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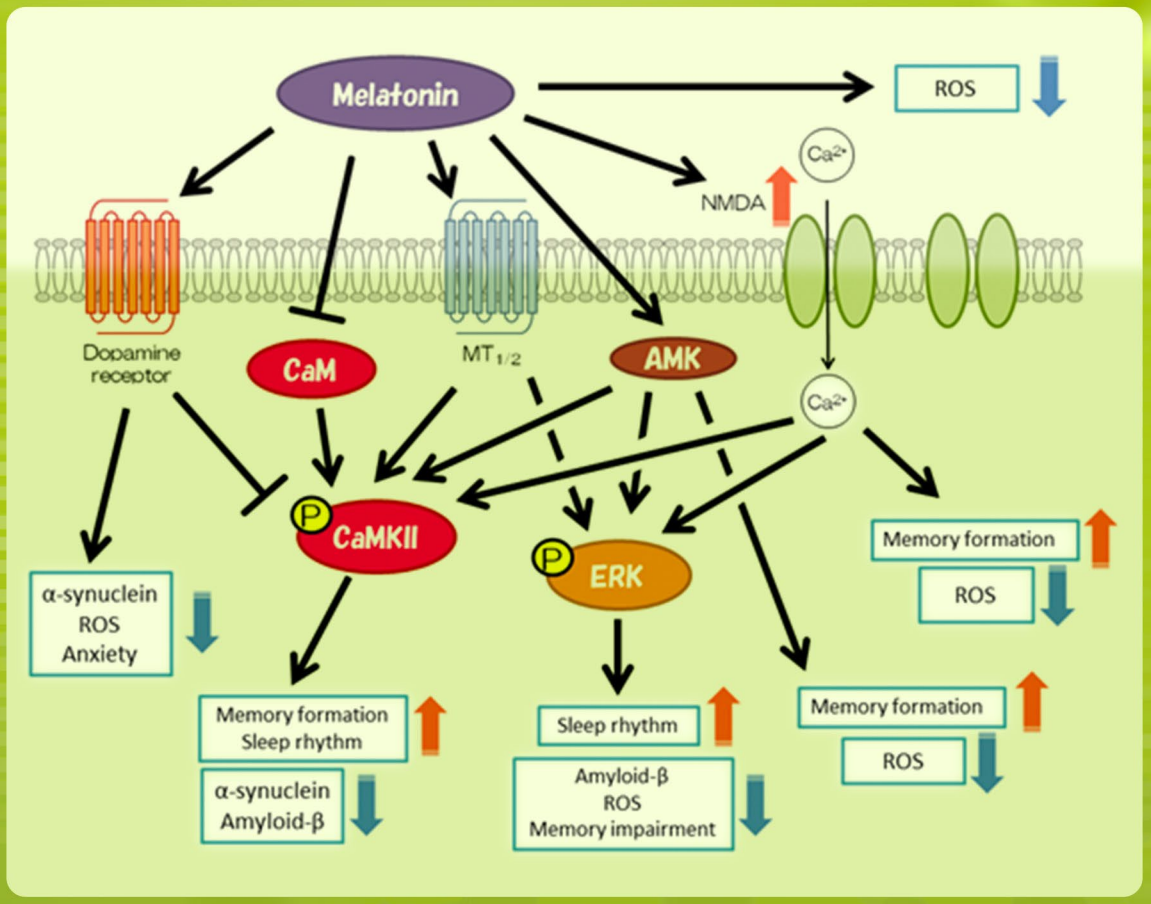

Melatonin & treatment of dementia

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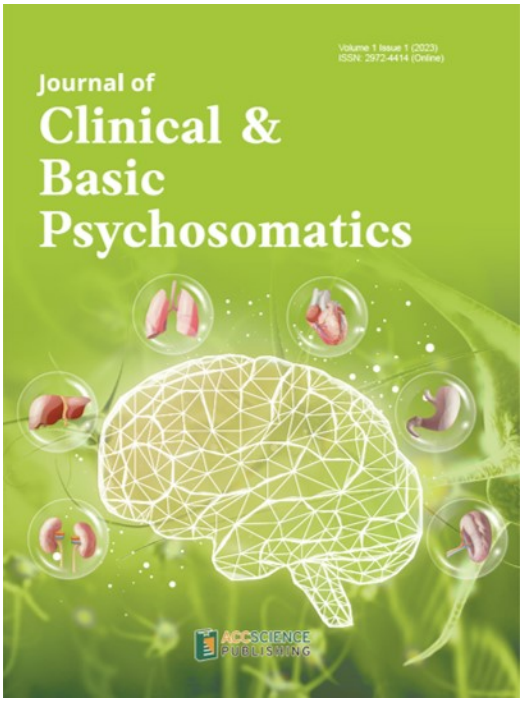

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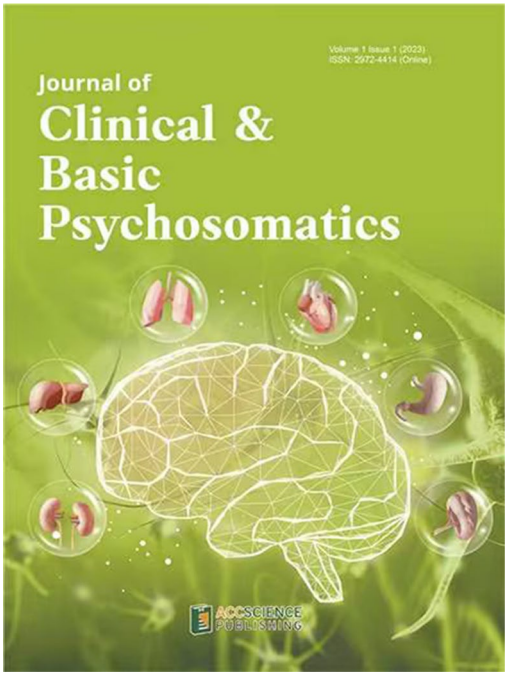

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REVIEW ARTICLE

Use of melatonin for the treatment of dementia: Addressing core symptoms and behavioral challenges

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Abstract

Dementia mainly includes Alzheimer's disease (AD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and vascular dementia (VaD). In addition to cognitive impairment, patients often suffer from behavioral and psychological symptoms of dementia (BPSD). Melatonin administration has emerged as a promising therapeutic strategy with potential benefits for BPSD. This review focuses on the therapeutic effects of melatonin on the core symptoms of dementia and BPSD. Specifically, the impact of melatonin on memory impairment, sleep disturbances, anxiety, depression, delusions, and hallucinations is reviewed. The melatonin's role in amyloid-β, synuclein aggregation, reactive oxygen species, and dementia subtypes are discussed. We aim to provide an up-to-date review of the emerging application of melatonin; thus, dementia patient care and social welfare can be improved by the appropriate usage of this medication.

Keywords: Dementia; Melatonin; Calcium/calmodulin-dependent kinase II; Extracellular signal-regulated kinase; Dopamine; Fatty acid-binding protein

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1. Introduction

Dementia is a disease in which brain function loss occurs due to injuries and diseases to the brain. It is a general term for diseases related to cognitive impairment and the resulting living difficulties. Alzheimer's disease (AD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and vascular dementia (VaD) are common types of dementia. Dementia also includes alcohol-related disorders and Creutzfeldt-Jakob disease, related to abnormal prion proteins.

AD causes apathy, depression, and mild dementia in the early stages, and AD progression leads to severe memory impairment and brain atrophy due to neuronal cell loss. Although the underlying mechanisms are poorly understood, the theory known as the "amyloid hypothesis" is reasonably well-supported. This theory suggests that the aggregation and accumulation of insoluble amyloid-β and oligomerization of soluble amyloid-β lead to abnormal tau phosphorylation, aggregation, and oligomerization. As a result, neuronal functioning is impaired, which leads to neuronal cell death and subsequent inflammation, causing the death of surrounding neurons[1]. At present, N-methyl-D-aspartate (NMDA) receptor antagonists and cholinesterase inhibitors

are administered to promote neuroprotection, suppress acetylcholine degradation, and improve memory impairment[2].

Common symptoms of VaD include apathy, depressive symptoms, and memory impairment, similar to AD symptoms. VaD is caused by neuronal cell death and partial loss of function due to various vascular disorders, such as cerebral infarction and cerebral hemorrhage, and is also correlated with transient ischemic attacks, hypertension, and hyperlipidemia[3]. VaD is a common condition for which there are currently no specific treatments because the underlying pathology is still unclear. However, medications that improve cerebral circulation and metabolism, such as nicergoline, antihypertensive drugs, and therapeutics, are the currently available medications used to improve the symptoms of AD[4,5].

Excessive aggregation of α-synuclein is the purported primary cause of DLB, which is similar to Parkinson's disease. DLB is characterized by an α-synuclein-mediated blockage of dopamine release, particularly from the substantia nigra to the striatum, leading to amnesia, visual hallucinations, and delusions. Cholinesterase inhibitors and NMDA inhibitors are used in the same way as in AD, and levodopa, a dopamine action enhancer that is also used as a therapeutic agent for Parkinson's disease, is used to treat DLB in some cases[6].

In FTD, decreased progranulin enhances the excessive phosphorylation of tau, and abnormally, aggregated tau is thought to cause neuronal cell death due to symptoms of dementia. However, it should be noted that there are also non-tau forms of FTD and that FTD is a neuropathologically and genetically diverse condition. FTD can be divided into two main categories: (i) the behavioral variant of FTD with changes in social behavior and personality, and (ii) primary progressive aphasias with gradual loss of language skills from the early stages. FTD is characterized by obsessive-compulsive repetitive behavior, hoarding behavior, anti-social behavior and lack of empathy in the behavioral variant, and difficulty remembering common words and poor word comprehension in primary progressive aphasias[7]. At present, there are no effective therapies for these cognitive impairments.

Among these four common types of dementia, AD, DLB, and FTD are classified as neurodegenerative diseases, and VaD is classified as a non-neurodegenerative disease. Abnormal protein aggregation is associated with AD, DLB, and FTD, as well as a wide range of neurodegenerative diseases, and developing treatments to inhibit protein aggregation has become increasingly necessary, and may be useful in treating other diseases, such as polyglutamine disease and amyotrophic lateral sclerosis[8]. Therefore, it is necessary to improve ameliorating drugs that act against the functional deterioration of the proteasome and autophagy and prevent the accumulation of denatured proteins due to aging or other factors.

In addition to the core symptoms of dementia, such as memory impairment, lack of judgment, and agnosia, behavioral and psychological symptoms of dementia (BPSD) may occur, which result in sleep disorders, depression, anxiety, delusions, and visual hallucinations. BPSD imposes a great physical and psychological burden, not only on the patient but also on the caregiver. Sleep disorder, one of the BPSD, contributes to a decline in cognitive function and an increased risk of dementia[9]. Some studies showed that the expression deficiency of *Bmal1*, a circadian clock gene, is an important contributor to aging-related diseases such as AD and that *Bmal1* expression is also attenuated with aging[10]. Thus, substantial attention and care are required for ameliorating BPSD.

2. Melatonin activity for improving dementia

In the central nervous system, melatonin, which is synthesized and secreted from the pineal gland, is mediated by the G-protein-coupled melatonin receptors, MT1/MT2, and is known to regulate circadian rhythm, seasonal reproduction, and plays a role in thermoregulation[11-14]. In addition, melatonin has been reported to exert receptor-mediated and non-receptor-mediated antioxidant and anti-inflammatory effects[15-18]. Some studies have reported that melatonin may be partly related to the modulation of apoptosis and protection of the cholinergic system, which is associated with AD[19]. Recently, it has been revealed that a single dose of melatonin enhances learning and memory functions, and that short-term and long-term memory enhancement is mediated by melatonin and N1-Acetyl-5-methoxykynuramine (AMK), which is a melatonin metabolite known to act as an antioxidant against free radicals[20-22]. Research has shown that the long-term administration of melatonin may attenuate memory deficits caused by aging through its antioxidant and anti-inflammatory effects[23-25]. These neuroprotective effects may also prevent the development of dementia. Moreover, it has been reported that melatonin may have sleep-promoting effects through the regulation of circadian rhythm and could improve sleep disorders caused by BPSD[12,15,23]. Research has indicated that long-term administration of melatonin improves cognitive performance, and single-dose administration of melatonin enhances memory and may ameliorate memory impairment caused by dementia[12,20,21]. Furthermore, melatonin has very minimal side effects that no acute toxicity was observed in mice that had been administered with doses of up to 800 mg/kg[26] and no serious side effects

were detected in patients undergoing major liver resection at doses up to 50 mg/kg[27]. Therefore, melatonin could possibly be used as a preventive and therapeutic agent for dementia.

Melatonin inhibits dopamine release from areas such as hypothalamus and hippocampus[28]. Through the prevention of dopamine release, melatonin administration exhibits dual properties of exacerbating symptoms and protecting against neurodegenerative disease in patients with Parkinson's disease[28]. It has been reported that melatonin suppresses the amphetamine-induced release of dopamine neurotransmitters and reduces α-synuclein overexpression[29]. Furthermore, melatonin is suggested to modulate dopaminergic neurotransmission through another mechanism[30], and this dopamine regulation may play a role in dementia, such as DLB.

Calcium/calmodulin-dependent kinase II (CaMKII), which is a major postsynaptic protein at excitatory synapses, is one of the Ca^{2+}/calmodulin-dependent protein kinases and is activated by calmodulin (CaM), which plays a pivotal role in Ca^{2+} signal transduction. CaMKII plays a fundamental role in synaptic plasticity and long-term potentiation, which are both closely related to learning and memory in the central nervous system[31]. In addition, the previous studies have suggested that the CaMKII is involved in α-synuclein aggregation, which has been implicated in DLB and Parkinson's disease, and the proteasome, which is a protein degradation system[32,33]. It has been reported that melatonin binds tightly to CaM and acts as a CaM antagonist[34]. Interestingly, AMK works similarly to melatonin, suggesting that many of the *in vivo* effects of melatonin may actually be mediated by AMK[35]. However, some studies have shown that melatonin decreases CaMKII activity in lipidic microenvironments and increases CaMKII activity in aqueous microenvironments, suggesting that a more complex interaction between melatonin and CaMKII may exist[36]. CaMKII and melatonin are associated with memory formation[21], and both have been implicated in dementia and Parkinson's disease[32,37]. There are some reports stating that the regulation of CaMKII by melatonin inhibits α-synuclein aggregation through the proteasome[27], and melatonin may also attenuate α-synuclein aggregation through pathways involved in autophagy[38]. Hence, the association between melatonin and CaMKII may be significant in improving dementia-related symptoms.

Studies have shown that melatonin increases NMDA receptors in the rat hippocampus[39], and the modulation of NMDA receptors leads to reactive oxygen species (ROS) reduction in ovariectomized rats[40]. An insufficiency of NMDA receptors is also suggested to be one of the major causative factors in AD pathology[41]; therefore, melatonin may play a role in slowing down AD progression through the regulation of NMDA receptors.

Extracellular signal-regulated kinase (ERK), which is largely involved in neuronal plasticity and neuronal cell death, is also involved in neuronal anti-inflammatory pathways[42] and some studies have shown that melatonin increases ERK expression through melatonin receptors[43]. Moreover, the previous studies have shown that MT2-mediated potentiation of ERK signaling may improve memory impairment[44]. Therefore, ERK-mediated anti-inflammatory and antioxidant effects may be associated with dementia.

AMK is thought to be primarily involved in the expression of ERK and CaMKII[45]. The previous studies have reported that age-related activation of the kynurenine pathway leads to tryptophan depletion and a decrease in melatonin[46]. However, AMK has been shown to upregulate its precursor, N1-acetyl-N2-formyl-5-methoxykynuramine, in *in vivo* models of inflammation[47]. AMK, which has stronger antioxidant and memory-enhancing effects, is involved in the expression of ERK and CaMKII, and, thus, may play a fundamental role in dementia.

It is generally accepted that melatonin improves sleep disorders and poor sleep quality through the regulation of circadian rhythm and may also reduce sleep-related breathing disorders and their complications during sleep[48]. Because sleep apnea syndrome is involved in heart inflammation and hypertension[49], it is possible that improved breathing during sleep through melatonin administration may be related to improvements in dementia and BPSD. Endogenous melatonin levels begin to increase 2 h before sleep onset and help to promote sleep through MT1/MT2 receptors[50]. Furthermore, exogenous melatonin easily crosses the blood–brain barrier and, thus, plays an important role in the treatment of insomnia. Therefore, melatonin is an effective treatment for insomnia caused by dementia. Furthermore, it is suggested that melatonin functions to remove amyloid-β, which leads to "brainwashing," and enhances sleep through the clearance of amyloid-β from the central nerve system, thus acting as a prophylactic agent against AD[51]. In addition, some studies reported that phosphorylation of CaMKII affects sleep in rats[50], while ERK has been shown to prepare the brain for sleep in mice[49]. Thus, it is suggested that melatonin's effect on sleep may be related to CaMKII and ERK.

Melatonin has been suggested to have antidepressant and anxiolytic effects and reportedly ameliorates anxiety and depression-like behavior through the ventral hippocampus in AD mice[52]. Furthermore, melatonin receptors

MT1/MT2 may act as potential targets for treatments of depression[53]. Research has shown that melatonin produces an antidepressant-like effect by interacting with dopamine receptors[54]. Furthermore, melatonin has been shown to be closely related to post-traumatic stress disorder (PTSD) and stress-related disorders associated with dementia[55], while ramelteon, a melatonin receptor agonist, has been reported to improve PTSD symptoms in fatty acid-binding protein 3 (FABP3) null mice[56]. FABP is a protein that is highly expressed in the central nervous system and is associated with dopamine 2 (D2) long isoform (D2L) receptors[57]. Administration of melatonin has been shown to increase the affinity of D2 dopamine receptors in rat brains[58]. It has also been suggested that melatonin may affect the function of D2L receptors in PTSD through FABP. CaMKII may also play a role in dopamine and glutamate signaling[50]. Research has shown that CaMKIIα interacts with D2 receptors and binds to D2 receptors *in vitro*[59]. Studies have also found that CaMKII and D2 receptors contribute to the drug reward system[60], and it is suggested that CaMKII acts on the reward system through D2 receptors. It has also been reported that inhibition of CaMKII activity in the amygdala, which is involved in reward learning, may inhibit the memory formation of inhibitory avoidance[61]. Thus, it is possible that the antidepressant or anxiety effects of melatonin may be mediated through the activation of dopamine receptors, which are induced by CaMKII.

These findings suggest that melatonin may act as a therapeutic agent for dementia through MT1/2 receptor-mediated and non-mediated mechanisms, dopamine and NMDA receptor-mediated mechanisms, and through CaM, CaMKII, ERK, and AMK (Figure 1 and Table 1).

3. Involvement of melatonin in the treatment of major types of dementia

3.1. Involvement of melatonin in the treatment of AD

Various studies have shown that melatonin plays a major role in reducing the production and aggregation of amyloid-β and in the treatment of AD. Melatonin is known to regulate the expression of *BACE1*, *APP*, and *ADAM10* genes through its antioxidant action and receptor-mediated action and may also alleviate the amyloid-β_{42}-induced reduction of Pin1 and suppress GSK expression to inhibit the promotion of amyloid-β production[62,63]. Research has also demonstrated that long-term oral melatonin administration has an implication on amyloid-β transport and autophagy and reduces the accumulation of amyloid-β[64]. In a previous study, melatonin was found to ameliorate cognitive impairment, amyloid-β production, tau aggregation, and decreased dopamine transporter expression in the hippocampus of methamphetamine-induced AD rats[62]. Another study reported that melatonin reduces amyloid-β accumulation, improves short-term memory[65], reduces memory impairment and tau aggregation, and improves diabetes mellitus, which is a risk factor for the development of AD, in a streptozotocin-induced AD rat model[66]. Other researches have also found that D-penicillamine regulates ADAM10 expression through the MT1 receptor and downstream PKA/ERK/CREB pathway and may improve the cognitive ability of APP/PS1 mice by reducing Aβ generation[67]. Together, these studies suggest that melatonin may ameliorate amyloid-β aggregation and cognitive impairment in AD through receptor-mediated and non-receptor-mediated pathways. It has been hypothesized that the melatonin-mediated amelioration of AD could be effected through the regulation of cholesterol[68], cholinergic system[19], neurogenesis[69], insulin,[70] and mitochondrial dysfunction[71].

