MINOCA and TS patients after the acute event, compared with both cardiac and non-cardiac populations, and over time.

Methods

This review was registered in the international Prospective Register of Systematic Reviews (PROSPERO 20202020 CRD42020160778). Methods and results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17]

Search strategy

An extensive systematic literature search was carried out in the following databases: the Cochrane Library, CINAHL, PsycINFO, PubMed, ASSIA, Web of Science, Scopus, and Embase from inception to May 2024. Search terms were tailored to each database and included terms for the exposure (MINOCA and Takotsubo) and outcomes (mental health status and QoL or associated symptoms). Search terms were based on Medical Subject Headings where available and complemented by free text searches. The full search strategy used for the CINAHL database is provided as an example in the appendix (see Supplementary material online, *Table S4*). The list of references from eligible papers was manually screened to additionally detect any potential studies not picked up by the database searches.

Study selection and eligibility criteria

Two authors independently screened the title and abstract of the retrieved studies, applying the same inclusion and exclusion criteria to determine study relevance. Full-text articles were assessed for eligibility after the initial screening. Disparities around inclusion criteria were resolved by discussion between the two reviewers and through consulting with a third independent reviewer, if necessary. Studies were eligible for inclusion if they (i) included adult patients diagnosed with MINOCA or TS or a diagnosis synonymous with MINOCA or TS; (ii) assessed the mental health status or QoL *after* the diagnosis; and (iii) utilized standardized and validated questionnaires or diagnostic interviews for assessment relating to the outcome of interest. Studies were excluded if they (i) were not written in English; (ii) were not peer-reviewed; (iii) did not have full-text availability; and (iv) followed case study design.

There is certain overlap between psychological states and psychological traits. As the purpose of this paper was to assess mental health status after the acute event, which may be due to the event itself, studies or results assessing psychological traits or personality were not included.

Data extraction

After full-text screening, data from the included studies were independently extracted by the two reviewers. This was done using an extraction form in which the following information was retrieved: general study characteristics (author, year, country), clinical characteristics (diagnosis, study group, sample size, time since event, control group characteristics), and outcomes (assessment tool or diagnosis). Quantitative data on severity (median or mean scores) and frequency (prevalence or incidence) of adverse mental health outcomes were extracted for each group or time point, as well as the accompanying comparison between them (e.g. *P*-value, odds ratio, relative risk).

Quality appraisal

Risk of bias was assessed in all studies that matched inclusion and exclusion criteria with the Newcastle–Ottawa Scale (NOS) for cohort studies and an adapted version for cross-sectional studies which is modified accordingly. The NOS has been recommended for use in assessing studies on psychiatric conditions.[18] The scales have three dimensions for which quality is assessed: selection, comparability, and outcome. Both versions have a maximum of four stars for selection and two stars for comparability. The cohort version has a maximum of three stars for outcome while the cross-sectional has two. It is possible to get a total of nine stars for cohort studies and eight stars for cross-sectional studies. The cut-off for high risk of bias is usually set at five stars or less,[18,19] medium risk for bias at seven to six stars for cohort studies and six stars for cross-sectional, and low risk of bias at seven to eight for cross-sectional and eight to nine for cohort studies.[19]

Included studies may have followed case-control, cohort, or cross-sectional design. However, for the purpose of this systematic review, the studies were categorized based on our research question, i.e. with MINOCA/TS as exposure and mental health status or QoL as outcome. For example, a case-control study investigating differences in exposures between MINOCA patients and healthy controls, but that also collected data on mental health status after the diagnosis, would be described and assessed as a cross-sectional study; and a cohort study investigating cardiovascular outcomes, but with psychosocial measurements at baseline, would be considered a cross-sectional study if they had no additional psychosocial outcomes at follow-up.

Data analysis

The results of included studies are presented as a narrative synthesis, and no statistical comparisons or pooling of data was conducted. These results are presented in detail in Supplementary material online, *Table S1* and *Table S2*. For the purpose of readability, the same results are presented synoptically in simplified tables and elaborated more comprehensibly in text. To make reading and comparing studies easier, some categorizations were made.

The included studies assessed mental health status and QoL at varying elapsed times since diagnosis of MINOCA or TS, as shown in Supplementary material online, *Table S1* and *Table S2*. To maintain a more parsimonious language in the narrative synthesis of results and in the simplified tables, we categorized these as (i) acute phase, defined as assessment made during hospital admission and before discharge; (ii) short-term follow-up, defined as after discharge up to 3 months after the event; and (iii) long-term follow-up, defined as more than 3 months after the acute event.

Referring to QoL, some studies only reported a composite score, consisting of both mental and physical aspects of QoL, and other studies reported specific sub-scale scores. If only the composite was available, we reported this score, but if separate sub-scale scores were available, we only reported the ones pertaining to mental QoL.

MINOCA and TS were compared with various diagnoses related to coronary heart disease (CHD). These include MI, acute MI, ACS, coronary artery disease, and non-ST-elevation MI. The specific diagnoses are specified in the Supplementary material online, *Table S1* and *Table S2* and are referred to as CHD in the narrative synthesis of results and in the simplified tables.