Many proteins linked to the production of amyloid-β have a putative calmodulin-binding domain, thus contributing to the hypothesis suggesting that calmodulin is critically involved in AD[72]. In connection with this hypothesis, calcineurin (CaN), which is activated downstream of soluble amyloid-β aggregates, is thought to play a pivotal role in AD[73]. A previous study reported that melatonin exhibits neuroprotective effects when oxidative damage-induced cell death occurs by preventing the CaN-activated nuclear translocation of activated T-cell nuclear factors in human neuroblastoma SH-SY5Y cells[74]. Interestingly, CaN and CaMKII are believed to have opposite functions in dendritic spines: CaMKII activity promotes long-term synaptic potentiation after a Ca^{2+} influx through NMDA-type glutamate receptors, and CaN responds to the reduced Ca^{2+} influx by inducing long-term depression through the same receptors[75]. It has also been suggested that CaN-dependent dephosphorylation inhibits CaMKII-mediated phosphorylation, and this inhibition increases phospho-CaMKII, thereby stimulating CaMKII-dependent cellular actions[76]. However, melatonin may suppress CaN through CaMKII, thereby promoting long-term potentiation (LTP), improving learning and memory functions, and exhibiting a neuroprotective effect that suppresses AD. CaMKII promotes the release of acetylcholine[77]; however, melatonin is expected to be a new symptomatic drug for AD that improves memory and cognition through a mechanism different from that of cholinesterase inhibitors.

AD is associated with various BPSDs. Research has shown that depression may worsen AD pathology in the hippocampus[78], while melatonin has been reported to ameliorate depression and anxiety in AD mice[52]. Studies have reported that melatonin and ramelteon improve sleep

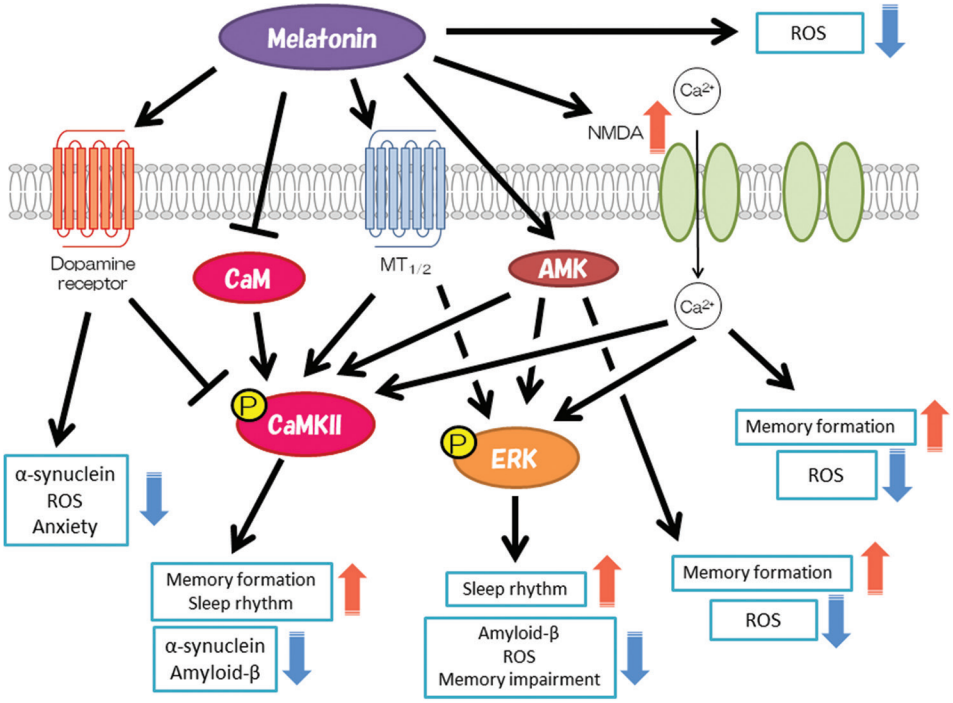

Figure 1. Schematic pathways of melatonin therapy and its effects on dementia. Melatonin acts through receptors and kinases for the treatment of dementia. Abbreviations: ROS: Reactive oxygen species; CaM: Calmodulin; CaMKII: Calcium/calmodulin-dependent protein kinase II; AMK: N1-Acetyl-5-methoxykynuramine; ERK: Extracellular signal-regulated kinase.

Table 1. Function of melatonin-related substances

Receptors/Kinases	Details	References
MT1/MT2	Melatonin receptors MT1/MT2 are part of the G protein-coupled receptor family and are involved in the regulation of circadian rhythm and memory formation. These receptors are localized in areas, such as the suprachiasmatic nucleus, prefrontal cortex, amygdala and the dentate gyrus, CA3 and CA1 regions, and subiculum of the hippocampus.	[11,12]
NMDA receptor	NMDA is an ionotropic glutamate receptor and ion channel and is localized in neurons. It plays a fundamental role in memory formation.	[38-41]
Dopamine receptor	Dopamine receptors are part of the G protein-coupled receptor family and are localized in the brain. The antidepressant-like effect of melatonin is required to activate the dopamine D1 and D2 receptors.	[53]
AMK	AMK, which is a melatonin metabolite protein, acts as a free-radical scavenger and promotes memory formation.	[20,22]
CaM	CaM acts as part of the calcium signal transduction pathway (Ca^2+sensor). Calcium-binding proteins target Ca^2+and activate CaM.	[31]
CaMKII	CaMKII is an abundant protein in the brain and a major constituent of postsynaptic density. It supports various synaptic functions involving learning and memory.	[31]
ERK	ERK, which is part of the MAPK signaling pathway, plays a role in various cellular processes, including metabolism, translation, transformation, and apoptosis.	[42,43]

Abbreviations: NMDA: N-methyl-D-aspartate; CaM: Calmodulin; CaMKII: Calcium/calmodulin-dependent protein kinase II; ERK: Extracellular signal-regulated kinase.

disorder in AD[79]; however, melatonin may not be an effective soporific agent in people with AD[80]. In addition, it has been suggested that hippocampal MT2 melatonin receptor expression is reduced in AD[81]. This data indicates that melatonin receptors may be impaired in the area of the brain that regulates sleep rhythm in some AD patients; however, melatonin may still be effective in treating sleep disorders resulting from AD.

3.2. Involvement of melatonin in the treatment of DLB

Numerous studies have found that melatonin acts to reduce neurotoxicity by inhibiting α-synuclein aggregation[38]

Table 2. Function of melatonin-related substances

Type	Human or animal	Model	Effect	References
AD	SD rat HT22 cell	$A\beta_{1-42}$-induced	MEL reversed the alteration in GSK3β, ERK, and AMPK activity induced by $A\beta_{1-42}$.	[14]
AD	C57BL/6 mice	APP transgenic	MEL attenuated memory deficits in step-down and step-through passive avoidance tests.	[19]
AD	Wister rat	OXYS rat	MEL ameliorated increased anxiety and decreased locomotor activity, exploratory activity, and reference memory.	[23]
AD	ICR mice	$A\beta_{1-42}$-induced	MEL attenuated the mitochondrial damage and reduced the expressions of the p-tau and some key proteins of apoptosis, and improved cognitive function of the mice induced by $A\beta_{1-42}$.	[24]
AD	C57BL/6 mice	Scopolamine-induced	MEL attenuated scopolamine-induced synaptic dysfunction and memory deficits by reducing oxidative brain damage, stress kinase expression, neuroinflammation, and neurodegeneration.	[25]
AD	B6129SF2/J mice	3×Tg-AD	MEL regulated the expression of the proteins (i.e., GSTP1 and CPLX1) linked to anxiety and depression behaviors.	[52]
AD	Wister rat	Methamphetamine-induced	MEL attenuated methamphetamine-induced toxicity in the hippocampus involving the amyloidogenic pathway.	[62]
AD	SH-SY5Y cell	$A\beta_{1-42}$-induced	MEL attenuated $A\beta_{1-42}$-induced alterations of βAPP-cleaving secretases, possibly through the Pin1/GSK3β/NF-κB pathway.	[63]
AD	APP/PS1 transgenic mice	APP/PS1 transgenic	MEL reduced Aβ deposition and improved spatial memory by a mechanism involved in the down-regulation of BACE1 and mitophagy.	[64]
AD	Wister rat	Streptozotocin-induced	MEL reduced Aβ levels but did not reduce GFAP levels.	[65]
AD	Wister rat	Streptozotocin-induced	MEL improved memory deficits in streptozotocin-induced hyperglycemia rats by restoring the insulin signaling pathway which is independent of its effects on blood glucose and insulin levels.	[66]
AD	Wister rat	$A\beta_{1-42}$-induced	MEL reversed oxidative stress and Aβ-induced alterations in cholesterol, lipids, and fatty acids alterations, protected mitochondrial membranes, and increased levels of linolenic and n-3 eicosapentaenoic acid, promoting endogenous anti-inflammatory pathways.	[71]
AD	Human		10 mg of MEL was not effective in improving sleep or agitation in patients with severe dementia.	[80]
DLB	Wister rat	Amphetamine-induced	MEL prevented amphetamine-induced toxicity in the hippocampus of postnatal rats possibly through its antioxidative effect and mitochondrial protection.	[29]
DLB	Wister rat	MPP+-induced	MEL attenuated MPP+-induced nigrostriatal dopaminergic damage through its ability to prevent the increase of GSSG/GSH ratio.	[83]
VaD	Wister rat	BCCAO-induced	MEL regulated inflammation and blood-brain barrier disruption and improved cognitive function in VaD rats, partly by activating the SIRT1/PGC-1α/PPARγ signaling pathway.	[86]
VaD	2K1C rat	2K1C	MEL receptor agonist agomelatine attenuated 2K1C-hypertension-induced memory deficits, endothelial function damage, nitrosative stress, mitochondrial dysfunction, inflammation, and brain damage.	[87]
VaD	Swiss albino mice	CCH-induced	MEL receptor agonist agomelatine reduced CCH-induced memory deficits and attenuated cholinergic dysfunction, oxidative stress, and tissue damage.	[89]
VaD	SD rat	BCCAO-induced	MEL might produce a neuroprotective effect through its antioxidant action and by increasing the expression of SMP30 and OPN that is not comparable with that of DON.	[90]

(Cont'd...)

Table 2. ***(Continued)***

Type	Human or animal	Model	Effect	References
VaD	Mongolian gerbils	ischemic stroke	MEL treatment after transient global cerebral ischemia improved cognitive deficit through restoration of myelin, increase of oligodendrocytes which are closely related to the activation of ERK1/2 signaling, and increase of glutamatergic synapses in the ischemic brain area.	[91]
VaD	Wister rat	BCCAO-induced	Treatment with MEL improved the cognitive deficits induced by BCCAO, accompanied by a reversal of oxido-nitrosative stress, neuroinflammation, BDNF depletion in the hippocampus region, and reduced BDNF expression of hippocampal protein. In addition, the treatment with MEL and resveratrol significantly decreased acetylcholinesterase activity.	[92]
FTD	Human	/	Ramelteon had no effect.	[94]
FTD	Human	/	Agomelatine, but not MEL, contributed to a significant reduction of apathy in FTD subjects and of caregiver distress due to patients' apathy.	[95]
KA	C57BL/6J mice	KA-induced	MEL might exert its neuroprotection by inhibiting KA-induced autophagy and subsequent mitochondrial loss as well as by reducing α-synuclein aggregation through an increase of α-synuclein ubiquitination in the CNS.	[38]
Aging	C3H/HeJ mice	*Klotho* mouse model	MEL attenuated oxidative stress and memory deficits induced by Klotho deficiency through signaling interaction between the MT2 receptor and ERK- and Nrf2-related antioxidant potential.	[44]
PD	SD rat	α-synuclein A30P	MEL offered protection against lenti-A30P-induced cell death and a total neuroprotective effect in both regions of the substantia nigra.	[84]
CCH	Wister rat	BCAS-induced	MEL improved cognitive deficits in the 2VO model, and these effects were associated with the reduction in oxidative stress, endoplasmic reticulum stress, and apoptosis.	[88]

Abbreviations: MEL: Melatonin; BCCAO: Bilateral common carotid artery occlusion; 2K1C: Two-kidney, one-clip; Aβ: Amyloid-β; CCH: Chronic cerebral hypoperfusion; KA: Kainic acid; BCAS: Bilateral common carotid artery stenosis; ERK: Extracellular signal-regulated kinase; AMPK: AMP-activated protein kinase; GSTP1: Glutathione S-transferase pi 1; CPLX1: Complexin 1; Pin1: Peptidyl-prolyl cis/trans isomerase NIMA-interacting 1; MPP: 1-methyl-4-phenylpyridinium ion; GSSG: Glutathione disulfide; GSH: Glutathione, reduced form; 2VO: The two-vessel occlusion.

and destabilizing preformed α-synuclein fibrils[82]. In addition, melatonin is reported to attenuate 1-methyl-4-phenylpyridinium-induced neurodegeneration and glutathione impairment in the nigrostriatal dopaminergic pathway in Parkinson's disease[83] and to prevent dopaminergic cell loss induced by lentiviral vectors expressing A30P-mutant α-synuclein[84]. CaMKII has also been reported to improve cognitive function by increasing proteasome activity in a DLB mouse model[32].

It has also been reported that melatonin improves rapid eye movement (REM) sleep behavior disorder, which is associated with DLB. Poor sleep quality and excessive daytime sleepiness are common and severe problems associated with DLB and are linked to depression. In addition, decreased melatonin production due to reduced REM is proposed to be associated with AD[85]. Therefore, the effect of melatonin on sleep disorder improvement is expected to prevent core symptoms in DLB and other diseases, such as BPSD.

3.3. Involvement of melatonin in the treatment of VaD

Research has shown that melatonin prevents blood–brain barrier disruption and inflammation in VaD rats[86]. Furthermore, it is thought that melatonin receptors are involved in the improvement of renovascular hypertension, which is closely related to VaD[87]. Melatonin improves cognitive function by suppressing endoplasmic reticulum stress and promoting synaptic plasticity during chronic cerebral hypoperfusion, which is the most common cause of cognitive impairment in rats[88]. The melatonin receptor agonist, agomelatine, ameliorates memory impairment, and reduces oxidative stress and tissue damage in mice with chronic cerebral hypoperfusion-induced VaD[89], and melatonin ameliorates brain oxidative stress and upregulates the oxidative stress markers, protein-30, and osteopontin, in rats with VaD[90]. These studies suggest that melatonin administration works to prevent VaD by suppressing the pathological factors related to VaD and may ameliorate memory impairment by reducing oxidative stress.

CaMKII, whose expression is regulated by melatonin, promotes pCaMKII signaling in the hippocampus, and suppresses ox-CaMKII signaling, thereby preventing neuronal cell death and improving cognitive function through neuroprotection in VaD rats[37]. Research has shown that ERK is increased after melatonin treatment, and melatonin may ameliorate cognitive impairment in adult gerbils with transient global cerebral ischemia[91]. It has also been demonstrated that melatonin may be beneficial in bilateral typical carotid artery occlusion-induced VaD rats through the expression of brain-derived neurotrophic factor (BDNF)[92], which is regulated by melatonin receptors[93]. These studies suggest that melatonin may act through CaMKII, ERK, and BDNF in VaD treatment.

3.4. Involvement of melatonin in the treatment of FTD

Few studies have reported the significant effects of melatonin in FTD because sleep disorders related to FTD exhibit different tendencies when compared to those observed in AD. Furthermore, the melatonin receptor agonist ramelteon also has no effect on the catatonoid frontal signs in FTD[94].

In contrast, agomelatine, which is associated with melatonin receptors and 5-HT2C receptors, has been reported to increase noradrenergic and dopaminergic neural activity in the prefrontal cortex and antagonize GABAergic neuron activity through 5-HT2C antagonism when treating apathy[95]. Therefore, melatonin may complement the action of the 5-HT2C receptor, instead of acting directly on the receptor.

These findings indicate that melatonin may have effects on various dementia and peripheral diseases (Table 2).

4. Conclusion

This review summarizes melatonin's effects on the core symptoms of dementia and BPSD and provides insights into the potential mechanisms in each of the four main types of dementia. Melatonin suppresses various symptoms through antioxidant, neuroprotective, anti-inflammatory, and anti-anxiety effects. In addition, melatonin is applied in multiple fundamental treatments, directly improving quality of life. In many cases, melatonin may be a valuable treatment for dementia. Many ongoing studies are still investigating melatonin to expand our understanding and corroborate it as a potential therapeutic agent for dementia.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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Ethics approval and consent to participate

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Availability of data

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Study on the relationship between feelings of psychological control, sense of benefit, and burden on caregivers for children with congenital skeletal malformations

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Abstract

Negative life events can lead to positive psychological changes despite the adverse effects. This study aims to investigate positive psychology in caregivers of children with congenital bone deformities. The research analyzes caregivers' burden, psychological control, and benefit. The results showed: The average burden on caregivers for children with congenital skeletal malformations was 36.46 (mild-to-moderate), the individual burden score was around 21.13, and the responsibility burden score was around 8.55. The burden of care was negatively associated with the sense of benefit, suggesting that higher levels of psychological control were associated with lower caregiver burden. The sense of benefit partially mediated between psychological control and the caregiver burden.

Keywords: Care burden; Sense of psychological control; Sense of benefit; Congenital bone deformity

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1. Introduction

Despite the negative impact, life adversity produces positive psychological and behavioral changes during the long-term coping process[1]. Caregivers are a vulnerable group and more attention was paid to their positive feelings and individual control. Beyond experiencing anxiety, depression, pressure, and burden, caregivers can also undergo positive changes, such as increased self-worth, personal growth, coping with challenges, interpersonal relationships, social support, and stronger family bonds. These positive changes in cognitive evaluation are known as a "sense of benefit," indicating the establishment of positive cognitive models to cope with crisis events[2]. Psychological control is also an important aspect of the cognitive mode in coping with pressure. Individuals realize this through psychological self-control, including achieving specific goals and controlling their emotions, behaviors, actions, and languages[3]. The sense of psychological control plays an essential role in the care burden and it can enhance the caregiver's ability to control stressful events[4].

It is confirmed that the sense of benefit significantly affects the care-receiving experience[5]. Cantó found that the sense of benefit helps caregivers effectively environment adaptation and improve their mental health[6]. Beibei *et al.* suggested

that positive coping styles can help individuals effectively perceive potential threats by gaining control over diseases and life[7]. Reitai proved that psychological control at work affects the experience of positive stress, which can be seen as a sense of career benefit[8]. Furthermore, Fife *et al.* found that the psychological control of cancer patients predicts stress levels. It is specifically manifested in enhancing the general control of cancer patients and a corresponding reduction of disease-related stress[9]. Therefore, the caregiver's sense of benefit is an important variable affecting the mind and behavior.

Concepts related to the sense of benefit, the sense of psychological control, and the burden of care are presently well-defined in the literature. Extensive research has provided a detailed analysis of the relevant definition, classification, and mechanism of action of each concept. In addition, the factors influencing these three concepts and their relationship with other variables have been thoroughly analyzed. It is concluded that individuals may develop a positive evaluation of stressful events over time. This positive evaluation enables them to experience a sense of benefit while coping with disease and pressure, regaining control over the stressful situation, and achieving a state of physical and mental balance. Notably, the sense of benefit plays an intermediary role in this process.

The previous studies mainly have primarily focused on the care burden experienced by caregivers of patients with chronic diseases, with few exploring the care burden of caregivers of children with congenital bone malformations. The caregivers of children with congenital bone malformations face two main challenges: Attending to the children's daily needs and providing support throughout the process of orthopedic surgery. Due to the children's skeletal dysfunction, they are unable to care for themselves, requiring caregivers to invest more time and energy. Consequently, caregivers experience additional physical and psychological pressure[10]. Caring burden, as a kind of pressure and crisis, negatively impacts the physical and mental health of both caregivers and care recipients [11]. Research has revealed that parents of children with cancer endure more physical, psychological, social, and economic pressures than parents of healthy children[12].

However, the group characteristics of caregivers of children with congenital bone malformations indicate their susceptibility to emotional stress and care burden, making it crucial to study this particular caregiving group. In addition, there is a lack of relevant research on whether the sense of benefit plays a mediating role in the relationship between psychological control and care burden. Therefore, building on the cognitive regulation theory of stress, this study aims to delve further into the influencing mechanism of caregiving stress among caregivers of children with congenital bone malformation. The present study assumed that caregivers' sense of psychological control would affect the caregiving burden through the mediating effect of the sense of benefit. Specifically, the present study aimed to explore the following research questions: (i) What are the current phycological status and the perceived benefits of the care burden among caregivers of children with congenital skeletal malformations? (ii) What is the relationship between caregivers' sense of psychological control, benefit, and care burden in children with congenital skeletal malformations? (iii) Does the sense of benefit play a mediating role between psychological control and care burden in caregivers of children with congenital skeletal malformations?

2. Methods

2.1. Research tools

The present study employed a questionnaire survey consisting of four parts: General demographic information scale, benefit sense scale (benefit finding scale [BFS]), general control sense sub-scale (Shapiro Control Inventory [SCI]), and care burden scale (Zarit Caregiver Burden Interview [ZBI]). The details are elaborated further as follows:

2.1.1. General demographic information

The general demographic information collected for children includes age, sex, age, only child, family history, and disease to pay for medical expenses.

The general demographic information collected for caregivers includes gender, age, ethnic group, education, occupation status, religion, marital status, caregiver-patient relationship, per capita monthly income, and family residence.

2.1.2. Benefit sense scale (BFS)

The scale used in this study is the Chinese version of the sense of benefit scale compiled by Bian Jing (2019) [13], which is divided into 5 dimensions and 22 items. Participants were asked to rate each item using a 5-point Likert scale, with options covering "no (1)," "a little (2)," "medium (3)," "quite a few (4)," and "very much (5)." The total score for the scale ranges from 22 to 110 points, with a higher score indicating a higher level of the feeling of benefit. This scale has been validated in cancer patients and the Alpha coefficient was 0.933.

2.1.3. General control sub-scale (SCI)

The psychological control scale utilized in this study is the Chinese version of the Shapiro control questionnaire[14], which has two factors, 15 items, and two dimensions,

divided into positive control sense and negative control sense. Participants were asked to rate each item on a scale encompassing "never (1 point)," "rarely (2) points," "occasionally (3)," "occasional (4)," "often (5)," "almost always (6)," and "always (7)." A higher score on the positive control sense indicates a higher sense of psychological control. On the other hand, a higher score on the negative control sense indicates a greater feeling of helplessness and disappointment in response to stressful events, leading to a tendency to passively accept the result. In this study, the alpha coefficient of the general control sense scale was 0.85.

2.1.4. Care burden scale (ZBI)

The care burden scale proposed by Zarit in 1985[15] has been widely used in various caregiver groups, including caregivers of elderly people with dementia, disabled elderly, Parkinson's disease patients, cancer patients, and other caregiving groups. The present study adopted the ZBI scale introduced by Wang *et al.*[16] to assess the caregiving burden. The ZBI scale comprises 22 items, divided into two dimensions: Role burden and personal burden. Participants were asked to rate each item on a 5-point scale, with response options encompassing "no (0)," "occasionally (1)," "sometimes (2)," "often (3)," and "always (4)." The total score on the scale ranges from 0 to 88 points. A score <21 indicates no burden, 21 to 39 indicates mild burden, 40 – 60 indicates moderate burden, and >60 indicates severe burden, with an Alpha coefficient of 0.87.

2.2. Study subjects and sample size

In the present study, family caregivers of children with congenital skeletal malformations who were treated in the pediatric orthopedics department at Shanghai L Hospital from July 2021 to January 2022 were selected as participants after obtaining consent from the relevant personnel involved in the caregiving process. Once inside the ward, the medical social worker identified the eligible caregivers who expressed their willingness to participate in the survey. Due to the limited number of children with congenital skeletal malformation, the present study adhered to the principle of selecting one caregiver per family. To determine the appropriate sample size, the rough estimation method proposed by Shunzhen was employed[17]. This method suggests a sample size that is 5 – 10 times the number of independent variables. As this Zarit scale contains 22 items, and considering a potential 20% sample loss rate, the minimum sample size required for this study was 115.

2.3. Data collection

From July 2021 to January 2022, a face-to-face questionnaire survey was conducted with the approval of the hospital and department and the consent of the participants, ensuring compliance with ethical principles and maintaining quality control. A total of 200 questionnaires were distributed to caregivers, and 190 were recovered, resulting in a recovery rate of 95%. One hundred and eighty-two questionnaires were considered valid, leading to an effective rate of 95.8%. Regarding the age distribution of children with congenital skeletal malformations, the majority of them fell within the age range of 3 – 7 years old (37.9%) and 7 – 14 years old (37.4%). Children aged 0 – 3 years old accounted for 11.5%, while those aged 14 – 18 years old accounted for 13.2%. The distribution is influenced by factors such as the typical age of hospitalization for children with congenital diseases and the optimal surgical timing for children with congenital skeletal deformities, which tends to be 4 – 8 years old. Among the 182 caregivers surveyed, their ages ranged from 27 to 56 years old. The majority of caregivers were mothers, accounting for 65.4% (119), while fathers made up 31.9% (58) of the caregiver population. This distribution can be related to the traditional Chinese cultural concept of "men leading the outside and women leading the inside." In terms of caregiver age, 49.5% were aged 30 – 40 years old, 22.5% were aged 20 – 30 years old, and 23.6% were aged 40 – 50 years old.

2.4. Data analysis

The questionnaire coding, data input, and subsequent data processing and analysis were conducted using SPSS 22.0. The significance level was set at $P < 0.05$ to determine statistical significance, provided that the data met the validity conditions. Descriptive statistical analysis was conducted to provide basic characteristics of the study participants. Three-scale score analysis and Pearson correlation analysis were employed to explore the correlation between three continuous variables. Multiple regression analysis was conducted to identify factors affecting care burden. A mediation effect test was conducted to explore whether the sense of benefit played a mediating role. All *P*-values in data analysis were subjected to the two-sided test.

3. Results

3.1. Reliability and validity of the scale

The care burden scale, benefit scale, sense of psychological control scale, and the scores of each dimension are shown in table.

As shown in Table 1, the reliability and validity of the care burden scale, benefits, and psychological control scale are all greater than 0.6, with high credit validity.

3.2. Correlation analysis of the variables

The current research used Pearson correlation analysis to study the correlation between the three continuous

Table 1. Results of the reliability and validity analysis

Dimension	Clone Bach, Alpha	Clone Bach Alpha based on the normalization term	Kaiser-Meyer-Olkin coefficient	Number of terms
Care burden scale	0.949	0.948	0.927	22
Personal burden	0.892	0.891	0.888	12
Burden of responsibility	0.893	0.894	0.858	6
Benefit Scale	0.963	0.964	0.927	22
Accept	0.847	0.848	0.679	3
Family relation	0.880	0.881	0.807	6
Personal growth	0.920	0.923	0.866	7
Human relations in society	0.941	0.942	0.746	3
Health behavior	0.889	0.889	0.730	3
Sense of psychological control scale	0.964	0.964	0.929	15
Positive sense of control	0.963	0.963	0.918	10
Negative sense of control	0.943	0.944	0.882	5

variables and the results are presented in Table 2. There was a significant positive correlation between feelings of psychological control and benefit (r = 0.84, P < 0.001), a significant negative correlation between the sense of psychological control and the caregiving burden (r = −0.76, P < 0.001), and a significant negative correlation between the care burden and the sense of benefit (r = −0.74, P < 0.001). That is, as the sense of psychological control strengthens, the burden of care decreases; as the sense of benefit increases, the burden of care decreases, and as the sense of psychological control strengthens, the sense of benefit heightens.

3.3. Multiple linear regression analysis of psychological control, benefit, and care burden

To further clarify the impact of demographic factors, sense of benefit, and psychological control on care burden, the present study employed multiple linear regression analysis. In the analysis, the care burden score served as the response variable. The following sets of variables were included in the regression model: The first group consisted of the general demographic information, such as age, disease time, whether the child is an only child, presence of family history, and the source of medical expenses, the second group consisted of caregiver age, caregiver education level, caregiver work status, caregiver family income, and caregiver family residence, and the third group consisted of psychological control score. The predictive effect of the control and explanatory variables on the care burden was analyzed by examining the changes in R^2 values in the regression model. The relevant results are presented in Table 3.

Table 2. Correlation analysis between caregiver care burden, sense of benefit, and psychological control (N=182)

	A sense of benefit	Psychological control	Take care of the burden
A sense of benefit	1		
Psychological control	0.84***	1	
Take care of the burden	−0.74***	−0.76***	1

Notes: *P<0.05; **P<0.01; ***P<0.001.

Table 3 shows the results of a multiple linear regression analysis of caregivers' care burden in children with congenital skeletal malformations. In Model 1, the influence of the general demographic characteristics of the children and caregivers on the care burden is explored, with all control variables treated as dummy variables for statistical convenience. Among the variables studied, the age of children, caregiver age, caregiver working status, and family monthly income were significantly affected by the care burden. After controlling for other factors, the age of children affected the care burden level. Compared with 14 – 18 years, caregivers of children under 14 years old felt more care burden, with differences of 0.52, 0.38, and 0.24 units for different age groups. The difference in caregiver age affected the care burden score when controlling for other factors. Caregivers between 40 and 50 years old and those between 30 and 40 years old increased by 0.24 units, indicating a lower level of care burden in caregivers between 30 and 40 years old. Caregiver working status played a role in the care burden score. Non-full-time caregivers experienced a higher burden compared to full-time caregivers, with an increase of 0.21 units. Under the control of other factors, the family monthly income affected the care burden score. Families with monthly

Table 3. Influence of psychological control and benefit on care burden multiple regression analysis (OLS)

Variable	Model 1 (net value)	Model 2 (a sense of benefit)	Model 3 (psychological control)	Variance inflation factor
Age of the child (14 – 18=0)				
0 – 3	0.52*** (5.27)	0.33*** (4.39)	0.30*** (4.16)	3.48
3 – 7	0.38** (4.01)	0.28** (3.26)	0.25** (3.08)	4.55
7 – 14	0.24* (3.62)	0.19* (2.93)	0.148 (2.78)	3.61
Time of disease (more than 3 years=0)				
≤1 year	−0.14 (3.17)	−0.11 (2.56)	−0.09 (2.42)	2.88
1 – 3 years	0.11 (3.48)	0.07 (2.81)	0.06 (2.65)	2.76
Is an only child (No=0)				
Yes	0.11 (2.32)	0.02 (1.90)	0.02 (1.80)	1.59
No family history (None=0)				
Have	0.40 (6.41)	0.028 (5.17)	0.07 (4.98)	1.10
Source of medical expenses (Medicare=0)				
At one's own expense	0.03 (2.77)	0.04 (2.25)	0.04 (2.22)	2.05
Rural cooperative medical service	0.03 (3.01)	0.01 (2.44)	−0.01 (2.30)	2.38
Caregiver age (30 – 40=0)				
20 – 30	−0.05 (3.30)	−0.00 (2.67)	−0.04 (2.54)	2.28
40 – 50	0.24** (2.87)	0.19** (2.32)	0.21*** (2.20)	1.75
More than 50	0.03 (5.90)	0.04 (4.76)	0.06 (4.51)	1.76
Education level (junior college or above=0)				
Junior high school and below	0.15 (3.78)	0.07 (3.06)	−0.04 (3.01)	4.21
High school or technical secondary school	0.05 (3.21)	0.03 (2.59)	−0.02 (2.48)	2.70
Working status (not working=0)				
Full-time	0.07 (2.83)	0.11 (2.29)	0.12 (2.17)	2.37
Non-full-time	0.21** (2.93)	0.08 (2.44)	0.07 (2.30)	1.69
Monthly family income, RMB (above 8000=0)				
≤3000	0.13 (5.98)	0.04 (4.87)	0.03 (4.61)	2.06
3000 – 5000	0.37** (4.05)	0.27** (3.29)	0.26** (3.11)	4.51
5000 – 8000	0.25** (3.18)	0.19** (2.578)	0.18* (2.43)	2.80
Family residence (rural area=0)				
City	−0.14 (3.02)	−0.03 (2.47)	−0.03 (2.33)	2.74
A sense of benefit		−0.57*** (0.06)	−0.26** (0.09)	4.09
Psychological control			−0.44*** (0.09)	4.68
Constant term	6.99 (8.60)	56.23 (8.75)	58.96 (8.28)	
F value	8.13***	15.94***	18.01***	
R^2	0.51	0.68	0.72	

Notes: N=182; P<0.05*; P<0.01**; P<0.001***; OLS: Ordinary least squares.

income between RMB 3000 and 5000 and RMB 5000 and 8000 experienced an average increase of 0.37 and 0.25 units, respectively, in the care burden compared to families with incomes over RMB 8000. Higher monthly income was associated with a lower perceived care burden, while lower monthly income correlated with a higher perceived care burden. After considering the effects of other control variables in Model 1, the duration of the disease, whether the child is an only child, family history, source of medical expenses, caregiver education, and family residence, did not show significant differences in the care burden.

In Model 2 of Table 3, the caregiver benefit perception (explanatory variables) was included in the regression

model alongside the control variables. The benefit variable improved the R^2 of Model 2 by 0.17 – 0.68, indicating that the explanatory power of Model 2 is enhanced compared to Model 1. The conclusion regarding the effect of the control variable on care burden in Model 2 is generally consistent with Model 1, except for the variable of caregiver working status, which was not found to be significantly different in Model 2. In addition, in the new Model 2, the caregiver benefit score demonstrated a significant negative effect on the care burden score at a 0.001 significance level. After controlling for other variables, an average increase of 1 unit in caregiver benefit perception was associated with a decrease of 0.57 units in care burden. The other variables reached the same conclusions as those observed in Model 1.

In Model 3 of Table 3**,** both the sense of psychological control and benefit (explanatory variables) were added to the regression model along with the control variables. The results in Model 3 are consistent with those in Model 2. Specifically, the newly included sense of psychological control score showed a significant negative influence on care burden, with a significant level of 0.001. After controlling for other factors, an average increase of 1 unit in the sense of psychological control was associated with a decrease of 0.44 units in the care burden score. This implies that the caregivers who have a higher sense of psychological control experienced a lower level of care burden. R^2 of Model 3 increased to 0.72 after adding the psychological control variables, which is an improvement of 0.04 compared to Model 2, indicating that Model 3 has a stronger explanatory power than both Model 1 and Model 2.

The R^2 of Model 3 is 0.72, which is the largest value among the three regression models shown in Table 3, indicating the strongest explanatory power. By checking the variance inflation factor (VIF) of each variable in the model, it is found that none of the VIF values exceeded 5, signifying the absence of serious multicollinearity problems among all the control variables and explanatory variables in the model. In addition, the *F*-values in Model 1, Model 2, and Model 3 are all significant at the level of 0.001. The summary of the results of multiple linear regression analysis is as follows:

(i). The age of the child, the age of the caregivers, and the monthly income of the family were found to all have a significant impact on the care burden. After controlling for other factors, caregivers for children under the age of 14 years old experienced more care burden than caregivers for children aged 14 – 18 years old. Furthermore, caregivers between the ages of 40 – 50 years old experienced lower care burdens than those between the ages of 30 – 40 years old. Moreover, caregivers with higher household monthly incomes experienced a lower care burden, whereas those with lower household monthly incomes felt a higher care burden.

(ii). When controlling for other factors, it was found that the higher the caregiver's sense of benefit, the lower the care burden. The sense of benefit of the caregiver negatively affects the care burden, which verifies the third hypothesis of the research.

(iii). When controlling for other factors, it was observed that a higher sense of psychological control is associated with a lower level of care burden. This finding confirms the first hypothesis of the research, which suggests a negative relationship between the sense of psychological control and the care burden.

3.4. Analysis of the mediation effect of psychological control feeling, benefit feeling, and care burden

The correlation analysis between the above variables reveals a significant pairwise correlation among caregivers' sense of psychological control, benefit, and care burden. Consequently, the present study further tested the mediation effect of psychological control and benefit on care burden. According to Zhonglin *et al.*, "Considering the influence of the independent variable X on the dependent variable Y, if the independent variable X has an effect on the dependent variable Y by affecting the mediation variable M, M is called the intermediary variable. Among them, the mediation effect belongs to the indirect effect[18]. Figure 1 shows that the sense of psychological control (X) acts on the burden of care (Y), and the path coefficient is "C," which represents the total effect of the sense of psychological control (X) on the burden of care (Y). Figure 2 shows the relationship between the sense of psychological control (X) and the burden of care (Y) after controlling for the variable sense of benefit (M). Where the coefficient "a" represents the indirect effect of the sense of psychological control (X) on

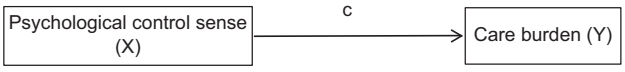

Figure 1. The total effect of the sense of psychological control on the care burden.

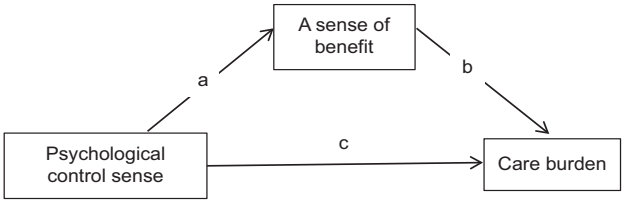

Figure 2. Schematic diagram of the benefit-sense mediation model.

the sense of benefit (M); "b" represents the indirect effect of the sense of benefit (M) on the burden of care (Y) under the condition of control X; "c" is the direct effect of the sense of psychological control (X) on the burden of care (Y) of the mediation variable (M). Therefore, in this study, the sense of psychological control of the independent variable, the burden of the dependent variable, and the sense of benefit of the intermediary variable were successively input to establish the schematic diagram of the intermediary variable, as shown in Figures 1 and 2:

Bootstrap is a non-parametric Monte Carlo method used to resample the observed information and then make statistical inferences about the distribution characteristics of the population. In the present study, the mediation effect was tested using the Bootstrap test method proposed by Zhonglin *et al.*[18], and the results are as follows (Table 4):

From the test results, the first coefficient, "c," was significant ($P < 0.001$). This indicates that the total effect "c" of the sense of psychological control on the burden of care is statistically significant, supporting the presence of an intermediary effect. Next, the path coefficient "a" of the sense of psychological control on the sense of benefit was 0.84 ($P < 0.001$), and the confidence interval does not include 0, confirming the statistical significance of this path. The path coefficient "b" of the sense of benefit on care burden was -0.35 ($P < 0.001$), and the confidence interval did not include 0, confirming the statistical significance of this path. Both coefficients "a" and "b" were significant, indicating a significant indirect effect (a*b), which represents the mediator effect. Regarding the direct effect coefficient "c," it was tested and found to be -0.47 ($P < 0.001$), and the confidence interval did not include 0, proving that the pathway varies significantly and indicating a significant direct effect. The total effect "c" is equal to "c'" added with a*b, which results in c = −0.76. This finding leads to the conclusion that the mediation effect exists. Specifically, the sense of benefit plays a partial mediation role between the sense of psychological control and care burden, with a mediation effect ratio of 38.58%.

4. Conclusions

In this study, a total of 182 caregivers of children with congenital bone malformation treated at Hospital L of Shanghai were assessed using general demographic information scale, general sense of control scale, sense of benefit scale, and care burden scale to study the care burden and explore its influencing factors and underlying mechanism. The results are concluded as follows:

(i). The burden score of the 182 caregivers for children with congenital bone malformation ranged from 3 to 73, with an average score of 36.46, indicating that the caregiver burden was at a mild-to-moderate level[19,20]. Specifically, the personal burden scores ranged from 1 to 40, with an average score of 21.13, while the responsibility burden scores ranged from 0 to 21, with an average score of 8.55. The results reveal that the personal burden of the caregiver was higher than their burden of responsibility[21,22].