Studies comparing MINOCA and TS with non-cardiac populations used varying matching methods and criteria, which are described in detail in the Supplementary material online, *Table S1* and *Table S2*. However, in the narrative synthesis of results and simplified tables, these will be categorized as CVD risk controls, if matched on CVD risk factors, or healthy controls, if not matched on CVD risk factors.

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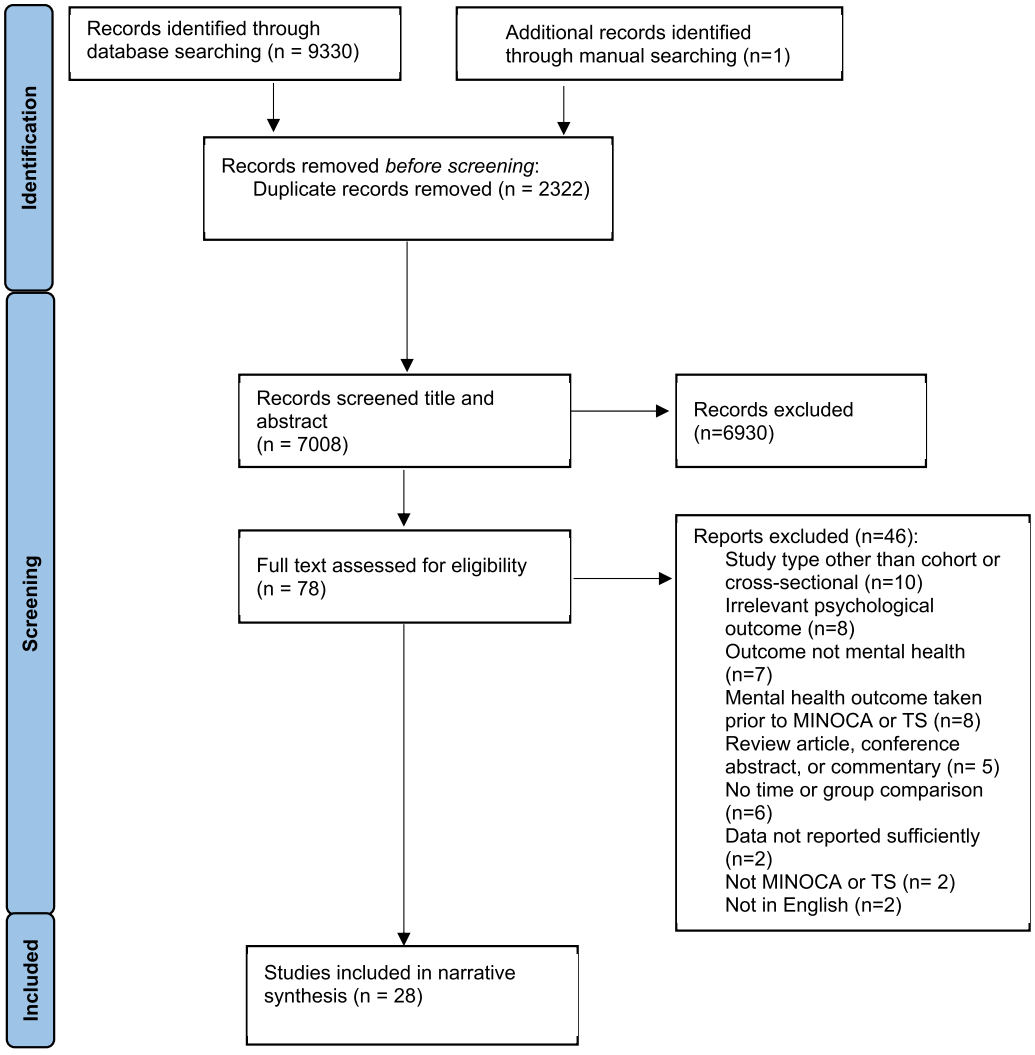

Figure 1 Flowchart demonstrating identification, screening, and inclusion of articles.

In the narrative synthesis, results are categorized and presented under ordered headings. The first level of headings describes one of the following: (i) MINOCA patients, (ii) TS patients, or (iii) comparisons within and between MINOCA and TS patients. Under the headings of MINOCA and TS patients, the results are further categorized in groups of (i) change over time within the group, (ii) change over time compared with other groups, (iii) cross-sectional comparisons with non-cardiac groups, and (iv) cross-sectional comparisons with cardiac groups. The studies of comparisons within and between MINOCA and TS patients are few and do not have any specific sub-headings. The non-cardiac groups are defined as healthy controls, CVD risk controls, and patients with non-cardiac chest pain (NCCP). The cardiac groups are defined as patients with either CHD or heart failure (HF).

Results

Search results

A total of 9330 publications were found, with 2322 being eliminated during the initial screening process due to duplicates. Further exclusions based on title and abstract screening resulted in the removal of 6930 articles. Subsequently, 78 full-text articles underwent eligibility assessment, resulting in the exclusion of 50. After comprehensive full-text screening, 28 studies were found to meet the inclusion criteria. The inclusion and exclusion criteria are shown in the PRISMA flowchart (*Figure 1*).

Study characteristics

Table 1 provides a summary of the characteristics of the studies. There were six studies describing MINOCA patients, 20 studies describing TS patients, and 2 studies describing both groups. Out of the studies describing MINOCA patients, one study explicitly states that TS patients were excluded, three studies explicitly state that TS patients were included, and two studies do not mention whether TS patients were excluded or included.

The sample sizes of the 28 studies ranged from 13 to 5322 participants, totalling 15 572 participants. Out of these, 1241 were MINOCA patients and 898 were TS patients (total 2193). The mean age of these patients was 60 years (mean range: 46–72.7), with females (1717) constituting 80% of the samples. These studies were conducted

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Table 1 Main characteristics of the included studies and population

Study characteristics	*n* (%)
Study design, *n* = studies	
Cohort	10 (36)
Cross-sectional	18 (64)
Diagnosis-related inclusion criteria, *n* = studies	
Takotsubo	20 (71)
MINOCA	6 (21)
Mixed (MINOCA/takotsubo/other)	2 (7)
Total sample size, *n* = studies	
<50	7 (25)
50–99	5 (18)
100–150	4 (14)
>150	12 (43)
MINOCA sample characteristics	5
Mean/median age, *n* = studies	
<55 years	2
55–65 years	2
>65 years	1
Sample characteristics	
Total	668
Female	586 (88)
Takotsubo sample characteristics	20
Mean/median age, *n* = studies	
<55 years	
55–65 years	8
>65 years	12
Sample characteristics	
Total	856
Female	754 (88)
Mixed MINOCA/takotsubo and other	3
non-obstructive CVD sample characteristics	
Mean/median age	
<55 years	
55–65 years	3
>65 years	
Sample characteristics	
Total	615
Female	377 (61)

CVD, cardiovascular disease; MINOCA, myocardial infarction with non-obstructive coronary arteries

in 13 different countries: Canada (2), Denmark (1), France (1), Germany (2), Iran (1), Italy (5), New Zeeland (1), Poland (1), Spain (1), Sweden (6), Switzerland (1), The Netherlands (1), and the USA (5).

Quality appraisal

Tables 2 and *3* displays the assessment of risk of bias in the included studies. Among the cross-sectional studies (range: 2–7, average: 4.6), the risk of bias was deemed low in 1 study, medium in 1 study, and high in 16 studies. Among the cohort studies (range: 5–9, average: 6.6), the risk of bias was deemed low in two studies, medium in six studies, and high in two studies.

Assessment tools

Across the 28 studies, mental health status and QoL were assessed with 36 different standardized questionnaires, and mental health disorders were diagnosed using the Mini International Neuropsychiatric Interview (for an overview, see Supplementary material online, *Table S3*).

Simplified summaries of cross-sectional and longitudinal comparisons of MINOCA- and TS-patients, together with the overall bias rating score from the Newcastle-Ottawa quality assessment scale are presented in *Tables 4–6*.

Mental health and quality of life of myocardial infarction with non-obstructive coronary arteries patients

Change over time within the group

Three studies investigated change over time among MINOCA patients.[20–22]

Two of the studies both found that self-reported QoL improved over the first year following the event.[20,21] On the other hand, two of these studies also assessed self-reported depression and found that symptoms remained unchanged after 2 months[22] and 1 year after the event.[21] Similarly, one of these studies also found that stress symptoms remained unchanged after 2 months.[22]

Change over time compared with other groups

One study followed MINOCA patients over the first 2 months after the acute event and found no differences in change of depressive and stress symptoms compared with CHD patients.[22]

Cross-sectional comparisons with non-cardiac groups

Mental health status and QoL among MINOCA patients were compared with healthy controls in three studies.[20,23,24]

All studies reported that MINOCA patients had worse mental health status compared with healthy controls. In the acute phase, patients reported lower emotional role functioning and social functioning,[20] and at short-term follow-up, they reported lower levels of mental QoL and higher levels of anxiety and depression.[23,24]

Cross-sectional comparisons with cardiac groups

Mental health status and QoL among MINOCA patients were compared with cardiac groups in six studies.[22–27]

Three studies reported that, in the acute phase, at short-term follow-up, and at long-term follow-up, MINOCA patients reported higher levels of anxiety and depression and lower mental QoL, compared with CHD patients.[23–25] Four studies reported no differences regarding anxiety, insomnia, or stress between MINOCA and CHD patients, either in the acute phase, at short-term follow-up, or at long-term follow-up.[22,24,26,27] One of the studies also found that MINOCA patients reported lower levels of stress in the acute phase and lower prevalence of high stress compared with CHD patients at short-term follow-up.[22]

Mental health and quality of life of takotsubo patients

Change over time within the group

Three studies investigated change over time in mental health status among TS patients.[28–30] While one study found no difference in

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Table 2 Newcastle–Ottawa quality assessment scale, cross-sectional studies