(ii). The psychological sense of control, the sense of benefit, and the burden of care of 182 caregivers of children with congenital bone malformation showed a pairwise correlation. Specifically, there was a significant negative correlation between the sense of psychological control and the burden of care[23], indicating a significant negative correlation between the sense of benefit and care burden and a significant positive correlation between the sense of benefit and the sense of psychological control.

(iii). The factors influencing the caregiving burden include general demographic information of children and caregivers, as well as the sense of benefit and psychological control. Regression analysis revealed that the age of the children significantly affects the care burden, with younger children leading to a greater care burden on caregivers. At the same time, the age of caregivers also significantly affects the level of care burden[24], with caregivers aged 40 – 50 years old experiencing a greater care burden, while those aged 30 – 40 years old experience a lower care burden. In addition, the monthly family income also has a

Table 4. Test of the mediating role of benefit sense between the sense of psychological control and care burden

Path	Coefficient	Effect size	Standard error	95% confidence interval	
				Lower limit	Upper limit
"A sense of benefit" to "Psychological control sense"	a	0.84***	0.04	0.76	0.92
"Psychological control sense" to "Care burden"	c	−0.76***	0.05	−0.86	−0.67
"A sense of benefit" to "Care burden"	B	−0.35***	0.09	−0.58	−0.18
"Psychological control sense" to "A sense of benefit" and "Care burden"	c'	−0.47***	0.09	−0.64	−0.30

Notes: N=182; *P<0.05; **P<0.01; ***P<0.001.

significant impact on the care burden. Caregivers with higher monthly family income tend to have a lower caring load level, while those with lower monthly family income feel a higher care burden[25]. In the sense of psychological control, a negative relationship was observed between the sense of psychological control and the care burden, indicating that a higher sense of psychological control is associated with a lower care burden. The sense of benefit also demonstrated a significant negative relationship with the care burden[26]. This implies that higher levels of the sense of benefit are linked to lower levels of care burden[27].

(iv). The functional mechanisms of the sense of psychological control, the sense of benefit, and the burden of care are as follows: The sense of benefit reduces the level of the care burden while promoting the sense of psychological control. In other words, the sense of benefit plays a partial mediating role between the sense of psychological control and the care burden[28].

The findings of the present study show that in addition to negative emotions, negative psychology, and care burden, caregivers of children with congenital bone malformations can also find a sense of benefit from stressful events in the process of caring, thus strengthening the sense of psychological control over stressful events, enhancing their ability to face difficulties, and producing positive cognitive evaluation and coping styles. In summary, stress levels can be reduced by changing perspectives on stress and strengthening self-efficacy.

5. Research recommendations

The stress and coping theory was proposed by Lazarus and Folkman in the 1980s[29]. According to this theory, after coping with a shock event, individuals will generally make relative responses to the crisis event through their own primary evaluation, secondary evaluation, and re-evaluation, allowing individuals to maintain a balanced mentality and positive coping style in the aftermath of the crisis. The cognitive regulation theory of stress highlights the importance of various factors, which include self-resources, status attribution, cognitive evaluation, and coping strategies, in affecting the adaptive outcome of individuals[30]. Moreover, cognitive evaluation and coping processes are regarded as important mediating factors affecting the outcome of stressful events.

Based on the cognitive regulation theory of stress and the results of the present study, it becomes evident that enhancing caregivers' beneficial and controllability evaluations regarding stressful events can effectively reduce their care burden and boost their confidence in facing diseases and stressful events. Therefore, the present study focuses on examining the characteristics of children with congenital bone malformations and their caregivers. Focusing on the influence of the sense of psychological control and the sense of benefit on the care burden, an intervention model based on the stress coping regulation theory was initially constructed, as shown in Figure 3.

5.1. Change the cognitive perspective and improve the sense of disease benefit

At present, most studies on caregivers, both at home and abroad, focus on measuring negative psychological emotions and stress assessment, among other factors. However, an excessive emphasis on negative psychological emotions may lead caregivers to become overly fixated on negative psychological attitudes, ultimately aggravating the harm of these negative psychological emotions on their well-being. Compared with negative emotions, sense of benefit can lead caregivers to focus on the positive attitudes behind negative events, such as family relationships, social relationships,

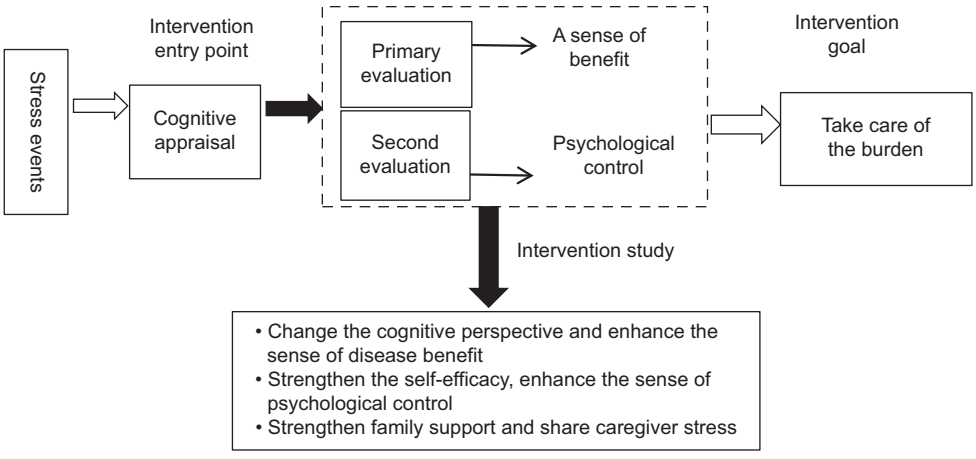

Figure 3. Intervention mode.

personal growth, and health behaviors[31]. By improving the sense of benefit, caregivers can boost their confidence in coping with the challenges posed by diseases, leading to the experience of positive emotions. Furthermore, it can foster the development of beneficial psychological qualities, empowering caregivers to better manage emergencies and expedite their recovery and adaptation processes.

Therefore, in the intervention for child caregivers, we can help them recognize the protective factors of care burden and the resources brought about by traumatic events by combing the advantageous perspective to enhance their sense of benefit and reduce their care burden. First of all, we should evaluate the benefit of caregivers in coping with stressful events in a timely and effective manner. According to their level of disease benefit, personalized intervention measures should be provided to improve their level of disease benefit. Second, caregivers can be guided to reflect positively on the disease and the caregiving process and attach importance to cognitive reconstruction. For example, caregivers can be guided to identify the positive aspects of the disease, attach importance to the meaning of surrounding life and feeling, and effectively use their resources to promote the improvement of the caregiver's sense of benefit from the disease. Many studies have demonstrated that psychological interventions such as cognitive-behavioral management[32], yoga[33], and mindfulness-based cognitive therapy[34] can effectively improve individuals' sense of benefit from disease.

5.2. Strengthen self-efficacy and enhance the sense of psychological control

The results of the present study demonstrate that the sense of psychological control, as a positive psychological quality, reflects the individual's ability to maintain self-control and represents good psychological resilience. As a consequence, it can effectively reduce the caregiver's care burden. When caregivers possess a sense of positive psychological control, it helps them establish good self-cognition and self-evaluation, encouraging individuals to take positive coping measures to address stressful events[35]. On the other hand, the presence of a negative sense of psychological control in caregivers indicates feelings of powerlessness and meaninglessness, which leads the individual to employ negative coping measures when faced with stressful events.

Therefore, attention should be paid to helping caregivers identify and make use of their existing or potential internal and external resources, strengthen self-efficacy, give full play to their own subjective initiative, strengthen caregivers' positive psychological control, and enhance individuals' ability to control themselves and cope with stressful events. If caregiver has a sense of helplessness, avoidance of negativity, or other emotional states, they can be guided to manage and express emotions, accept the negative impact of stressful events, and then help them build a meaningful life and enhance their ability to cope with pressure. Research shows that family empowerment interventions are effective measures to enhance caregivers' self-efficacy[36]. Motivational interviews can also improve the self-efficacy level of caregivers of children, reduce their anxiety level, and effectively alleviate the disease of children[37]. Furthermore, enabling health education can effectively alleviate caregivers' negative psychological state through positive evaluation and empowerment, improve their self-efficacy level, enable them to understand their own health, and foster a positive attitude in patients[38].

5.3. Strengthen family support and share caregiver pressure

Studies have shown that many important physical, psychological, social, and economic problems are closely related to family dysfunction and family relationship breakdown[39]. The results of the present study reveal that caregivers' caring pressure primarily originates from their worries about the children and the family's future. Caregivers with low care burdens often receive enough support from the family, thereby reducing the caregiver's caring load. The survey indicates that the caring pressure on a single caregiver is often higher than that on multiple caregivers because multiple caregivers can effectively share the pressure of caregiving, providing support in terms of economy, time, and energy, among other supports. On the other hand, older caregivers experience higher caring pressure than younger caregivers, mainly because younger caregivers can share the caring pressure with the help of other family members. In contrast, older caregivers tend to be single caregivers.

Therefore, the family support system for family caregivers plays an important role in reducing the stress of caregiving. The family support system can support the family in carrying out normal activities and help them self-regulate to adapt to external environment changes and internal conflicts. Medical social workers can help clients make reasonable use of the family support system, evaluate the cooperative relationship among family members, and strengthen the division of labor and cooperation among family members. For families with weak family support, strengthening social support can be beneficial.

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Conflict of interest

There are no conflicts of interest in this study.

Author contributions

Conceptualization: Xian Liu
Format analysis: Xian Liu
Investigation: Xian Liu
Writing – original draft: Xian Liu, Huijing Wu
Writing – review & drafting: Huijing Wu

Ethics approval and consent to participate

Ethical approval and informed consent was suspended because the hospital was at the height of COVID-19 when the article was written, but this study was conducted with hospital approval.

Consent for publication

Participants were clearly informed of the purpose of the study and of their rights before the survey was conducted and all participants agreed.

Availability of data

Supporting data can be obtained from corresponding author following formal request.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Impact of parents' satisfaction of home-school cooperation on adolescent mental resilience: Chain mediating effects of education anxiety and emotional warmth

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Abstract

In response the continuous increase of academic stress among the Chinese teenagers, the Chinese government has introduced policies related to home-school cooperation, which may to some extent affect the psychological resilience of adolescents, helping them adapt to the academic pressure. This study aims to explore the relationship between parents' satisfaction of home-school cooperation and adolescents' psychological resilience, and the mediating role of parents' educational anxiety and parenting style. A total of 335 parents and their children were surveyed using questionnaire star conceptualized based on scale of parents' satisfaction of home-school cooperation, parents' education anxiety scale, simplified parenting style scale, and psychological resilience scale. The results showed that parents' satisfaction was positively correlated with emotional warmth and psychological resilience and was significantly negatively correlated with education anxiety. Education anxiety was negatively correlated with emotional warmth and mental resilience. There was a significant positive correlation between psychological resilience and emotional warmth. The mediating path of parents' satisfaction influencing psychological resilience through education anxiety, emotional warmth, and their chain mediating effects was statistically significant. In conclusion, parents' satisfaction of home-school cooperation has an impact on adolescent psychological resilience by playing an independent mediating role or a chain mediating role through parents' education anxiety and emotional warmth.

Keywords: Parents' satisfaction of home-school cooperation; Education anxiety; Parenting style; Mental resilience

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1. Introduction

The Chinese senior high school entrance examination and college entrance examination are among the most competitive in the world, constituting enormous academic pressure

among the adolescents[1]. Coupled with the impacts of COVID-19 pandemic such as reduced social interactions with peers and decreased physical activity, mental health issues among the adolescents have become particularly prominent in China[2]. For example, a study conducted in 2020 showed that the prevalence of adolescents' depression and anxiety was 43.7% and 37.4%, respectively[3]. This also has inevitably induced anxiety among parents[4]. In response, the Chinese government has engaged in guiding the development and reforms of the education system. For example, the General Office of the Chinese Communist Party Central Committee and the General Office of the State Council issued the "Opinions on Further Reducing the Homework and Extracurricular Training Burden of Students in Compulsory Education" (i.e., the "Double Reduction" policy) on July 24, 2021. This policy emphasizes constructing a sound educational ecosystem, reducing parents' anxiety, and fostering both the physical and mental health of primary and secondary school students. Furthermore, on April 20, 2023, the Ministry of Education, together with 17 other departments, jointly issued the "Special Action Plan for Comprehensive Strengthening and Improvement of Student Mental Health in the New Era (2023–2025)." This plan attaches great importance to the cooperation between schools and families to promote adolescents' mental health.

One of the most important indices of mental health is mental resilience, which refers to the behavioral tendencies to adapt to the consistently changing environment and the ability to recover from stress[5,6]. Studies have shown that positive parenting styles, safe school climates, and low levels of educational anxiety are conducive to adolescent mental resilience[7-9]. High mental resilience could aid adolescents in adapting to the school environment and handling both academic and interpersonal pressures[10]. According to Bronfenbrenner's ecological system theory, the family, as the primary environment in which students interact with others, exerts significant impacts on individuals' mental development[11]. In line with this theory, the practice of home-school cooperation aims to offer a better family atmosphere for adolescents' mental growth[12]. In practice, the schools are required to regularly communicate with parents through workshops, teacher-parent meetings or social media, comprehend the learning environment within the students' families, and discuss with parents on how to improve their education practices[13-15]. The previous studies provided evidence that both the teacher-parent relationship and the degree of parental involvement in home-school cooperation crucially determine its success[16,17], which entails parents' positive attitudes toward home-school cooperation. According to the theory of planned behavior, parents' attitudes contribute, at least in part, to the development of students' behaviors[18]; therefore, the parents who are satisfied with home-school cooperation tend to involve more and actively build relationships with teachers, thereby achieving better outcome. In support of this, Hampden-Thompson and Galindo conducted a study in 2017 about home-school cooperation among 10,000 British secondary school students, and they found that parents' satisfaction strongly mediated the teacher-parent relationship and academic achievement[19]. As such, this study aims to examine whether higher parents' satisfaction of home-school cooperation is associated with higher mental resilience, which is regarded as another potential outcome of home-school cooperation.

The exact mechanism underlying the association between parents' satisfaction of home-school cooperation and adolescent mental resilience remains unknown. One candidate pathway is that higher satisfaction leads to the lower parents' education anxiety, which gives rise to a warm and authoritative parenting style that is a key contributor to high mental resilience. Education anxiety refers to the anxiety and tension experienced by parents concerning their high expectations towards their children's education, academic outcomes and learning environment[20]. Suffering from education anxiety is a prevalent phenomenon among parents in China, where parents tend to set high expectations toward their children's education, since, influenced by the Confucian culture, they strongly believe that education can change one's destiny[21]. A study conducted in 2018 showed that 68% of 3205 families in China felt anxious about their children's education. Parents' higher anxiety might be transmitted to children through interactions, and they may engage in improper education behaviors[22]. For example, the previous studies suggested that parents with the higher education anxiety were less warm and supportive, and tend to criticize their children for having bad scores and give their children more homework, and also restrict them from joining extracurricular activities[23]. These characteristics align more with the authoritarian parenting style rather than the authoritative parenting style[24].

Parenting style is the integration of parents' attitudes, beliefs and behaviors towards their children, which reflects the nature of the parent-child relationship[25,26]. Two main dimensions – emotional warmth (EW) and control – have been identified to distinguish four types of parenting style: authoritative (higher EW and higher control), permissive (higher EW and lower control), authoritarian (lower EW and higher control), and neglectful (lower EW and lower control)[27]. Numerous researchers found that higher mental resilience is associated with an authoritative parenting style and lower mental resilience is associated with an authoritarian and permissive parenting style[28-31].

Authoritative parents are emotionally warm towards their children and sensitive to their needs, and encourage autonomy and set clear behavioral rules for them. This assists children in mastering crucial developmental tasks during the early stages and using this foundation to develop more complex and differentiated abilities to confront environmental challenges in later life[32,33]. In contrast, authoritarian parents are neglectful of their children's emotional needs, criticize them frequently, and discourage their autonomy[34], which could be harmful to their mental resilience. There is also literature suggesting that parents' anxiety affects parenting styles; for instance, anxious parents tend to be less warm and positive, allow less autonomy, and adopt a more critical and disastrous parenting style[35]. Therefore, higher parents' education anxiety might result in a shift from the authoritative parenting style to the authoritarian one, which negatively impacts the children's mental resilience.

Overall, this study attempts to investigate the relationship between the parents' satisfaction of home-school cooperation and the adolescent mental resilience, and the mediating roles of parents' education anxiety and parenting style in this relationship. There are four hypotheses in this study: (i) Parents' satisfaction of home-school cooperation is positively correlated to children's mental resilience, (ii) parents' education anxiety mediates the correlation between parents' satisfaction and children's mental resilience, (iii) parenting style mediates the correlation between parents' satisfaction and children's mental resilience, and (iv) parents' education anxiety and parenting style are sequential mediators in the correlation between parents' satisfaction and children's mental resilience.

2. Methods

2.1. Participants

From February to April 2023, random and convenient sampling was adopted to survey the mothers and fathers of junior high school and senior high school students in three cities in Hebei province, China, using online questionnaires. In total, 500 questionnaires were distributed and 450 questionnaires were recovered. The response rate of the questionnaire was 90%. After eliminating questionnaires with incomplete answers or missing data, 335 groups of valid questionnaires were retained. The enrollment criteria are as follows: (i) Children aged 12–18 years old; and (ii) students who go to school regularly. The exclusion criteria are as follows: (i) Children with mental state and intellectual disabilities; and (ii) people with communication difficulties. Among these parents, 155 participants (46.3%) were aged between 30 and 39, 144 participants (43.0%) were aged from 40 to 49, and 36 participants (10.7%) were aged 50 and above. Furthermore, 23 participants (6.9%) have completed primary school, 166 (49.6%) have completed junior high school, 66 (19.7%) have completed high school, and 80 (23.9%) have graduated from colleges or above. No monetary rewards were given to these participants for participating in this study.

2.2. Instruments

2.2.1. General demographic questionnaires

Participants were inquired about their demographic details, including gender, age, educational background, occupation, monthly income of family, and whether the children live on campus or at home.

2.2.2. Mental resilience questionnaires

The Resilience Scale-11 (RS-11) developed by Gao *et al*.[36] was used to survey the children. This questionnaire includes 11 items, which adopts a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). The higher scores mean higher mental resilience. This questionnaire demonstrates good validity and reliability, with a Cronbach's α coefficient of 0.88 and a KMO value of 0.89.

2.2.3. Questionnaires for parents' satisfaction of home-school cooperation

The questionnaire for parents' satisfaction of home-school cooperation developed by Ma[37] was used to survey the parents. This questionnaire includes 18 items, which can be categorized into four dimensions: Cooperation efficacy, cooperation atmosphere, teacher involvement, and platform characteristics. It uses a 4-point Likert scale which ranges from 1 (strongly disagree) to 4 (strongly agree), where higher scores mean higher parents' satisfaction. The overall Cronbach's α coefficient for the four dimensions is 0.85, and the individual Cronbach's α coefficients are 0.85, 0.84, 0.80, and 0.87, respectively, for the four dimensions. The KMO value is 0.96, which shows good reliability and validity.

2.2.4. Parenting style questionnaires

The Chinese version of the short form of the Egna Minnen av Barndoms Uppfostran, which measures parenting styles and was revised by Jiang in 2010[38], was used to survey the children. This questionnaire includes 21 items, which can be categorized into three dimensions: Rejection, emotional warmth, and overprotection, and a 4-point Likert scale is adopted, ranging from 1 (never) to 4 (always). The higher scores in any dimension indicate a higher level of that parenting style. The Cronbach's α coefficients for the three dimensions are 0.87, 0.88 and 0.70, respectively, and the

KMO value is 0.91, demonstrating good reliability and validity.