Study	Total score	Selection				Comparability	Outcome	
		Representativeness of the sample	Sample size	Non-respondents	Ascertainments of exposure	Based on design and analysis	Assessment of outcome	Statistical test
Christensen *et al.* (2016)	5	*		*	*		*	*
Compare *et al.* (2018)	5	*			*	*	*	*
Daniel *et al.* (2018)	5	*		*	*		*	*
Daniel *et al.* (2017)	5	*		*	*		*	*
Delmas *et al.* (2013)	5	*		*	*		*	*
Goh *et al.* (2016)	6	*			*	**	*	*
Gorini *et al.* (2022)	4	*			*		*	*
Izquierdo Coronel *et al.* (2023)	5	*		*	*		*	*
Kastaun *et al.* (2014)	4	*			*		*	*
Lazzeroni *et al.* (2022)	3				*		*	*
Naegele *et al.* (2016)	5	*	*		*		*	*
Olliges *et al.* (2020)	4	*			*		*	*
Sabisz *et al.* (2016)	2				*		*	
Salmoraigo-Blotcher *et al.* (2016)	5	*			*	*	*	*
Sancassiani *et al.* (2018)	4	*			*		*	*
Smeijers *et al.* (2016)	4				*	*	*	*
Wallström *et al.* (2016)	7	*		*	*	**	*	*
Zarifeh *et al.* (2012)	4	*		*	*		*	

A * signifies having met the quality assessment criteria for the Newcastle-Ottawa quality assessment scale. A maximum of one star is possible for each section, except for the section "Comparability", where a maximum of two stars is possible.

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Table 3 Newcastle–Ottawa quality assessment scale, cohort studies

Study	Total score	Selection				Comparability	Outcome		
		Representativeness of the exposed cohort	Selection of non-exposed	Ascertainment of exposure	Demonstration that outcome was not present at the start of the study	Based on design and analysis	Assessment of outcome	Length of follow-up	Adequacy of follow-up
Auger *et al.* (2019)	9	*	*	*	*	**	*	*	*
Berg *et al.* (2023)	5	*		*	*		*	*	
Compare *et al.* (2014)	7	*	*	*		*	*	*	*
Grodznisky *et al.* (2015)	7	*	*	*	*		*	*	*
Hausvater *et al.* (2023)	5		*	*	*		*	*	
Parvand *et al.* (2022)	6	*	N/A	*	*		*	*	*
Saffari *et al.* (2017)	6	*	*	*	*		*	*	
Safdar *et al.* (2018)	9	*	*	*	*	**	*	*	*
Sundelin *et al.* (2020)	6	*	N/A	*	*		*	*	*
Waldenbourg *et al.* (2011)	6	*	N/A	*	*		*	*	*

N/A, selection of non-exposed not applicable due to sample only consisting of exposed.
A * signifies having met the quality assessment criteria for the Newcastle-Ottawa quality assessment scale. A maximum of one star is possible for each section, except for the section "Comparability", where a maximum of two stars is possible.

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Table 4 MINOCA patients—cross-sectional comparison (simplified)

Study	*n*	Quality rating	Follow-up	Comparator	Symptom	Direction
Safdar *et al.* (2018)	2690	9	Acute phase	CHD	Depression, perceived stress	+/–
Grodzinsky *et al.* (2015)	5539	7	Acute phase	CHD	Depression	–
Daniel *et al.* (2018)	296	5	Short-term	Healthy controls	Depression, anxiety	–
				CHD	Depression	+/–
					Anxiety	–
Daniel *et al.* (2017)	270	5	Short-term	Healthy controls	Mental and physical QoL	–
				CHD	Mental QoL	–
					Physical QoL	+/–
				TS[a]	Mental health	+
					Mental and physical QoL	+/–
Berg *et al.* (2023)	459	5	Short-term	TS[a]	Emotional well-being, social functioning, fatigue	+
					Emotional role functioning, bodily pain	+/–
			Long-term	Healthy controls	Social and emotional role functioning	–
					Emotional well-being, fatigue, and bodily pain	+/–
				TS[a]	Social and emotional role functioning and bodily pain	+
					Emotional well-being and fatigue	+/–
Hausvater *et al.* (2023)	486	5	Acute phase	CHD	Stress, depression	+/–
			Short-term	CHD	Stress	+
					Depression	+/–
Izquierdo Coronel *et al.* (2023)	533	5	Acute phase	CHD	Anxiety and insomnia	+/–

Risk of bias: high (1–5), medium (6), and low (7–8). Direction refers to the outcome in MINOCA patients compared with the comparator. '–' denotes worse, '+/–' denotes non-different, and '+'denotes better mental health or quality of life.
[a]Comparison of non-TS MINOCA with TS MINOCA.

symptoms of post-traumatic stress and depression between the acute phase and 3 months,[28] another noted reductions in self-reported stress at 6 months that remained at 1 year after the acute event.[29] The third study found that TS patients reported worse emotional well-being and higher prevalence of depression 1 year after the acute event, but no difference with regard to anxiety.[30]

Change over time compared with other groups

Change in mental health status compared with other groups was assessed in two studies.[30,31] The first study found deteriorations of emotional well-being and depression 1 year after the event that were worse for TS patients than for CHD patients, but found no differences in change of anxiety.[30] The second study followed TS patients over 15 years and found they had a higher risk of rehospitalization for stress and anxiety disorders, but not for mood disorders, compared with healthy controls.[31] On the other hand, the same study found no difference in risk for rehospitalization over 15 years when comparing TS patients with CHD patients.

Cross-sectional comparisons with non-cardiac groups

Mental health status and QoL among TS patients was compared with non-cardiac groups in nine studies.[32–40] Two studies found that TS patients had higher levels of psychological distress at short-term follow-up[35] and lower QoL at long-term follow-up[36] compared with healthy controls. On the other hand, two studies found no differences in QoL, neither compared with healthy controls at short-term follow-up,[32] nor compared with CVD risk controls at long-term follow-up.[33] Similarly, two studies found no differences at long-term follow-up, neither regarding psychological distress compared with CVD risk controls,[33] nor psychiatric symptoms compared with healthy controls.[34]

Higher levels of anxiety for TS patients compared with healthy controls were observed in three studies, both in the acute phase[36] and at long-term follow-up.[37,38] Two studies observed no differences regarding anxiety at long-term follow-up, neither in anxiety levels,[39] nor in lifetime prevalence of anxiety disorders[32] as compared with healthy controls. Similarly, one study found no differences in anxiety at short-term follow-up, compared with NCCP patients.[40]

Three studies found that levels of depression were higher in TS patients compared with healthy controls, both in the acute phase[36] and at long-term follow-up.[34,38] Similarly, one study found that TS patients had a higher lifetime prevalence of major depressive disorders than healthy controls, assessed at short-term follow-up, but no difference in prevalence of bipolar disorder.[32] On the other hand, one study found no difference in levels of depression for TS patients, when compared with NCCP patients.[40]

One study found higher levels of stress in TS patients compared with healthy controls at short-term follow-up.[35] However, no difference was observed in two studies regarding stress at long-term follow-up.[34,38]

While one study found TS patients to report higher levels of post-traumatic stress than healthy controls at short-term follow-up,[35] two other studies reported no differences at short-term follow-up, neither

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Table 5 Takotsubo patients—cross-sectional comparison (simplified)

Study	*n*	Quality rating	Follow-up	Comparator	Symptom	Direction
Auger *et al.* (2019)	3650	9	Long-term	CHD	Stress, anxiety	+/–
				Healthy controls	Stress, anxiety	–
Compare *et al.* (2014)	74	7	Acute phase	CHD	Anxiety, depression, QoL	+/–
			Long-term	CHD	Psychological distress	–
Wallström *et al.* (2016)	127	7	Short-term	CHD	Anxiety, depression, stress, sleep disturbance	+/–
Goh *et al.* (2016)	184	6	Long-term	CHD	Anxiety	–
					Depression	+/–
Saffari *et al.* (2017)	188	6	Acute phase	CHD	Sexual functioning, anxiety, depression	–
			Long-term	CHD	Sexual functioning	–
Christensen *et al.* (2016)	173	5	Long-term	CHD	Well-being, anxiety, depression	–
				Healthy controls	Well-being, depression	+/–
					Anxiety	–
Delmas *et al.* (2013)	95	5	Acute phase	CHD	Psychiatric diagnoses	–
Neagele *et al.* (2016)	43	5	Long-term	Matched controls	QoL	+/–
Salmoirago-Blotcher (2016)	107	5	Acute phase	CHD	Psychological distress, stress, post-traumatic stress	–
				Healthy controls		
Kastaun *et al.* (2014)	59	4	Long-term	CHD	Psychiatric symptoms, depression, stress	+/–
				Healthy controls	Psychiatric symptoms, stress	
					Depression, chronic worry	–
Olliges *et al.* (2020)	136	4	Long-term	Healthy controls	Anxiety, depression, QoL	–
				CHD	Anxiety, depression, QoL	+/–
Sancassiani *et al.* (2018)	95	4	Short-term	Healthy controls	QoL, anxiety disorders, post-traumatic stress disorder	+/–
					Major depressive disorder	–
Smeijers *et al.* (2016)	56	4	Long-term	Heart failure	Anxiety, depression, stress	+/–
				Healthy controls	Anxiety, depression	–
					Stress	+/–
Zarifeh *et al.* (2012)	17	4	Short-term	NCCP	Anxiety, Depression, post-traumatic stress	+/–
				CHD		
Gorini *et al.* (2022)	40	4	Short-term	CHD	Anxiety, post-traumatic stress	+/–
					Reassurance seeking	–
					Fear of death, interference	+
Lazzeroni *et al.* (2022)	19	3	Long-term	Healthy controls	Depression, anxiety	+/–
Sabisz *et al.* (2016)	26	2	Long-term	Norm values	Anxiety	–
					Depression	+/–

Risk of bias: high (1–5), medium (6), and low (7–8). Direction refers to the outcome in MINOCA patients compared with the comparator. '–' denotes worse, '+/–' denotes non-different, and '+' denotes better mental health or quality of life.
CHD, coronary heart disease; QoL, quality of life; NCCP, non-cardiac chest pain.