2.2.5. Parents' education anxiety questionnaires

The Parents' Education Anxiety Scale, developed by Li[39], was sent to the parents to measure their education anxiety. This questionnaire includes 14 items measuring anxiety from three sources: employment, exams, and health. It adopts a 5-point Likert scale which ranges from 1 (never) to 5 (always), where the higher scores in any dimension indicate a higher anxiety level in that dimension. The overall Cronbach's α coefficient is 0.95, and the Cronbach's α coefficients for the three dimensions are 0.93, 0.85, and 0.78, respectively, and the KMO value is 0.95, exhibiting good reliability and validity.

2.3. Statistical analysis

The data were analyzed with SPSS26.0 and the PROCESS macro (version 4.1). Tests for common methods bias, descriptive statistics, correlation analysis, and regression analysis were conducted on SPSS26.0. The chain mediation effects were analyzed using Model 6 in PROCESS macro, and the fit of the chain mediation model was assessed using AMOS (version 24). Results with $P < 0.05$ and 95% confidence intervals not including zero were considered statistically significant in this study.

3. Results

3.1. Common method bias test

Herman's single-factor test, borrowed from Tang and Wen's research[40] of common method bias testing, was employed to detect common method bias in this study. Exploratory factor analysis (without rotation) was performed on the items of parents' satisfaction with home-school cooperation, mental resilience, education anxiety, and parenting style. It was found that 11 factors had eigenvalues larger than one. The first factor explained 23.52% of the variance, which was smaller than the standard threshold of 40%, suggesting that the common method bias was non-significant.

3.2. Descriptive statistics and correlation analysis

The descriptive statistics and correlation analysis for each variable are shown in Table 1. The result of Spearman's correlation analysis showed that parents' satisfaction of home-school cooperation was significantly positively correlated with mental resilience ($r = 0.25$, $P < 0.001$), and emotional warmth ($r = 0.22$, $P < 0.001$), and significantly negatively correlated with education anxiety ($r = -0.24$, $P < 0.001$), rejection ($r = -0.30$, $P < 0.001$), and overprotection ($r = -0.26$, $P < 0.001$); mental resilience was significantly positively correlated with emotional warmth ($r = 0.42$, $P < 0.001$) and was significantly negatively correlated with rejection ($r = -0.18$, $P = 0.001$), and overprotection ($r = -0.16$, $P = 0.003$).

3.3. Test for the chain mediation effect

The results of regression analysis are presented in Table 2. It showed that, first, parents' satisfaction significantly negatively predicted education anxiety ($\beta = -0.237$, $P < 0.001$), and significantly positively predicted emotional warmth ($\beta = 0.176$, $P = 0.001$) and mental resilience ($\beta = 0.123$, $P < 0.014$); second, education anxiety significantly negatively predicted emotional warmth ($\beta = -0.179$, $P = 0.001$) and mental resilience ($\beta = -0.228$, $P < 0.001$); third, emotional warmth significantly positively predicted mental resilience ($\beta = 0.344$, $P < 0.001$).

This study used AMOS (version 24) to establish a structural equation model (SEM) and examine the significance of the path coefficient between these variables. The results showed that the path coefficient between these variables was all significant, indicated that: (i) Parents' satisfaction can influence children's mental resilience directly and (ii) both education anxiety and emotionally warm parenting style are independent mediators and chain mediators in the relationship between parents' satisfaction and children's mental resilience. The hypothesized model is shown in Figure 1.

Based on the SEM, a bias-corrected percentile bootstrap method with 5000 iterations was performed with the PROCESS macro: Parents' satisfaction was the independent variable, children's mental resilience the dependent variable, and education anxiety and parenting style the mediating variables. The result of this analysis is shown in Table 3. It showed that the 95% confidence interval for path 1, which is mediated by education anxiety, was [0.03, 0.12], with a small effect size of 0.007, indicating that parents' satisfaction can alleviate education anxiety and hence enhance children's mental resilience. Again, the 95% confidence interval for path 2, which was mediated by emotionally warm parenting style, was [0.03, 0.13], with a small effect size of 0.07, implying that higher satisfaction tends to elicit emotionally warm parenting style, which improves children's mental resilience. In addition, the 95% confidence interval for path 3, which was mediated mutually by education anxiety and emotionally warm parenting style was [0.00, 0.04], and the 95% confidence interval for the total mediation effect was [0.10, 0.22], with a small effect size of 0.16. This suggests that higher satisfaction can also firstly alleviate education anxiety, further promoting an emotionally warm parenting style, through which children's mental resilience is enhanced. The effect sizes of the three paths, relative to the total

Table 1. Means, standard deviations, and Spearman's correlation coefficient for each variable

Variables	M	SD	1	2	3	4	5	6
Parents' satisfaction	59.04	9.43	—					
Mental resilience	52.68	11.35	0.25***	—				
Education anxiety	43.77	13.96	−0.24***	−0.33***	—			
Rejection	9.36	3.47	−0.30***	−0.18**	0.23***	—		
Emotional warmth	19.53	4.77	0.22***	0.42***	−0.22***	−0.36***	—	
Overprotection	16.48	3.80	−0.26***	−0.16**	0.26***	0.71***	−0.19**	—

Note: *p<0.05, **p<0.01, ***p<0.001

Table 2. Regression analysis in the models for each variable

Predicting variables	Model 1 (Education anxiety)		Model 2 (Emotional warmth)		Model 3 (mental resilience)	
	β	t	β	t	β	t
Parents' satisfaction	−0.237	−4.461***	0.176	3.249**	0.123	2.469*
Education anxiety			−0.179	−3.304**	−0.228	−4.595***
Emotional warmth					0.344	6.953***
R^2	0.056		0.078		0.252	
F	19.904***		14.080***		37.228***	

Note: *p<0.05, **p<0.01, ***p<0.001

Table 3. Standardized indirect effects and 95% confidence intervals

Path	Estimated	95%CI	Effect size
X→M1→Y	0.07	[0.03,0.12]	43.75%
X→M2→Y	0.07	[0.03,0.13]	43.75%
X→M1→M2→Y	0.02	[0.00,0.04]	12.50%
Total indirect effects	0.16	[0.10,0.22]	100%

Estimated was the standardized indirect effect of each mediate pathway; effect size was calculated by using the ratio of the total effect of the mediating effect. Empirical 95% CI did not overlap with zero; all pathways were significant.
Abbreviations: X: Parents' satisfaction; M1: Education anxiety; M2: Emotional warmth; Y: Mental resilience.

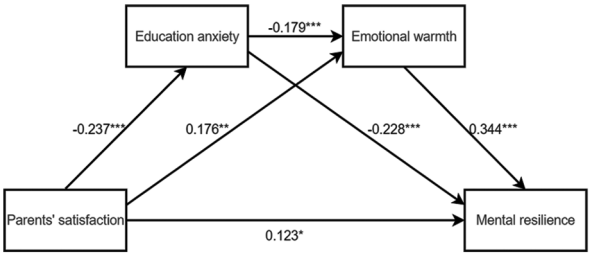

Figure 1. Multiple mediating models between parents' satisfaction and mental resilience.

indirect mediation effect size, are 43.75%, 43.75%, and 12.50%, respectively.

4. Discussion

This study aims to examine the association between parents' satisfaction of home-school cooperation and children's mental resilience, and whether parents' education anxiety and parenting style serve as the chain mediators in this association. All four of our aforementioned hypotheses were supported by the results. We found that, first, parents' satisfaction of home-school cooperation directly impacts children's mental resilience. Second, education anxiety and emotionally warm parenting style can serve as both chain and independent mediators in the relationship between the two variables. In other words, higher parents' satisfaction can directly foster children's mental resilience and indirectly achieve it by alleviating education anxiety, which paves the way for an emotionally warm parenting style.

Parents' satisfaction of the school has direct effects on the children's mental resilience. Consistent with past research, in the process of home-school cooperation, positive relationships between teachers and students, and frequency of communications between parents and teachers could improve parents' satisfaction, which might be due to the less uncertainty coming with such practices[41]. Therefore, this can be used as one of the ways to promote the development of mental resilience in adolescents. Higher parents' satisfaction could render them more supportive and warmer toward their children, making the family atmosphere more democratic and harmonious, and nurturing their children's mental resilience. Specifically, when children have autonomous regulation of their

behaviors regarding their development, they tend to seek challenges and set goals for themselves that go beyond the minimal requirements from schools[42]. They tend to have higher self-efficacy, which means that they are convinced of their abilities to cope with life challenges, and so demonstrate perseverance in the face of obstacles[16].

Education anxiety partially mediated the relationship between parents' satisfaction and children's mental resilience, and significantly correlated with the two variables. The overlapping spheres of influence theory suggest that children's development is influenced by the interaction between family, schools, and communities[43]. A high level of parents' satisfaction could alleviate their education anxiety and promote harmony among the family members, which is conducive to children's mental resilience. In addition, this study found that education anxiety is related to rejection and overprotective parenting styles, which is not only detrimental to parent-child interaction[44], but also damaging to the development of psychological resilience of adolescents[45].

Emotional warmth also partially mediated the relationship between parents' satisfaction and mental resilience, and significantly correlated with these two variables. This indicates that consistent with the previous research[46], higher parents' satisfaction could induce their emotionally warm parenting style, which is conducive to children's mental resilience. Specifically, when the children perceive that they are connected to others and lovable, they tend to have higher self-esteem and self-worth, which help them bounce back from stress[47]. The parents who are satisfied with home-school cooperation had fewer complaints about it, a lower desire to control their children, and more positive interactions with them, which benefits the development of children's mental resilience[34,48].

Furthermore, both education anxiety and emotional warmth functioned as the chain mediators in the relationship between parents' satisfaction and children's emotional resilience. Based on the chain mediating model in this study, higher parents' satisfaction would reduce their education anxiety, give rise to an emotionally warm parenting style, and further improve the children's mental resilience. As such, based on the current situation that the mental resilience of Chinese teenagers is at a lower level, this study provided empirical evidence supporting the necessity of improving parents' satisfaction of home-school cooperation, reducing their education anxiety, and educating parents about developing and maintaining an emotionally warm autonomous parenting style. Furthermore, this study also provides powerful measures for parents and schools to improve students' stress resilience in the warm and harmonious family, and safe and comfortable campus environment. We believe that most of the improvement of adolescent mental resilience depends on a good living atmosphere.

Several limitations of this study warrant our attention. First, this cross-sectional study cannot verify the temporal relationship between parents' satisfaction of home-school cooperation and the other three variables; therefore, the causal relationship between parents' satisfaction and children's mental resilience still awaits verification by longitudinal studies in future. Second, the self-reported questionnaire used in this study might be vulnerable to subjectivity, especially since the previous research found that parents tend to exhibit positive response bias when reporting their satisfaction of education services[49]. The participants in this study is of varying proportions in terms of gender, with 222 (66.3%) male and 113 (33.7%) females, which might confound the results, because the previous research found that fathers and mothers have different child-rearing beliefs, parenting styles and education anxiety level[47]. Thirdly, the effect size of this study is relatively small (0.07, 0.07, and 0.02), which is partly affected by the subjectivity of the subjects, and it also means that its practical significance may be relatively small.

5. Conclusion

This study proves that high parents' satisfaction of home-school cooperation, low level of educational anxiety and emotional warmth of parenting style promote the improvement of adolescent psychological resilience. Future work should focus on exploring the methods to improve parents' satisfaction in the process of home-school cooperation and proposing specific measures according to the actual situation, such as increasing the frequency of communication between teachers and parents.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

The Ethics Committee of The First Hospital of Hebei Medical University grants the approval to carry out this study (20220933). Study participants gave their verbal consent to participate in the study.

Consent for publication

Study participants gave their verbal consent for publishing their data in this paper.

Availability of data

The original data can be obtained from corresponding author following formal request.

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ORIGINAL RESEARCH ARTICLE

Mutuality of thyroid hormones and psychiatric disorders

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Abstract

Abnormalities in thyroid function may induce affective, anxious, psychotic, and cognitive disorders and are a potential marker for assessing suicidal risk in patients suffering from psychiatric disorders. This retrospective, cross-sectional, electronic, and data-based study, comprising 118 adult psychiatric patients, aimed to establish differences in the concentrations of total T3, T4, and thyroid-stimulating hormone among patients diagnosed with common psychiatric disorders. The analysis encompassed the levels of these hormones in patients who had attempted suicide and those who had not. Lower values of total T3 were observed in patients with depressive disorder compared to patients with psychotic and bipolar disorder, as well as the control group. Furthermore, lower total T3 values were observed in patients who had reported a suicide attempt in their lives compared to participants who had not attempted suicide. These findings suggest a potential link between thyroid hormones and the regulation of central serotonin activity. The study underscores the importance of routinely assessing thyroid function in clinical practice to facilitate early detection of suicidality and the prevention of suicide.

Keywords: Thyroid hormones; Hypothalamic-pituitary-adrenal axis; Suicide prevention; Psychiatric disorders; Suicidality

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1. Introduction

Thyroid dysfunction, both clinically significant and subclinical, affects 5 – 8% of the general population[1]. A study conducted in Tehran reported a significant increase in the prevalence rate of overall thyroid dysfunction, rising from 1.4% at baseline to 10.5%[2]. The prevalence of psychiatric disorders is higher among patients with various thyroid dysfunctions compared to the general population. Indeed, observational studies have linked both hypo and hyperthyroidism to affective disorders[3].

Abnormalities in thyroid function can induce affective, anxious, psychotic, and cognitive disorders[4,5]. Furthermore, the degree of abnormality in the thyroid hormone levels correlates with the severity of psychopathological symptoms in psychiatric disorders[6,7].

Receptors for thyroid hormones are localized in the limbic structure, implying their involvement in mood regulation[8]. Hypothyroidism is associated with clinically relevant mood and cognition deterioration[9]. Augmentation with thyroid hormone has demonstrated therapeutic efficacy in treating resistant depression[10,11]. In addition, the thyroid hormone status has been recognized as a predictor of therapeutic response in major depressive disorder and bipolar affective disorder[12].

Thyroid-stimulating hormone (TSH) secretion is known to change, especially during nighttime, under the influence of various conditions[13,14]. Existing literature presents somewhat contradictory findings regarding the relationship between thyroid hormone levels in psychiatric patients. Most psychiatric patients exhibit disturbances in thyroid hormone and TSH levels, even in the absence of thyroid disease[4]. The underlying reasons for these hormone level changes in psychiatric disorders have yet to fully unravel[15,16]. There are indications that this phenomenon may be linked to alterations in TSH secretion, induced by abnormalities in key neurotransmitters (serotonin, noradrenaline, and dopamine)[17,18].

Changes in thyroid hormone levels are known to influence a diverse range of health conditions. For example, even when within normal limits, low TSH levels have been linked to poorer control of chronic diseases such as arterial hypertension, Type 2 diabetes mellitus, and cardiovascular diseases[19]. Thyroid dysfunction is common in patients within the schizophrenia spectra but remains understudied[20]. It is also essential to consider the effect of psychiatric medications on thyroid hormone status[6,21]. Routine monitoring of thyroid hormone levels is not typically conducted in patients taking antipsychotic medications unless they exhibit symptoms of thyroid disease[22,23].

Certain studies have indicated thyroid dysfunction in patients with schizophrenia who do not exhibit clinically relevant thyroid-related symptoms[24,25]. There appears to be a disorder in the regulation of the thyroid hormone levels in these patients. Furthermore, the homeostasis of thyroid hormones plays a role in maintaining the network of neurotransmitters in the brain, but further research is necessary to understand this issue to a greater extent[21,24].

Suicide is an important psychopathological phenomenon, posing one of the most challenging clinical dilemmas for psychiatrists in their daily practice. Central to the understanding of suicide are questions regarding its nature, etiology, and even its definition. These inquiries guide the psychiatric interventions and the identification of predictors of suicidality, which are essential for the timely detection and prevention of fatal outcomes in routine clinical settings[1,25]. The most common psychiatric conditions associated with suicide include affective disorders, addictions, personality disorders, and psychotic disorders. These conditions vary with respect to gender, age, and geographic location[26,27]. Considering the absence of an efficient algorithm for predicting suicide in clinical practice, mostly attributable to the etiologic heterogeneity, gathering information on clinical, psychological, sociological, and biological factors can help in identifying patients at high risk and providing valuable insights for their treatment[28].

Different neurobiological factors related to suicide are currently under investigation[1,28]. Neuroendocrine hormones play an important role in the regulation of emotions in both healthy individuals and those with psychiatric conditions[26]. The neurotransmitter systems, including the serotonergic system, may have a connection to the regulation of the hypothalamic-pituitary-adrenal (HPA) axis and hypothalamic-pituitary-thyroid (HPT) axis in individuals at risk of suicide[29,30]. Dysregulation of the HPT axis has been observed in various psychiatric conditions, including those associated with suicidality[31,32].

Genetic polymorphism in the serotonergic system, HPA axis, noradrenergic system, and polyamines may predispose patients to suicidal behavior[6,33-35]. Chronic stress and hypercortisolism can result in hyperstimulation of the HPA axis, leading to alterations in the 5-HT pathway. Consequently, the observed 5-HT abnormalities in suicidal patients may be secondary, stemming from the hyperactivity of the HPT axis[33]. The existing literature presents contradictory findings concerning the relationship between suicidality and the HPT axis[31,36]. Changes in the HPT axis activity have been documented in patients diagnosed with depression and schizophrenia, both in conjunction with the previous suicide attempt[31,37-41].

The literature indicates a connection between disorders in the HPT axis and certain personality traits, such as panic, as well as a link between agitation, suicidality, and a decreased response in the production of TSH[42]. People with a history of suicide attempts and higher levels of aggressiveness may exhibit a decreased T3/T4 ratio[43,44].

The first hypothesis of the present research posited that thyroid hormone abnormalities are involved in the etiopathogenic mechanism of psychiatric disorders. The second hypothesis proposed that these thyroid hormone abnormalities serve as predictors of suicidality.

The primary objective of this research was to establish differences in the concentration of the total T3, T4, and TSH among patients diagnosed with common psychiatric disorders. The secondary objective was to determine whether

these hormone levels differed between patients who had attempted suicide and those who had not.

2. Materials and methods

2.1. Participants

This retrospective, cross-sectional, electronic, and data-based study was conducted through a review of medical documentation from the Psychiatric Hospital Sveti Ivan for the period spanning January 2016 to March 2017. A total of 118 adult psychiatric inpatients were included in this study. Selection criteria were based on the availability of laboratory test results for TT3 (total triiodothyronine), TT4 (total thyroxine), and TSH.

Of the study participants, 83.1% were women. The average age of participants was 42.59 years (SD = 16.03). Patients known to have pre-existing thyroid disorders or undergoing thyroid-targeted medication were excluded from the sample.

Participants were divided into groups based on their ICD-10 primary diagnoses as follows: Psychotic disorder (29.9%, n = 35), depressive disorder (20.5%, n = 24), bipolar affective disorder (10.3%, n = 12), personality disorder (6.8%, n = 8), schizoaffective disorder (6.8%, n = 8), reactive states (6.8%, n = 8), anxious disorder (6.8%, n = 8), addiction (3.4%, n = 4), delusive disorder (3.4%, n = 4), somatoform disorder (2.5%, n = 3), dementias (1.7%, n = 2), and organic affective disorder (1.7%, n = 2).

Participants were further stratified based on whether they had a history of suicide attempts (6.8%, n = 8) or not. Among those who had attempted suicide, the primary psychiatric diagnoses included depressive disorder (n = 3), anxious disorder (n = 2), reactive states (n = 2), and schizoaffective disorder (n = 1).

Given that the majority of participants were diagnosed with psychotic disorders, depressive disorders, and bipolar affective disorders, these groups were selected as the primary focus for comparing thyroid parameter levels.

Regarding medication usage, 56.8% of participants were on antidepressants, 46.6% were on mood stabilizers, 87.3% were on antipsychotic medications, and 59.3% were on anxiolytics and hypnotics.