with regard to self-reported levels nor in lifetime prevalence of post-traumatic stress disorders.[32,40] It was also reported that TS patients had higher sexual distress and more sexual dysfunction compared with healthy controls in the acute phase,[36] and they reported more symptoms of chronic worry at long-term follow-up.[34]

Cross-sectional comparisons with cardiac groups

Mental health status and QoL among TS patients was compared with HF or CHD patients in 11 studies.[30,34–36,38,41–46] Compared with CHD patients, in the acute phase, one study found higher psychological distress for TS patients[35] and two studies found lower emotional well-being at long-term follow-up.[30,42] Two other studies reported no differences in QoL compared with CHD patients, in the acute phase,[36] or in psychiatric symptoms at long-term follow-up.[34]

Regarding self-reported anxiety, four studies found TS patients to have higher levels compared with CHD patients, both in the acute phase[36] and at long-term follow-up.[42,44,45] On the other hand, three studies found no differences in anxiety levels compared with either HF or CHD patients, neither in the acute phase,[30] at short-term follow-up,[43] nor at long-term follow-up.[30,38] Additionally, one study found TS patients to report more fear of death and reassurance seeking related to health anxiety but no difference regarding state anxiety compared with CHD patients at short-term follow-up.[46]

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Table 6 MINOCA and takotsubo patients—longitudinal comparisons (simplified)

Study	n	Quality rating	Follow-up	Comparator	Symptom	Direction
Safdar et al. (2018)	2690	9	3 years	CHD	Depression and perceived stress	+/–
Compare et al. (2014)	74	7	12 months	Within group	Depression and emotional well-being	–
					Anxiety	+/–
				CHD	Depression and emotional well-being	–
					Anxiety	+/–
Sundelin et al. (2020)	20	6	6 months	Within group	Stress	+
			12 months			
Waldenbourg et al. (2011)	13	6	3 months	Within group	Post-traumatic stress, depression	+/–
Parvand et al. (2022)	154	6	12 months	Within group	QoL, mental health	+
Hausvater et al. (2023)	486	5	2 months	CHD	Stress, depression	+/–
Berg et al. (2023)	459	5	6 months	Within group	Bodily pain, fatigue, social and emotional role functioning, emotional well-being	+
			12 months	Within group	Fatigue, emotional well-being	+
					Bodily pain, social and emotional role functioning	+/–

Risk of bias: high (1–5), medium (6–7), and low (8–9). Comparator indicates either only change over time within the group or the difference in change over time compared with another group. Direction refers to the outcome in MINOCA patients compared with the comparator. '–' denotes worse, '+/–' denotes non-different, and '+'denotes better mental health or quality of life.
CHD, coronary heart disease; QoL, quality of life; TS, takotsubo syndrome.

Regarding self-reported depression, three studies found higher levels for TS patients compared with CHD patients, both during the acute phase[36] and at long-term follow-up.[42,45] Similarly, one study found the prevalence of major depressive disorder to be higher in the acute phase in TS patients than in CHD patients.[41] Conversely, there were five studies that found no differences in depression between TS patients and CHD patients, neither in the acute phase,[30] at short-term follow-up[43,46] nor at long-term follow-up.[38,44]

One study found TS patients to have more symptoms of stress than CHD patients in the acute phase.[35] However, in follow-up assessments, none of the three studies identified any differences in stress symptoms, neither compared with CHD patients at short-term follow-up,[43,46] nor HF patients at long-term follow-up.[38] Similarly, one of these studies did not find any differences in symptoms of mental fatigue nor sleep disturbance at short-term follow-up[43] compared with CHD patients.

One study found that in the acute phase, TS patients had higher symptoms of post-traumatic stress compared with CHD patients.[35] However, at short-term follow-up, another study found no differences in post-traumatic stress compared with CHD patients.[46] One study found that TS patients reported more sexual distress and experienced more symptoms of sexual dysfunction compared with CHD patients, both in the acute phase, and at long-term follow-up.[36]

Comparisons within and between myocardial infarction with non-obstructive coronary arteries and takotsubo syndrome patients

Two studies compared MINOCA patients with TS patients and found that patients with TS had lower emotional and social well-being and vitality in the acute phase, worse mental health status at short-term follow-up, and more impairment of emotional and social role functioning at long-term follow-up compared with MINOCA patients.[20,23]

Another study found that TS patients who reported an emotional trigger to the event had higher levels of depression compared with TS patients that did not report an emotional trigger at long-term follow-up.[47] The same study also reported that CHD patients who had reported an emotional trigger had higher levels of depression than TS patients that did not report an emotional trigger. No differences were found between CHD and TS patients that both reported emotional triggers.[47]

Discussion

Summary of findings

In this paper, studies of mental health status and QoL in MINOCA and TS patients after cardiac event have been systematically reviewed, compared with healthy controls, CVD risk controls, and cardiac patients, both cross-sectionally and in change over time. Generally, MINOCA and TS patients report worse mental health status and QoL than non-cardiac groups and at least as poor mental health status and QoL compared with cardiac patients. Results of longitudinal change were inconsistent, showing improved, worsened, or unchanged mental health status and QoL over time for MINOCA and TS patients.

Quality assessment and study-specific discussion

The quality assessment of included studies varied, with many studies demonstrating a high risk of bias (18/28). Only three studies were deemed at low risk of bias and should be primarily considered when evaluating the evidence regarding mental health status and QoL of MINOCA and TS patients, after the acute event. Among these studies, results were not completely congruent.

The first study compared MINOCA patients with CHD patients and investigated the prevalence of angina compared with patients with coronary artery disease.[25] Additionally, they collected data on QoL using

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the SF-12 during the follow-ups and on depression using the PHQ-9 at baseline. They found that during the acute phase, MINOCA patients reported both higher levels of depression and worse mental QoL compared with the CHD patients. Additionally, at the 12-month follow-up, MINOCA patients still reported worse mental QoL.

The second study also compared MINOCA patients with CHD patients, with the purpose of characterizing the socio-demographic, psychosocial, and clinical presentations of these patients, as well as predicting clinical outcomes and QoL.[27] They used the SAQ to collect angina-related QoL, the PHQ-9 for depressive symptoms and the PSS for symptoms of stress. Compared with the first study, they found no differences in symptoms of stress or depression during the acute phase. Additionally, while unadjusted analyses showed that CHD patients reported worse angina-related QoL at the 12-month follow-up, this association did not remain in adjusted analyses. On the other hand, at the 1- and 12-month follow-ups, ratings of stress and depression were numerically higher for the MINOCA patients, but no statistical tests of difference of these assessments were conducted.

The third study compared TS patients both with CHD patients and healthy controls, aiming to investigate differences in mortality, morbidity, and future hospitalizations.[31] Mental disorders [grouped as (i) schizophrenia, (ii) stress and anxiety, and (iii) mood disorder] were collected through hospital registries. They found that TS patients had a higher risk for stress and anxiety disorders, but not schizophrenia or mood disorders compared with healthy controls. And although the hazard ratios were higher for TS patients for rehospitalization for any mental disorder, they were not statistically significant compared with CHD patients.

These three studies reflect the general findings, with results indicating that MINOCA and TS patients have worse mental health status and QoL than healthy controls and either worse or non-different compared with CHD patients.

Between group comparisons in mental health and quality of life

In the comparisons of MINOCA and TS patients with CHD patients, all but one of the included studies showed that there was either no difference in mental health status or QoL or that it was worse for MINOCA and TS patients. Only one study[22] found that CHD patients reported higher stress and depression than their MINOCA counterparts. However, this study had a high risk of bias, and differences reported were minimal and most likely not clinically relevant. While it is possible that in certain cases, MINOCA patients experience better mental health status and QoL than CHD patients, there is little evidence currently supporting this. Current conclusions based on empirical findings are heavily inclined towards MINOCA and TS patients having at least as bad mental health status and QoL compared with CHD patients after the acute event.

Only two of the included studies compared MINOCA patients with TS patients.[20,23] These studies found that TS patients either had comparable mental health status and QoL or worse than MINOCA patients. It is known that around one-third of TS cases are reported to be triggered by emotional stress.[5] It is possible that the difference in mental health and QoL between MINOCA and TS may be driven by that TS patients have experienced an emotional trigger to a greater extent. Indeed, one of the studies compared TS patients with an emotional trigger vs. those without and found that those who experienced an emotional trigger suffered from worse mental health status in the aftermath of the event.[47] Yet, we must emphasize that studies comparing these patients are few and more research is needed.

Change over time in mental health and quality of life

When scrutinizing studies investigating longitudinal change of mental health status and QoL, it was hard to discern any consistent trends. Some symptoms were reported to improve over time,[20,21,29] while other symptoms were not.[20,27,28,30] One study even found depression and emotional well-being to become worse over time.[30] This suggests that, in many cases, mental health status and QoL in MINOCA and TS patients do not improve spontaneously. For CHD patients, it is commonly reported that in about 50% of cases, mental health status and QoL do not naturally improve after the acute event.[48–51] Among these patients, predictors for maintained poor mental health status are history of mental distress, worse mental health status at baseline, poor socioeconomic status, and younger age.[50–52] Perhaps, there are similarities between the CHD patients with persistently worse mental health status and QoL and MINOCA and TS patients. We know, for example, that MINOCA and TS patients are on average younger and more often have previously identified mental health disorders, compared with CHD patients.[5,6,10] While more research is needed to clarify risk factors and prognosis for mental health status and QoL in MINOCA and TS patients, the results presented in this review indicate that there are persistent mental health issues among these patients that need to be addressed. A previous study found that these patients valued psychological support and that the conduct of a psychological intervention RCT was feasible.[53] We believe that based on these findings, interventional studies for improving mental health status and QoL, after the acute event, could prove highly beneficial.

Mechanisms of association between diagnosis and mental health and quality of life

Given the results presented in this review, the association between mental health status and QoL and the diagnosis of MINOCA or TS seem undeniable, but it is at this point difficult to draw any firm conclusions regarding a potential causal relationship. The review is based only on observational data, and as none of the included studies used causal diagrams to guide their analyses, and many only presented unadjusted analyses, still much uncertainty exists regarding this question.