A healthy control group, consisting of 20 volunteers (13 female and seven male) who were all employees of the hospital, was used for comparison. The average age of this control group was 41.20 years (SD = 15.840).

The average value of body mass index (BMI) is 26.44 (SD = 5.636), which falls within the overweight category. BMI values ranged from a minimum of 17.92 to a maximum of 47.81. Among these participants, 59.2% of patients were classified as overweight (BMI >25), while 28.8% fell into the obesity range (BMI >29.9). Patients were not categorized by metabolic syndrome.

Data on the clinical characteristics of patients and their thyroid parameter values (TT3, TT4, and TSH) were acquired from the hospital's electronic medical database. All participants were informed about the objectives of the research and provided their consent. The Hospital's Ethical Committee approved the research.

2.2. Methods

2.2.1. Determining TT3, TT4 and TSH

Blood samples for thyroid hormone and TSH determination were collected from patients on their admission to the hospital in the morning, following a standard routine procedure. These samples were collected using a glass tube without the anticoagulant (6 ml). After resting at room temperature for 30 min, the blood sample was centrifuged at 3500 rpm for 10 min. The thyroid hormones and the TSH were quantified using the chemiluminescent immunoassay (CLIA) method on the Acces 2 Immunoassay System (Beckman Coulter, USA) with the manufacturer's reagent. The reference range, recommended by the device and reagent manufacturer and verified according to the CLSI C28-A3 protocol for reference range validation, was used[45].

The coefficient of variation (CV%) for determining the concentration of the TT3 is 3.31% at a concentration of 1.2 nmol/L and 3.83% at a control sample concentration of 2.72 nmol/L. For TT4, it is 2.96% at a concentration of 61 nmol/L and 3.66% at a concentration of 149 nmol/L. The CV% for determining the concentration of TSH is 2.78% at a concentration of 0.35 mIU/L and 1.56% at a concentration of 5.26 mIU/L.

2.2.2. Statistical analysis

The statistical analysis was conducted using SPSS version 20.0. The normality of the distribution of thyroid parameters was assessed using the Kolmogorov–Smirnov test. Non-parametric tests, including the Chi-square test, Kruskal–Wallis test, and Mann–Whitney U test, were employed to compare data across different diagnostic groups. The association between age and thyroid parameter values was examined using Spearman's correlation coefficient. The significance level was set at $P \leq 0.05$.

3. Results

The difference in TT3 values among participants showed statistical significance across diagnostic groups (Kruskal–Wallis test, $\chi^2 = 16.693$, $P = 0.001$) (Table 1).

Subsequent *post hoc* analysis revealed that individuals with depressive disorders had significantly lower TT3 values than those with psychotic disorders, bipolar disorders, or the control group. Nevertheless, there was no significant difference in TT3 values among patients with psychotic disorders, bipolar disorders, and the control group. In addition, the differences in TT4 and TSH values did not exhibit significant variations between the analyzed groups (Table 2).

In the group of patients with depressive disorder, a higher proportion of patients had values of TT3 outside the reference range compared to those with values of TT4 and TSH outside the reference range (Chi-squared = 8.26; df = 2; $P = 0.016$). Conversely, there was no significant difference in the proportion of participants with values outside of the reference range for TT3, TT4, and TSH in patients with the psychotic disorder (Chi-squared = 1.95; df = 2; $P = 0.376$) or bipolar disorder (Chi-squared = 1.49; df = 2; $P = 0.473$).

Older patients exhibited significantly lower T3 hormone values (Spearman's rho = −0.201, $P = 0.033$) and significantly higher T4 hormone values (Spearman's rho = 0.258, $P = 0.019$). In other words, as age increased, T3 values decreased while T4 values increased.

There were no significant differences in thyroid hormone parameters between male and female participants.

When comparing participants who had attempted suicide with those who had not, it was found that the values of TT3 were significantly lower in those who had attempted suicide compared to those who had not (Mann–Whitney U = 226,500, $P = 0.034$) (Table 3).

No statistically significant differences were observed in the use of antidepressants (Chi-square = 3.208, df = 1, $P = 0.073$), stabilizers (Chi-square = 0.031, df = 1, $P = 0.861$), and antipsychotics (Chi-square = 1.140, df = 1, $P = 0.286$) as shown in Table 4. However, a significant difference was found in the use of anxiolytics and hypnotics (Chi-square = 4.097, df = 1, $P = 0.043$). Specifically, those who had not attempted suicide used significantly more anxiolytics and hypnotics compared to those who had attempted suicide. It is important to note that the sample had a very small number of attempted suicides (only 8).

Statistically significant differences were observed only for antidepressants, specifically in TSH hormone values (Mann–Whitney U = 1300,000, $P = 0.035$). Patients who take antidepressants have significantly lower TSH hormone values compared to those who do not take antidepressants. Among patients diagnosed with psychotic disorders, there is a significantly lower percentage of overweight patients compared to patients with other psychiatric diagnoses (18.8% vs. 32.9%, $\chi^2 = 7.646$, $P = 0.006$) as shown in Table 5.

Among patients taking antipsychotics, there is a significantly higher percentage of overweight individuals compared to patients not taking antipsychotics (63.3% vs. 30.8%, $\chi^2 = 4.988$, $P = 0.026$). No statistically significant differences were observed for other psychiatric drugs in relation to overweight. Regarding obesity, a statistically significant difference was found between patients taking anxiolytics and those who do not take them. Specifically, among patients taking anxiolytics, a significantly higher proportion was obese compared to those who did not take

Table 1. The proportion of patients with different psychiatric diagnoses in the sample

Psychiatric conditions (*N*=118)	Frequency (*n*)	Percent
Psychotic disorder	35	29.9
Depressive disorder	24	20.5
Bipolar affective disorder	12	10.3
Personality disorder	8	6.8
Schizoaffective disorder	8	6.8
Reactive states	8	6.8
Anxious disorder	8	6.8
Addiction	4	3.4
Delusive disorder	4	3.4
Somatoform disorder	3	2.5
Dementias	2	1.7
Organic affective disorder	2	1.7
Suicide attempt	8	6.8

Table 2. Comparison of thyroid parameter values between different diagnostic groups (psychotic disorder, depressive disorder, and bipolar affective disorder)

Hormones	Participants with psychotic disorder (*n*=35) (mean [SD])	Participants with depressive disorder (*n*=24) (mean [SD])	Participants with bipolar disorder (*n*=12) (mean [SD])	Control group (*n*=20) (mean [SD])	χ^2 (Kruskal-Wallis test)	*P*-value
TT3	1.57 (0.35)	1.33 (0.33)	1.46 (0.27)	1.71 (0.28)	16.693	0.001*
TT4	112.18 (29.67)	102.97 (24.67)	107.82 (42.43)	106.45 (18.70)	1.508	0.680
TSH	2.06 (1.28)	1.64 (1.14)	1.51 (0.92)	1.80 (0.75)	2.737	0.434

Notes: *Statistically significant at $P \leq 0.05$. The reference ranges were: TT3 (1.34 – 2.73 nmol/L), TT4 (78.38 – 157.40 nmol/L), and TSH (0.38–5.33 mIU/L).

Table 3. Comparison of values of TT3, TT4, and TSH between the participants who had attempted suicide and those who had not within the overall sample

Hormones	Participants who attempted suicide (*n*=8), mean (SD)	Participants who did not attempt suicide, *n*=110, mean (SD)	Mann–Whitney U test	*P*-value
TT3	1.24 (0.27)	1.54 (0.81)	226,500	0.034*
TT4	102.31 (22.76)	107.54 (27.52)	139,000	0.760
TSH	1.50 (0.96)	1.93 (1.34)	353,500	0.392

Notes: *Statistical significance at $P \leq 0.05$. The reference ranges were: T3 (1.34 – 2.73 nmol/L), T4 (78.38 – 157.40 nmol/L), and TSH (0.38 – 5.33 mIU/L).

Table 4. The relationship between psychopharmaceuticals and thyroid parameters

Hormones	Participants with antidepressive medicines (Mann–Whitney U [*P*-value])	Participants with mood stabilizers (Mann–Whitney U [*P*-value])	Participants with antipsychotic medicines (Mann–Whitney U [*P*-value])	Participants with anxiolytics and hypnotics (Mann–Whitney U [*P*-value])
TT3	1.277,500 (0.104)	1.623,000 (0.713)	659,500 (0.561)	1.534,000 (0.925)
TT4	865,000 (0.787)	803,000 (0.815)	505,000 (0.473)	827,000 (0.727)
TSH	1.300,000 (0.035*)	1.835,500 (0.476)	755,000 (0.775)	1.899,500 (0.157)

Note: *Statistically significant at $P \leq 0.05$.

Table 5. Comparison of overweight and other patients regarding thyroid hormones and medications

Thyroid hormones	Mann–Whitney U (*P*-value)
TT3	1.026,000 (0.348)
TT4	553,000 (0.412)
TSH	1.240,000 (0.892)
Medications	**χ^2 (*P*-value)**
Antidepressive medications	3,534 (0.060)
Mood stabilizers	0,155 (0.694)
Antipsychotic medications	4,988 (0.026)*
Anxiolytics and hypnotics	0,013 (0.908)

Note: *Statistically significant at $P \leq 0.05$.

them (35.8% vs. 18.2%, $\chi^2 = 4.027$, $P = 0.045$). For other psychiatric drugs, no statistically significant differences were identified with regard to obesity.

Regarding the value of thyroid parameters in relation to BMI, no statistically significant differences were identified.

A comparison was conducted between individuals taking a certain type of medication and those not taking that type, focusing on the values of thyroid parameters (comparisons were conducted separately for each type of medication). A statistically significant difference was found only for antidepressants, specifically in TSH hormone values (Mann–Whitney U = 1300,000, $P = 0.035$). Patients taking antidepressants exhibited significantly lower TSH hormone values compared to those not taking antidepressants.

The average value of BMI is 26.44 (SD = 5.636), placing it within the overweight category. The BMI ranged from a minimum value of 17.92 to a maximum of 47.81. Of the patients, 59.2% were classified as overweight (BMI >25). A comparison was conducted between overweight patients and others concerning thyroid parameter values and psychiatric drug usage. No statistically significant differences were observed with regard to thyroid parameters. However, among patients taking antipsychotics, a significantly higher percentage were overweight, compared to patients not taking antipsychotics (63.3% vs. 30.8%, $\chi^2 = 4.988$, $P = 0.026$). No statistically significant differences were found for other psychiatric medications.

4. Discussion

The objectives of this research were (i) to establish differences in the concentration of TT3, TT4, and TSH among individuals diagnosed with common psychiatric disorders and (ii) to establish whether these hormone levels differed between patients who had attempted suicide and those who had not.

The first hypothesis was partially confirmed. The results of this study indicated lower TT3 values in patients with depressive disorders compared to those with psychotic and bipolar disorders as well as the control group. These findings suggest that thyroid hormones might be involved in a complex compensatory mechanism aimed at correcting the reduction in central serotonin activity.

Furthermore, this study also indicated lower TT3 values in patients with depressive disorders compared to those with psychotic and bipolar disorders, as well as the control group.

Lower TT3 values were observed in patients who reported a history of suicide attempts, in comparison to participants who did not. A majority of participants exhibited TT3 values outside the reference range in the group of participants with depressive disorders, in comparison to those with other psychiatric conditions in the focus of this study. These findings align with previous evidence suggesting that patients with depression often exhibit lower TT3 values[43,46]. The present study reinforces the association between reduced TT3 hormone values in patients with depressive disorders when compared to participants with other psychiatric disorders and the control group. The low T3 syndrome, in the absence of other systemic diseases, may serve as a distinctive marker for a specific subgroup of patients with depression[46,47].

The relationship between bipolar affective disorder and the observed change in thyroid hormone values, as documented in previous literature, may be attributed to the use of lithium therapy[48,49]. This is particularly significant considering that examples from the literature suggest the absence of abnormalities in thyroid hormone and TSH levels among patients experiencing a manic episode[50], consistent with the results of the present study.

Our study results also indicate that older patients exhibit significantly reduced TT3 values and significantly increased TT4 values, which is in line with previous research on the association between age and thyroid function changes[34]. The impact of psychiatric pharmacotherapy and pathophysiological changes in psychiatric conditions warrants further investigation.

The second hypothesis was partially confirmed as the TT3 values were significantly lower in participants who had attempted suicide. These results suggest the potential utility of T3 levels as a marker for assessing suicidal risk in patients. However, it is important to note that our study had a relatively small sample of patients who had attempted suicide.

The results of our research indicate variations in thyroid hormone values related to suicidality. Significantly lower values of the TT3 hormone were observed in participants who had attempted suicide in comparison to those who had not. Existing literature supports these findings, suggesting lower TT3 levels in suicidal patients[19]. In addition, other studies have demonstrated a negative correlation between the T3 hormone levels and Beck suicidality score levels[40,51]. The literature further suggests an association between a history of suicide events, suicidality, and low values of the T4 hormone[31,32,52,53], as well as a tendency toward lower TSH values in suicidal patients[52], while the results of the present study did indeed reveal changes in the levels of TT4 and TSH hormones in relation to suicidality.

When considering normal TSH values in combination with low TT3 values, it may suggest temporary changes during the response to stress related to a suicidal crisis. Hypersecretion of thyrotropin-releasing hormone could be considered a compensatory mechanism aimed at preserving normal thyroid hormone secretion and normalizing serotonin activity in depressive patients[54].

Limitations of this study include the relatively small number of participants for certain psychiatric conditions and the small number of participants who had attempted suicide. In addition, this study conducted a joint analysis of data related to suicide attempts. Further studies should explore the possibility of increasing the sample size and including specific diagnostic categories to conduct a more comprehensive comparison between individuals with and without suicidal behavior. Furthermore, it may be wise to investigate the potential influence of obesity and metabolic syndrome on the obtained thyroid hormone values.

5. Conclusion

The present research demonstrates that patients with psychotic disorders had higher values of TT3 in comparison to patients with depressive disorders. Nevertheless, it did not reveal significant differences in TT3, TT4, and TSH values among participants with psychotic disorders, the control group, and those with bipolar disorder. These contradictory findings warrant further research to determine whether thyroid dysfunction is a common feature in patients with psychotic disorders, as it appears to be in patients within the depression spectra, as suggested in the previous literature[39].

Further studies should include larger patient samples to investigate whether assessing thyroid function in routine clinical practice might aid in early recognition of suicidality and suicide prevention. In addition, these studies can highlight the importance of addressing thyroid function abnormalities as an additional intervention in suicidal patients.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

The research was approved by the Ethics Committee of the Clinic (approval ID: 03-1226/2-17), and each participating patient provided informed consent to participate in the study.

Consent for publication

All patients participating in the study gave written consent. Their names were not recorded anywhere, but the laboratory material and completed questionnaires were delivered under a code.

Availability of data

Supporting and original data can be obtained from corresponding author following formal request.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Wisdom capacities in people with and without chronic mental health problems: A representative survey on a general German adult population

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Abstract

Wisdom capacities are important for coping with difficult and ambiguous life situations. People with chronic mental health problems often have problems in coping with life problems. Until now, there are no comparative and representative data on the distribution of wisdom capacities people with and without chronic mental health problems. Identifying strengths and limitations in wisdom capacities in both groups will give a basis for specific focus in wisdom training in clinical settings and public health. This cross-sectional observation study examined a German population with a representative sample of 2505 persons aged 16 – 95 years in 2019. Sociodemographic data as well as chronic mental illnesses data were collected, and wisdom capacities were assessed by the 12-WD Wisdom Scale. The surveys were carried out using interviews and self-report questionnaires at the respondents' homes by an experienced social research company. The wisdom capacities value and problem relativization, as well as emotion acceptance were scored the highest by people with and without chronic mental health problems. Uncertainty tolerance, sustainability and perspective change received the lowest scores. People with chronic mental health problems had slightly lower overall wisdom affinity (M = 7.00, SD = 1.41 on a scale of 0 – 10) as compared to mentally healthy people (M = 7.7, SD = 1.38). Specifically, persons with chronic mental health problems reported the lowest ratings on wisdom capacities requiring active cognitive reflections (sustainability, perspective change, and uncertainty tolerance). In conclusion, since there are rather small quantitative differences between persons with and without chronic mental health problems, the wisdom concept seems appropriate to be applied to all individuals, regardless of the severity and nature of mental health problems. Wisdom enhancement, for instance, by means of wisdom training, may be focused on wisdom capacities which were rated comparably low, including perspective change, uncertainty tolerance and sustainability.

Keywords: Wisdom; Mental health; Coping; Representative

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1. Introduction

Global challenges such as wars, climate change, and migration, on a greater scale, have huge implications on a person's life. In addition to these global challenges, people are encountering problems, either small or big, in their lives, such as making decisions to

marry or remain single, have children or kickstart a career – or both leading to nonstop stress, or buy expensive or cheap products to save money for vacation. It is often not right or wrong in the decisions made because all options have their own advantages and disadvantages. Nevertheless, different levels of capacities are required for coping with difficult interpersonal, cognitive, and factual problems. Thus, having a spectrum of capacities for complex problem solving is a prerequisite for choosing the fitting capacity in specific situations. This is what one would call "wisdom" and what would be helpful for everybody.

Modern research on wisdom has been carried out for about three decades[1]. Wisdom is mainly understood as an expertise in dealing with difficult problems in life, such as problems about life planning, design and interpretation[2-6]. Wisdom is not a disorder-specific symptom, but a multidimensional and transdiagnostic capacity. Like other capacities (e.g., assertiveness or endurance), wisdom can be trained[7]. In psychosomatic diagnostics and treatment, diagnosis and training of wisdom can also be carried out by non-licensed professionals, such as social therapists or occupational therapists. This is an important advantage for further application in prevention, treatment, and rehabilitation in clinics or outpatient settings, for example, occupational health prevention.

Since life stresses and dilemma target different aspects and topics (e.g., family, money, profession, and living) which require different coping strategies, wisdom is understood as a multidimensional capacity[8,9]. Based on the summarization of different wisdom capacities[10], 12 different capacities were found to constitute wisdom in an integrative wisdom model. Wisdom capacities are constituted by attitudes and behavior strategies, which can be used to solve different life problems. Wisdom capacities can also be trained. The integrative wisdom concept includes the following wisdom capacities: (1) Factual knowledge, (2) contextualism, (3) value relativism, (4) change of perspective, (5) empathy, (6) relativization of problems and aspirations, (7) self-relativization, (8) self-distance, (9) emotion acceptance, (10) emotional serenity and humor, as well as the ability to accept conditions and translate them into forward-looking behavior (11) tolerance of uncertainty, and (12) sustainability[10] (Linden *et al.*, 2019).

Wisdom is the opposite of rigid, dogmatic, and inflexible thinking and behavior[5]. There is no correlation between wisdom and desire to behave wisely or having formal education. Wisdom is the best predictor of life satisfaction and can counteract negative impacts of aging more than what objective life conditions, economic, environmental, social, and financial context aspects could do[11]. People with high wisdom can better distance themselves from stressful events and thus calm down, use active coping strategies for cognitive reassessment ("reframing") or cope with life problems, and apply gained life experiences in new problem situations. In contrast to "non-wise" persons, "wise" persons recognize that it is not the external situation, but their own reaction that influences their well-being. "Wise" persons are more concerned with the well-being of others rather than of their own[2,5,12].

In the modern psychosocially and cognitively demanding world, people with common chronic mental health problems (e.g., anxiety, depression, and adjustment disorders) often report a lack of life and stress coping capacities, which comes along with problems in work and societal integration. Thus, wisdom capacity trainings have been performed, and it has been found that such trainings achieved positive effects in psychosomatic medicine and rehabilitation[7,10,13-15].

Wisdom as a multidimensional life and stress coping capacity is especially important for persons with chronic mental health problems. However, it is also relevant for healthy people, because everybody has to cope with life problems and critical situations. Until now, the distribution of wisdom capacities in the general population remains unknown. Wisdom has been investigated either in non-clinical or clinical populations[10], but comparative studies on wisdom in persons with and without chronic mental health problems are scarce[16,17]. There are currently no systematic data representative of a population to illustrate the distribution of wisdom capacities in a general population. The population-representative data are necessary for determining the number of people (with and without chronic mental health problems) who have problems with certain wisdom capacities and might benefit from specific education or training in these capacities, to be better prepared for coping the unavoidable life problems. Representative data also contribute to basic research in the field of psychosomatics by providing norm data that can be used for comparisons of specific (clinical) samples with the general population.