However, if the associations reflect causal relationships, it is still unclear to what role mental health status plays. Even though the results presented in this study only concern assessments of mental health status and QoL after the acute event, we cannot exclude their presence preceding the event. On the one hand, a common hypothesis for TS is that it is triggered by emotional stress,[5] and it is possible that poor mental health increases the risk for MINOCA or TS through behavioural or physiological factors.[54] On the other hand, in addition to that a cardiac event may be life-threatening and potentially traumatic,[55] the uncertainty regarding cause, treatment, and prognosis of MINOCA and TS is likely a further burden to the patients. Indeed, patients have described themselves as having an increased stress sensitivity after the event.[29] Perhaps, what is most likely is a combination of the two, acting bi-directionally. While more research is needed to clarify potential confounders, and the nature and potential direction of this association, one thing remains clear: after the acute event, many MINOCA and TS patients suffer from worse mental health status and reduced QoL.

Methodological discussion

Including many studies with small sample sizes and data that has a high risk of bias may seem superfluous. However, as this is, to our knowledge, the first review of mental health status and QoL among

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MINOCA and TS patients after the acute event, there is a value in reporting all conducted studies to provide an overview of the field. It is not only important to discuss the outcomes assessed in the included studies but also the quality of available data. Initially, our wish was to conduct a meta-analysis, pooling the results of included studies. However, at the present, it is difficult to conduct a meta-analysis for this research question, due to the high heterogeneity in study designs and high risk of bias for these outcomes.

We would again like to remind the reader that the bias assessment was made based on the data and analyses corresponding to our research question. This means that while the data of mental health status and QoL of MINOCA and TS patients have a high risk of bias, the study itself might not have been poorly conducted in regards to its primary aim. The most common issues with bias were lacking descriptions of sample size calculation, descriptions of non-respondents, and adjustment for confounding in the analyses (see *Tables 2* and *3*). Lacking sample size calculations may lead to a higher risk of Type 2 errors. As the number of non-responders is unknown, the observed estimates might be biased either towards or away from the null, depending on the characteristics of these subjects. Lacking adjustment for confounding, either by study design or statistical models, increases the risk of observing spurious associations between variables. This lack of information hinders making solid claims regarding the mental health status and QoL among MINOCA and TS patients after the acute event, and more high-quality studies are needed, specifically addressing these questions.

A growing evidence base of high-quality studies will also facilitate investigation of specific symptom clusters. Currently, even when assessing the same construct, there are variations regarding the assessment procedure, such as which tools were used, if data were self-reported or collected by a clinician, length of follow-up, if data were reported at symptom levels or as clinical diagnoses, and if it was on a graded scale or dichotomous. For example, two of the studies with low risk of bias demonstrated seemingly contradictive results regarding depression in MINOCA patients.[25,27] This could be due to procedures of data handling. Helpfully, both studies used the PHQ-9 to assess depression, but one dichotomized the variable (cut-off ≥ 10),[27] and the other reported the variable on a continuous scale.[25] It is known that dichotomization increases the risk of Type 2 errors,[56] and it is possible that the *P*-value (which was $P = 0.06$) would have been deemed statistically significant if PHQ-9 was analysed continuously.

Finally, a limitation is the shifting definitions of diagnoses and updates of diagnostic procedures of MINOCA and TS. Depending on the year of publication, the definition and diagnostic procedures of MINOCA may vary. For example, in 2018, both myocarditis and TS were excluded from the definition of an MI,[8] perhaps another explanation for the contradictory results of Safdar *et al.*[27] and Grodzinsky *et al.*[25] as the latter did not mention any exclusion of TS patients. Furthermore, recent studies have shown that for example using cardiovascular magnetic resonance imaging greatly improves correct diagnosis of MINOCA patients.[57] As such, although we describe and narratively compare studies of MINOCA and TS patients, uncertainties remain whether the different studies actually refer to the same patients.

Taken together, these issues remain an obstacle in making firm conclusions regarding specific symptoms and trends of mental health and QoL, in MINOCA and TS patients, and more high-quality research is needed.

Conclusion

In this systematic review, we have reviewed mental health status and QoL in MINOCA and TS patients after the acute event. The current literature suggests that these patients more often have worse mental health status and QoL than non-cardiac groups. Compared with CHD patients, it is yet difficult to conclude whether mental distress and QoL are equal or worse for MINOCA and TS patients. Studies investigating longitudinal change were few and showed no coherent trends, but gave concerns regarding persistent poor mental health status and reduced QoL. Many of the studies had a high risk of bias and suffered from small sample sizes calling for a need for more high-quality research, investigating this specific question.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

C.H., E.M.G.O., E.R., P.Le., P.T., and S.H. contributed to the conception or design of the work. S.H. contributed to the acquisition of data for the work. P.Le. and S.H. contributed to the analysis and interpretation of the data for this work. P.Le. and S.H. drafted the manuscript. A.N., A.U., C.H., E.M.G.O., E.R., J.S., L.K., P.Le., P.Ly., P.T., and S.H. critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

All relevant data are within the manuscript and its supporting information files.

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