1.1. Research questions

Against this background, the main question is whether people with chronic mental health problems have different profiles of wisdom capacities as compared with people without chronic mental health problems. This analysis is part of a larger representative study[18] which investigates the distribution of wisdom capacities in a general national population.

The research questions are as follows:

(i) Is there a significant difference in the wisdom capacities between those with and without chronic

mental health problems?[10] (12-WD Wisdom Scale, Linden *et al.*, 2019)?

(ii) Are there differences in the ranking of wisdom capacities in people with and without chronic mental health problems?

2. Methods

2.1. Procedure

This cross-sectional observation study examined a large population-representative sample of 2509 people aged 16 – 95 years. The study was conducted by a professional social research company (USUMA GmbH, Berlin), which is experienced in conducting population-based representative surveys[19].

The sampling procedure was a three-stage process: Sampling areas were selected by random sampling. USUMA worked in 250 sample areas throughout Germany, and ten interviews were carried out per area. In the second stage, households were randomly selected within these areas, based on on-site inspection. In the third stage, the interviewer identified the households and selected an person per household for an interview, using a predetermined random procedure called Kish selection grid ("Swedish key,"[20]), which is used for the random selection of respondents in households with several persons. The application of Kish selection grid is particularly necessary in surveys that initially selected a sample treating households as a whole (household sample). Thereupon, in the next step, each person in the respective household was given the same chance to be an interviewee by means of the Swedish key.

The surveys were conducted by means of interviews and self-report questionnaires with the respondents on site. Sociodemographic data and chronic physical or mental disorders data were collected during the interview. Wisdom capacities were assessed using the 12-WD Wisdom Self-Rating Scale[10]. Ethics approval was obtained from the Technische Universität Braunschweig (D-2021-03). All interviewed persons participated in this survey with written informed consent.

2.2. Assessment of wisdom capacities using 12 WD Wisdom Scale

In this population-representative study, the self-rating Wisdom Scale[10] (12-WD Wisdom Scale, Linden *et al.*, 2019) was used for assessing 12 wisdom capacities, according to the integrative wisdom model[10]. Participants were asked how strongly they apply the 12 wisdom capacities in life problem situations. The instruction of the 12-WD Wisdom Scale is: "Below you will find very different statements and principles on how people can react to difficulties and life stresses. Please think of the situation just presented. For each statement, decide to what extent it makes sense or not to you personally in this situation." Responses are given per item on a Likert scale from 0 (strongly disagree) to 10 (strongly agree). Each of the 12 statements represents one of the 12 theoretically based wisdom capacities, and they can be grouped into five larger domains (Table 1).

A global wisdom score can be calculated as a mean value of all 12 items of the 12-WD Wisdom Scale. The idea is that a person has an understanding of these different capacities and can then be ready to choose selected capacities for problem solving in concrete life situations. The mean score of all 12 wisdom capacities can be interpreted as global wisdom affinity.

Cronbach's alpha for the 12-WD Wisdom Scale was 0.868 in the present investigation. To achieve sufficient differentiation in the items' rating, and because positively formulated attitude items tend to be answered positively, we adjusted the rating scale from the original scale of 1 – 6[10] to a scale of 0 – 10 for each item. For interpretation of the global wisdom score, Linden *et al.* (2019)[10] defined below-average values for 12-WD mean scores <3.5 (on a scale 1 – 6). In our case, wisdom deficits were thus assumed for 12-WD mean scores <5 on a scale of 0 – 10. This results in the division of the wisdom capacity mean values into three categories: "low (rating 0 – 4)", "moderate (rating 5 – 9)", or "high (rating 10)" wisdom.

2.3. Chronic mental health problem

Chronic mental health problems with accompanying impairments are understood according to the definition of common mental disorders (anxiety, depression, and adjustment disorders). Chronic mental health problems are defined by specific symptomatology with suffering and impairment in daily life activities and coping with stress or life challenges[21]. About 80% of patients who are under treatment have chronic mental health problems, and mental disorders are lifetime disorders given their nature[21,22]. In the present representative study, chronic mental health problems were assessed with questions as follows: "Do you regularly have - now and earlier - complaints such as anxiety, mood or interactional problems, which lead to impairments in your daily life routines? Have you been in treatment because of these problems, or have others suggested that you should go for treatment (by physicians or psychologists)?" Chronic mental health problems have been assessed this way in other studies[21,23]. The above-mentioned questions for assessing chronic mental health problems have been proofed content-valid and comprehensible and have also been validated with a standardized interview[21]: In the validation study, chronic mental health problems were reported by 307 patients in primary care services according

Table 1. Twelve wisdom capacities according to the 12-WD Wisdom Scale, based on the integrative wisdom model by Linden *et al.*, 2019[10]

View of the world	(1). Factual and procedural knowledge: General and specific knowledge about problems, what constitutes problems, and the possibilities of solving them (2). Contextualism: Knowledge about the temporal and situational character of problems and the numerous conditions in which life is embedded (3). Value relativism: Knowledge of the diversity of values and life goals and the need to look at other people within their value system without losing sight of one's own values
View of other people	(4). Change of perspective: The ability to describe a problem from the perspective of other people (5). Empathy: The ability to understand and feel the emotional experience of another person.
View of one's own person	(6). Relativization of problems and aspirations: The ability to be humble and to accept that one's problems may not be that important compared to many problems in the world (7). Self-relativization: The ability to accept that one is not always the most important individual and that most things do not follow one's will or are not aligned with one's interests. (8). Self-distancing: The ability to recognize and understand the perception and evaluation of oneself from the perspective of other people
View of one's own emotional experience	(9). Perception and acceptance of emotions: The ability to recognize and accept one's own emotions (10). Emotional serenity and humor: The ability to be emotionally balanced, to control one's own emotions depending on the situation, and to view oneself and one's own difficulties with humor
View to the future	(11). Tolerance of uncertainty: Knowledge and acceptance of the fact that future developments can never be reliably predicted or controlled (12). Sustainability: Knowledge of short- and long-term consequences, which can contradict each other

to the above definition and assessment questions. All of them fulfilled the criteria of common mental disorders according to the structured diagnostic mini interview[21].

Since mental health problems are usually chronic and recur over the life span, with relapses or even continuous problems[21,22,24], a separate assessment for acute mental health problems was of no use in this study. Of interest is whether someone is repeatedly confronted with mental health problems that mentally impair them in their daily life.

2.4. Statistical analysis

Descriptive data were calculated (mean values, standard deviations, and frequencies), and people with and without chronic mental health problems were compared by χ^2 test or *t*-test. All analyses were performed using SPSS.

2.5. Participants

In 2021, 2509 people from the general population in Germany were surveyed, from which 2505 provided complete data on the 12-WD Wisdom Scale. Data collection was carried out by USUMA GmbH. The sample contained 49% men and 50.9% women, and three persons (0.1%) identified themselves as diverse. In this survey, 22.5% of the surveyed individuals had a higher school education (12 years, i.e., Abitur/A-Levels); 95.2% were employed at the time of survey; 59.8% had a partner; 34.3% lived in a single household; 69.6% had religious denomination affiliation; 4.9% had no own income; 44.1% had a personal monthly income up to 1500 €, and 51% more than 1500 €; and 13.2% reported having chronic mental health problem of any kind, which was lower than the general prevalence of acute mental disorders[25] and slightly lower than the prevalence of chronic mental health problems in primary care[21], which was higher than that in the general population.

The majority of participants with chronic mental disorders were female (65% women in the chronic mental health problem group, as compared to 49% in the mentally healthy; Table 2), concurring with the previously reported data[25,26]. Potential influence of psychosocial factors (femininity and masculinity), brain structures, genetic factors, and fluctuations in sexual hormones are regarded as multifactorial causes of more frequent and qualitatively different mental disorders in women[27,28]. People with chronic mental health problems were often unemployed (63%, as compared to 42% in mentally healthy), which is consistent with published data[29]. Very often, they also had lower income (61.7% below 1500 €/$/month). There were no differences between people with and without chronic mental health problems in terms of age, size of town in which they were living, and percentage of persons affiliated with religious denomination (Table 2).

3. Results

3.1. Wisdom capacities in persons with and without chronic mental health problems

People with chronic mental health problems had a lower global wisdom score as compared with the mentally healthy group (M_{MH} = 7.00 versus M_{H} = 7.70 on scale 0 – 10, $P < 0.001$; Table 3). They also had lower ratings

Table 2. Characteristics of persons with and without chronic mental health problems from a German representative sample

Characteristics	All (N=2505)	With chronic mental health problem (N=331; 13.2%)	Without chronic mental health problem (N=2174; 86.6%)	*P*-value in group comparison
Sex				<0.001
Male	49.1%	35.0%	51.2%	
Diverse	0.1%	0.3%	0.1%	
Female	50.8%	64.7%	48.7%	
Age in years	49.48 (17.80)	51.12 (17.27)	49.24 (17.88)	0.074
Education (A-levels)	22.5%	28.7%	21.6%	0.004
Times of being unemployed during one´s life	0.99 (1.60)	1.59 (1.94)	0.90 (1.53)	<0.001
Never have been unemployed	55.0%	37.1%	57.8%	
Personal monthly income in €				<0.001
No own income	5.0%	4.3%	5.1%	
<1500 €/$	44.1%	57.4%	52.1%	
>1500 €/$	50.9%	38.3%	52.9%	
Number of persons living in the household	2.12 (1.12)	2.00 (1.20)	2.14 (1.10)	0.039
Single household	34.3%	43.5%	32.9%	
Town size (number of inhabitants)				0.218
<2000	9.4%	7.6%	9.7%	
2000 – 20000	32.5%	32.1%	32.5%	
20000 – 100000	24.0%	25.7%	23.8%	
100000 – 500000	16.2%	13.9%	16.6%	
>500000	18.0%	20.8%	17.5%	
Affiliation to religious denomination	69.7%	68.5%	69.9%	0.618

Note: Data are expressed as either percentages or means (standard deviation), and results of group comparison are shown (χ^2 test or *t*-test, N=2505).

than the mentally healthy in nine out of twelve wisdom capacities, i.e., problem solving, contextualism, perspective change, problem and self-relativization, self-distancing, emotional composure, uncertainty tolerance, and sustainability. Both groups had similar ratings for value relativism and emotion acceptance (Table 3).

Considering chronic physical illness and chronic mental health problem together, 5.2% of the whole sample were affected by both (MP), 78.2% had no health problem (NN), 8.0% had mental health problems only (M), and 8.6% had physical health problem only (P). Global wisdom score was highest in NN (M = 7.73, SD = 1.37), followed by P (M = 7.28, SD = 1.44), whereas participants with mental health problems had lower global wisdom scores (MP: M = 6.99, SD = 1.53; M: M = 6.99, SD = 1.33; ANOVA $P < 0.001$).

Considering the potential impact of age on wisdom, the correlation between these two variables was calculated. There was no correlation between age and global wisdom score (r = 0.035, Spearman's correlation; r = 0.053 in participants with mental health problem, r = 0.039 in participants without mental health problem).

3.2. Ranking of wisdom capacities

The ranking of wisdom capacities was similar in both groups (Table 3 and Figure 1): Highest rating was found in the wisdom dimension value relativism (M_{MH} = 8.55, M_H = 8.72, Table 3 and Figure 1), followed by emotion acceptance (M_{MH} = 8.01, M_H = 8.09), problem relativization (M_{MH} = 7.73, M_H = 8.34), and factual and procedural knowledge (M_{MH} = 7.14, M_H = 8.31). Comparably lower rating was given to the wisdom capacities sustainability (M_{MH} = 5.38, M_H = 6.83.), uncertainty tolerance (M_{MH} = 6.16, M_H = 7.15), empathy (M_{MH} = 6.88, M_H = 7.20), and self-relativization (M_{MH} = 6.81, M_H = 7.33) (Table 3). In terms of categorical presentation (Figure 1), more than 95% of all participants scored high or moderate in value relativism and emotion acceptance, with no differences between persons with and without chronic mental health problems. A portion of the people with chronic mental health problems had low ratings on certain wisdom capacities, that is, sustainability (35%), tolerance of uncertainty (26%), and perspective change (23%) (Figure 1).

Table 3. Wisdom capacities and global wisdom score of persons with and without chronic mental health problems

Items of the 12-WD Wisdom scale according to the 12 wisdom capacities[10]	All (N=2505)	With chronic mental health problem (*N*=331; 13.2%)	Without chronic mental health problem (*N*=2174; 86.6%)	*P*-value in group comparison
(1) Before reacting to a problem, it is important for me to understand what the problem is.	8.16 (2.05)	7.14 (2.55)	8.31 (1.92)	<0.001
(2) What is good or bad depends essentially on the circumstances.	7.70 (2.17)	7.07 (2.31)	7.79 (2.13)	<0.001
(3) In my opinion everyone should be happy in their own way.	8.70 (1.72)	8.55 (1.83)	8.72 (1.69)	0.086 (n.s.)
(4) It is interesting for me to look at what others may think about a topic.	6.73 (2.53)	6.08 (2.69)	6.82 (2.50)	<0.001
(5) I always try to empathize with how my counterpart feels.	7.16 (2.27)	6.88 (2.43)	7.20 (2.24)	0.024 (n.s.)
(6) If you are satisfied with what you have, you are better off than if you cry over what you do not have.	8.26 (1.97)	7.73 (2.22)	8.34 (1.92)	<0.001
(7) As far as possible I try not to take myself so important.	7.26 (2.27)	6.81 (2.31)	7.33 (2.26)	<0.001
(8) I cannot expect others to like me if I do not behave accordingly.	7.95 (2.08)	7.44 (2.31)	8.03 (2.03)	<0.001
(9) I cannot demand to be always in a good mood.	8.08 (1.92)	8.01 (1.93)	8.09 (1.93)	0.479 (n.s.)
(10) If possible, I try not to get upset, because there is nothing to gain by getting myself upset.	7.63 (2.15)	6.78 (2.52)	7.76 (2.06)	<0.001
(11) I am one of those people who say that things happen as they happen.	7.02 (2.54)	6.16 (2.75)	7.15 (2.48)	<0.001
(12) I always see crises also as an opportunity for the future.	6.64 (2.57)	5.38 (2.74)	6.83 (2.49)	<0.001
Global wisdom score (mean score of all 12 items)	7.60 (1.40)	7.00 (1.41)	7.70 (1.38)	<0.001

Note: Data are expressed as means (standard deviation), and group comparison statistics are reported (*t*-test, N=2505). n.s.: Not significant.

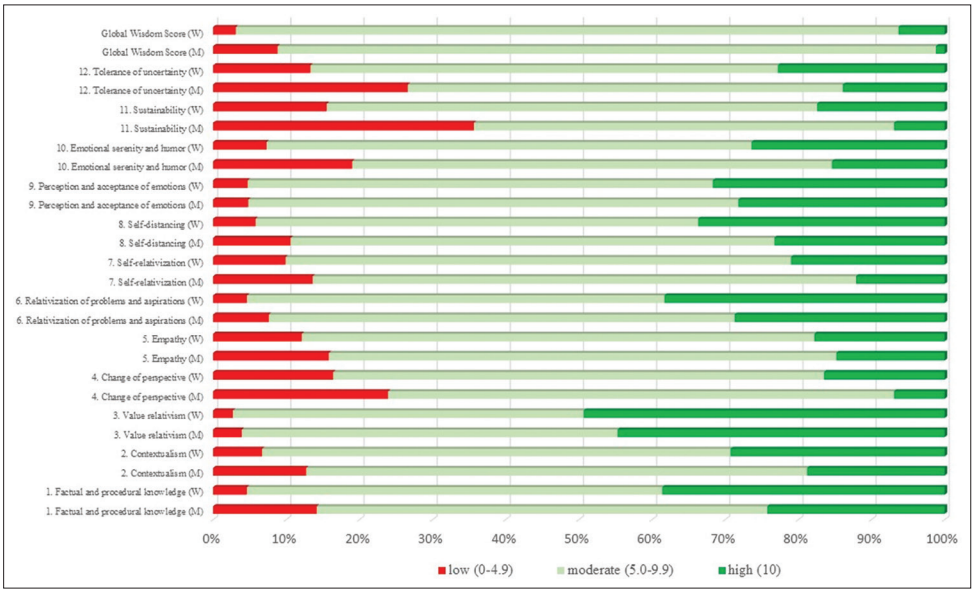

Figure 1. High, moderate, or low wisdom capacities in persons with (M) and without (W) chronic mental health problems (*N* = 2505).

4. Discussion

4.1. Wisdom capacities in persons with and without chronic mental health problems

The analysis of the representative data revealed the differences in the degree of self-reported wisdom capacities between persons with and without chronic mental health problems. People with chronic mental health problems had a lower global wisdom score. In particular, the wisdom capacities which require self-distancing and accepting perspectives of other people or uncertain future events seem to score lower in persons

with chronic mental health problems, as compared to mentally healthy group.

The results from this representative study concur with findings from several comparative observations[16,17]. Researchers found (partly, not even overall) weaker degrees of reflective and cognitive wisdom capacities in persons with chronic mental health problems as compared to mentally healthy persons[17]. A study showed that it is a challenge for patients with mental disorders to employ uncertainty tolerance, sustainability, perspective change, and self-relativization in face of tackling problems, as evidenced by their rather lower ratings in these capacities[10].

4.2. Ranking of wisdom capacities

The ranking of wisdom capacities is similar in people with and without chronic mental health problems. Wisdom capacities which were rated rather good were value and problem relativism, and emotional acceptance. In contrast, uncertainty tolerance, sustainability, and perspective change were perceived comparably weak.

Some wisdom capacities are more pronounced than others, possibly because the different wisdom capacities require different degree of active involvement into external and somewhat uncontrollable issues. This is in line with the phenomenon of control perception: It is a basic human characteristic that events become more difficult to handle when they are perceived as out of control of a person[30,31]. Wisdom as the complex capacity for coping with difficult, non-routine events in life requires coping with external stressors, uncontrollable uncertainty, unknown or stressful events. It may be rather difficult to *actively cope* with crisis in a future-oriented way, in order to make the best out of it (sustainability) and make one's peace with the idea that uncontrollable things will continue to happen in life (uncertainty tolerance). In contrast, it might be easier to just *accept* one's own concrete observable emotions (emotion acceptance) or accept that other persons have other specific values and perspectives (value and problem relativism).

4.3. Limitations and strengths

The strength of this representative investigation is that it gathered data from a large national population, including all age, gender, and social groups. The distribution of people with chronic mental health problems is within the expectable range, and its prevalence rate is lower than that of acute mental disorders (about one third of the general population suffer from acute mental health problems)[25], but similar to the prevalence rate of chronic mental disorders in primary care setting[21]. The inclusion of treatment proneness and chronicity of mental health complaints ("now and earlier") as the criteria for classifying a disorder as a chronic mental health problem in this representative study is the plausible reason that the prevalence rate of mental health problems is comparably lower than the rate reported in epidemiological studies on mental disorders[25]. Nevertheless, despite being a valid investigation that employed a reasonably big sample[25], this study considered only persons with self-reported chronic mental health problems, which had not been assessed with a differential diagnostic process.

Another limitation of this study is its cross-sectional design, which limits extrapolation of the current findings to other populations. Thus, we cannot draw conclusions concerning the stability or (situational) changeability of wisdom capacities. Furthermore, selecting only 10 persons per area were interviewed is regarded as a limitation, although the present study involved a rather large size of sample with diverse backgrounds.

The ratings of wisdom capacities reflect the level of behavior intention, instead of wise behavior. The latter requires assessment with situational tests and behavior observation in relevant contexts because intention-behavior gaps might exist in the application of wise behavior[32].

5. Conclusion

Although the wisdom score self-reported by people with chronic mental health problems was lower than that by the mentally healthy, the wisdom capacities of both groups shared a similar ranking order, especially the wisdom capacities requiring active cognitive reflections (sustainability, perspective change, and uncertainty tolerance). Since there are rather small quantitative differences (but no ranking differences) between persons with and without chronic mental health problems, the wisdom concept seems appropriate to be applied to all individuals, regardless of the severity and nature of mental health problems.

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Conflict of interest

The author declares that they have no conflict of interest.

Author contributions

This is single-authored article.

Ethics approval and consent to participate

A positive ethics vote has been obtained from the faculty of life sciences at the Technische Universität Braunschweig (D-2019-03).

Consent for publication

Permission was obtained from each of the participants to scientifically use and publish their anonymized data in aggregated data.

Availability of data

Data and material can be made available from the author on reasonable request.

Further disclosure

Part of findings has been presented in conferences in German national rehabilitation and psychotherapy conferences in 2022.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Clinical characteristics of somatization symptoms of Chinese outpatients in the Department of Cardiology

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Abstract

Somatization symptoms are common in patients with cardiovascular disease (CVD). However, it is challenging to improve these symptoms as the cardiologists in general hospitals, whom these patients sought medical attention from, are imperceptible to signs of psychological disorders, thereby leading to unnecessarily high medical costs and failure of improving the symptoms. Therefore, this study aimed to explore the clinical characteristics and factors that affect somatization symptoms in Chinese outpatients with CVD, providing results that could benefit the improvement of diagnosis and intervention of psychological disorders in the future. We conducted a cross-sectional and observational study in a tertiary general hospital in Hunan, China, from August 2020 to July 2021. Patient health questionnaire-15 (PHQ-15), general anxiety disorder-7 (GAD-7), PHQ-9, and a general demographic data questionnaire were used to screen outpatients for suspected psychiatric disorders. Of the 808 patients in this study, somatization symptoms occurred in 93.1% (752/808) of the sample. In patients with somatization symptoms, the mean total score on the PHQ-15 was 8.54 ± 2.67, and the prevalence of anxiety or depression was 78.7%. The PHQ-15 symptom items with a positive rate of >50% were sleep disorders, chest pain, headache, dyspnea, palpitation, and dizziness. The severity of somatization symptoms differed based on gender (P = 0.0341) and past hospitalization history (P = 0.023). In addition, there was a correlation between somatization symptoms and scores on the GAD-7 (P = 0.0282) and PHQ-9 scales (P = 0.0011). Linear correlation analysis found that PHQ-15 scores were significantly linked to GAD-7 (r = 0.4787, P < 0.001) and PHQ-9 scores (r = 0.5141, P < 0.001) in patients with somatization symptoms. Stepwise logistic regression analysis indicated that female gender, PHQ-9, and GAD-7 scores could positively predict somatization symptoms. In conclusion, somatization symptoms are prevalence in Chinese outpatients treated in the cardiology department. Anxiety, depression, and gender are the main factors affecting somatization symptoms.

Keywords: General hospitals; Outpatients; Somatic symptoms; Anxiety; Depression

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1. Introduction

Compared with the general population, patients with cardiovascular disease (CVD) have a higher prevalence of psychiatric disorders[1,2]. Anxiety and depression are the most common types of psychiatric disorders in patients with CVD[1,3]. One recent

research showed that the incidence rate of anxiety and depression was 42.5% among cardiology outpatients in the general hospital[4]. The correlation between psychological disorders, especially anxiety and depression, and progression of CVD, has been confirmed by previous research[1,5-7]. The occurrence of somatization symptoms, including chest pain, fatigue, shortness of breath, and dizziness, is often accompanied by common psychological problems, such as depression and anxiety[8-11]. Once affected, the patients often consult general practitioners or physical medicine specialists, instead of psychologists, as they do not have a deeper understanding of psychological problems[7-9], but most physical medicine specialists do not have the expertise to identify and redress psychological disorders[12-14]. Seeking medical attention from physicians having no experience in treating psychological illnesses is a non-viable solution to treating somatization symptoms, and this often leads to repeated visits to clinics or hospitals and increased medical costs[14]. Therefore, it is imperative to improve the identification of psychological problems in general hospitals. Unfortunately, there is limited clinical research on somatization symptoms in outpatients with CVD in general hospitals.

In view of the above, this study was designed to investigate the clinical features and factors affecting somatization symptoms in cardiology outpatients with psychiatric disorders in a Chinese tertiary general hospital. The present study involved patients who complained of physical discomfort and were screened for risk of psychological disorder using the "three questions" method recommended by the Chinese Expert Consensus on Psychological Prescriptions of Cardiovascular Patients in 2014[15].

2. Materials and methods

2.1. Participants

In this cross-sectional and observational study, we recruited outpatients who complained of physical discomfort and visited the cardiology department at the Xiangya Hospital, Central South University, Changsha, Hunan, China, from August 2020 to July 2021. Patients who met the following criteria were included: (i) Patients who gave at least two positive responses to the "three questions"[15] and were suspected of having psychological disorder; and (ii) patients over 18 years old who were willing to cooperate and were able to complete the scales and questionnaires. Exclusion criteria of the present study are as follows: (i) Having severe hypertension, heart failure above NYHA Grade III, severe arrhythmias such as ventricular tachycardia and atrial fibrillation; (ii) having somatic diseases such as diabetes mellitus, severe nervous diseases, dementia and cognitive impairment, hepatic and renal insufficiency, respiratory failure, difficulties in communication such as language or writing; (iii) having schizophrenic psychiatric symptoms and severe depression with suicidal tendencies and behaviors; and (iv) having a history of taking or was still taking related drugs at the time of questionnaire, such as anti-anxiety and depressive drugs, sedative and hypnotic drugs, and analgesic drugs, after the onset of somatization symptoms.

Eight hundred and fifty patients suspected of psychological disorders were screened using the "three questions" method[15]. Among them, 42 patients refused to complete the scales and questionnaires because they were unwilling to disclose personal data and rejected the self-rated psychological scale. In the end, 808 eligible adult outpatients, who completed all questionnaires, were included in this study. The Ethics Committees of Xiangya Hospital, Central South University, approved the study protocol, and informed consent was obtained from all participants.

Of the 808 patients, 503 (62.3%) were women aged 18 – 82 years, with a mean age of 51.3 ± 10.1 years. A total of 442 (54.7%) were diagnosed with CVD, of which 238 patients were diagnosed with hypertension, 70 with unstable angina pectoris, 64 with stable angina pectoris, and 70 with arrhythmia such as frequent ventricular premature, frequent atrial premature, and short paroxysmal atrial tachycardia. In addition, 205 patients (25.4%) were diagnosed with other somatic diseases, including 96 with chronic gastritis, 54 with multiple lacunar infarctions of the brain, and 55 with carotid atherosclerosis or cervical spondylosis. One hundred and sixty-one cases (19.9%) were confirmed as having no somatic diseases.

2.2. Methods

The study participants were assisted by coordinators in completing the questionnaires and scale assessments. Said coordinators owned a certificate of a second-level psychological counselor and had received unified training.

2.2.1. General demographic data

The demographic data collected from the participants include age, gender, marital status, education, occupation, techniques used for diagnosing current disease (e.g., by doctors, electrocardiography, echocardiography, and other auxiliary methods), duration of the disease, and medical consultation and treatment for main somatization symptoms in the past year.

2.2.2. Chinese version of generalized anxiety disorder-7 and patient health questionnaire-9 (PHQ-9)

Anxiety and depression were measured with the generalized anxiety disorder-7 (GAD-7) and PHQ-9, respectively[16,17].

The GAD-7 and PHQ-9 are commonly used as self-report tools to evaluate the severity of anxiety and depression. A patient with a score of five or higher was identified as suffering from anxiety or depression.

2.2.3. Chinese version of PHQ-15

Somatization symptoms were assessed using the somatic symptom module of the PHQ-15[18], which takes into account the most prevalent DSM-IV somatization disorder somatic symptoms. Subjects were asked to rate the severity of 13 symptoms with 0 ("not bothered at all"), 1 ("bothered a little"), or 2 ("bothered a lot") during the 4 weeks before answering the questionnaires. Two additional physical symptoms – feeling tired or having little energy and trouble sleeping – were included in the PHQ-9 depression module. Their responses were coded as 0 ("not at all"), 1 ("several days"), or 2 ("more than half the days" or "nearly every day"). The total PHQ-15 score ranges from 0 to 30, and scores of ≥5, ≥10, and ≥15 represent mild, moderate, and severe levels of somatization, respectively.

2.3. Statistical analysis

All data were analyzed with SPSS version 17.0 (IBM, Armonk, NY). Quantitative data are expressed as mean ± standard deviation, whereas categorical data are expressed as rank or percentage. For normally distributed quantitative data, one-way analysis of variance was used to compare the mean between groups. Chi-square test was used to compare the categorical data and ratios. Linear correlation analysis was adopted for examining the two-variable relationship, and step-wise logistic regression analysis coupled with the forward conditional method was used for multivariate analysis. A two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1. Occurrence of anxiety or depression and somatic symptoms

A significant majority of the 808 patients selected for this study manifested symptoms of anxiety and/or depression. Specifically, 70.7% had anxiety symptoms, and 76.2% had depression symptoms. Of those with depression symptoms, 60.0% of them also had anxiety symptoms, adding to 82.3% of the total selected patients displaying symptoms of anxiety and/or depression. In addition, somatization symptoms were identified in 752 patients (93.1%).

In the patients with somatization symptoms, the average score on the PHQ-15 was 8.04 ± 2.67. Of these patients, 636 patients (78.7%) were also experiencing symptoms of anxiety or depression. The patients were then divided into three categories based on their PHQ-15 score: 254 (33.8%) had mild symptoms, 399 (53.1%) had moderate symptoms, and 99 (13.0%) had severe symptoms.

3.2. Positive rates of somatization symptoms in affected patients based on PHQ-15 responses

Table 1 presents data on 752 patients with somatization symptoms, of which 4851 positive PHQ-15 symptom items were detected, comprising 3424 items with a score of 1 and 1427 items with a score of 2. Symptoms with more than 50% positive rate were sleep disorder, chest pain, headache, dyspnea, palpitation, dizziness, nausea, flatulence, or dyspepsia. Conversely, symptoms with < 10% positive rate were menstrual problems or cramps, sexual pain, or dysfunction.

3.3. Comparison of general demographic data in patients with different degrees of somatization symptoms

Table 2 presents an overview of the comparison among patients with different degrees of somatization symptoms. There was no significant difference in the average age, marital status, education level, employment status, duration of illness, and comorbidities. However, a significant

Table 1. Prevalence of somatization symptoms in affected patients based on PHQ-15 responses

Somatization symptoms	Bothered a little (score=1)	Bothered a lot (score=2)	Total positive rate (%)
Stomach pain	242	132	49.7
Back pain	217	120	44.8
Pain in arms, legs, or joints	140	93	31.1
Menstrual problems or cramps*	36	4	8.5
Headaches	382	127	67.7
Chest pain	429	143	76.1
Dizziness	285	95	50.6
Fainting spells	82	39	16.1
Feeling your heart pound or race	199	98	62.79
Shortness of breath	368	118	64.6
Pain during sexual intercourse	30	5	4.65
Constipation or diarrhea	129	60	25.2
Nausea, flatulence, or dyspepsia	294	85	50.4
Feeling tired or having low energy	203	115	42.3
Trouble sleeping	388	193	77.3
Number of positive symptom items	3424	1427	

Note: *Only women were asked about menstrual symptoms. PHQ-15: Patient health questionnaire-15.

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Table 2. The comparison of general demographic data in patients with different degrees of somatization symptoms

	Mild symptom (*n*=254)	Moderate symptom (*n*=399)	Severe symptom (*n*=99)	χ^2/F	*P*
PHQ-15 score	6.79±2.01	12.33±1.39	17.86±3.16	13.675	0.002
Average age (years)	53.5±10.2	51.2±9.8	50.7±9.9	1.241	0.442
Female (%)	55.9%	61.4%	74.7%	5.492	0.030
Education level (%)					
Primary school and below	34.4%	37.8%	39.7%	0.875	0.708
Middle school	46.8%	45.0%	42.6%		
College degree and above	18.8%	17.1%	17.6%		
Marital status					
Married	86.4%	88.4%	82.4%	0.811	0.634
Unmarried	9.74%	7.97%	11.76%		
Divorced or widowed	3.90	3.59%	5.88%		
Employment status					
Employed	35.1%	26.8%	32.4%	1.399	0.264
Unemployed or student	46.8%	52.2%	50.0%		
Retired	18.2%	20.7%	17.6%		
Duration of illness (years)	1.3±0.9	2.2±1.2	2.5±1.3	1.106	0.295
Comorbidities					
CVD	49.4%	54.6%	51.5%	2.873	0.181
Other somatic diseases	31.2%	25.1%	22.1%		
No somatic diseases	19.5%	20.3%	26.4%		
Average number of outpatient visits and hospitalizations	4.6±1.8	6.5±2.9	10.3±3.8	9.964	0.023

Abbreviations: CVD: Cardiovascular disease; PHQ-15: Patient health questionnaire-15.

difference was observed in the proportion of women and the average number of outpatient visits and hospitalizations due to the main somatic symptoms within the past year.

3.4. Comparison of anxiety and depression scores among patients with different degrees of somatization symptoms and analysis of the correlation between PHQ-15 score and anxiety or depression

According to Table 3, the anxiety and depression scores increase with the severity degree of somatization symptoms. There were significant differences in anxiety and depression scores among the three groups with different levels of somatic symptoms. A correlation analysis revealed that patients with somatization symptoms had a significant correlation coefficient of 0.4787 between PHQ-15 and GAD-7 scores ($P < 0.001$) and a significant correlation coefficient of 0.5141 between PHQ-15 and PHQ-9 scores ($P < 0.001$).

3.5. Analysis of predictive factors for somatization symptoms

Variables such as the scores of PHQ-9 and GAD-7 and demographic factors such as females, which showed significant differences, were tested in the step-wise logistic regression analysis in search for predictive factors of somatization symptoms. Table 4 shows the predictive factors of somatization symptoms, that is, female, PHQ-9, and GAD-7 scores. The probability of somatization increased by 6.526 and 8.020 times, respectively, for each 1-point increase in GAD-7 and PHQ-9 scores. The likelihood of females suffering from somatization symptoms increased by 4.440 times.

4. Discussion

The somatization symptoms of patients who seek treatments in general hospitals have become an increasingly recognized clinical and public health problem[19,20]. Somatization symptoms[21] refer to the experience and presentation of somatic discomfort, which cannot be explained by medical knowledge or experience. Clinically speaking, somatic symptom disorder is distinctly different from somatization symptoms in terms of their disease-specific clinical characteristics.

Somatization symptoms are prevalent in patients seeking treatments in general hospitals[11,19]. These patients

Table 3. Comparison of anxiety and depression scores among patients with different degrees of somatization symptoms

	Mild symptom (*n*=254)	Moderate symptom (*n*=399)	Severe symptom (*n*=99)	F	*P*
GAD-7 score	6.61±2.32	8.42±2.16	12.81±3.31	9.781	0.023
PHQ-9 score	8.62±2.17	10.12±2.31	13.91±3.21	14.552	0.001

Abbreviations: GAD-7: General anxiety disorder-7; PHQ-9: Patient health questionnaire-9.

Table 4. Logistic regression analysis of predictive factors of somatization symptoms

Variable	Regression coefficient	Standard error	Wals's value	Odds ratio	95% confidence interval	
					Lower limit	Upper limit
GAD-7 score	1.943	0.550	13.197	6.526	2.903	13.045
PHQ-9 score	2.105	0.571	15.148	8.020	3.470	18.930
Female	1.540	0.416	8.451	4.440	1.059	9.073
Constant	1.463	0.947	2.385	0.232		

Abbreviations: GAD-7: General anxiety disorder-7; PHQ-9: Patient health questionnaire-9.

do not have a clear understanding of psychological problems and consider that somatic diseases cause somatization symptoms, so they often seek medical help from cardiologists, instead of psychologists, in a tertiary hospital. Anxiety and depression are common psychological disorders in outpatients of the cardiology department[4], which are often manifested by various prominent symptoms of cardiovascular somatization, such as "heart distress" or "racing heart." A report by Ye *et al.*[22] found that the incidence of somatization symptoms in cardiology outpatients was as high as 64.2%.

Unlike other published studies, this study enrolled cardiology outpatients who were not only suspected of psychological disorders, but also screened using the "three questions" method[15]. Furthermore, this study used the three DSM-5-recommended questionnaires, namely, GAD-7, PHQ-9, and PHQ-15, in Chinese versions as research tools. Several previous studies[18,23-25] confirmed that these three scales could screen anxiety, depression, and somatization symptoms and assess the severity with good validity and reliability in general hospitals in China.

The results of this study showed that the total detection rate of anxiety or depression and somatization symptoms was 81.1% and 93.1%, respectively, among the participants. The finding further confirmed that the "three questions" method[15] has a high validity for the initial screening of psychological disorders. The results also suggested that the incidence of somatization symptoms in the patients with psychological disorders screened by the "three questions" method[15] was much higher than that in the general cardiology outpatients (64.2%)[22].

The present study found that patients with somatization symptoms scored an average of more than 8 on the PHQ-15 scale. The PHQ-15 symptoms with a high positive rate include CVD-related symptoms, such as chest pain, palpitation, and dyspnea. The nervous system is also affected by symptoms such as headache and dizziness, while the digestive system is affected by gastralgia and abdominal distention. The incidence of sleep disorder surveyed using PHQ-15 questionnaire was as high as 77.38%, indicating that sleep disorder is an important clinical feature of somatization symptoms in patients with psychological disorders. Item 4 (menstrual problems) and item 8 (sexual problems) displayed extreme floor effects. These floor effects were also reported in previous Chinese and Western studies[24-26], which may be related to the impact of Chinese cultural tradition and the patients' unwillingness to discuss about these private matters.

The present study found that anxiety and depression in patients with mild-to-moderate somatization symptoms could not be detected using only the GAD-7 and PHQ-9 scales. Despite the overall positive detection rate of 78.7%, anxiety or depression in patients with somatization symptoms might not be detected for several reasons[27,28]. First, the scale, which was compiled by psychologists, focuses on psychological moods and symptoms that patients are not familiar with. Second, patients tend to emphasize their somatization symptoms and may only have mild or moderate psychological disorders. Third, due to stigma and cultural traditions, patients often deny having psychological and emotional problems. Greden's study found that 69% of patients with depression only complained of somatization symptoms, and 11% denied having any psychological symptoms of depression when inquired directly[29]. Several recent reports focusing on the incidence of and factors that affect somatization symptoms among patients of general hospitals confirmed that somatization symptoms were closely related to anxiety and

depression[19,20,22,30]. In the present study, the results showed that the scores of GAD-7 and PHQ-9 increased with the severity of somatization symptoms, and there were significant differences in GAD-7 and PHQ-9 scores among patients with different degrees of somatization symptoms. Except for the female patients with varying degrees of somatization symptoms, there were no statistically significant differences in average age, marital status, level of education, employment status, duration of illness, or comorbidities. Step-wise logistic regression analysis also found that the female and scores of PHQ-9 and GAD-7 were positive predictors of somatization symptoms. The results of our study were consistent with the relevant research[19,20,30], further revealing that anxiety, depression, and gender were the main determinants of somatization symptoms.

The correlation between somatization symptoms and anxiety or depression[31,32] can be explained in different ways. First, depression and anxiety are common direct causes of somatization, where somatization symptoms can be manifested as anxiety and depression due to neuromodulation. Second, depression and anxiety are triggering factors of some somatic diseases, such as hypertension and coronary heart disease. Third, anxiety and depression may aggravate the symptoms of somatic diseases. In addition, the female is the determining factor of somatization symptoms, which may be associated with a woman's personality, social and family status, and Chinese cultural traditions.

The present study has several limitations. First, this was a single-center and cross-sectional study, whose findings may not be generalizable to other populations. Furthermore, the study participants in this study were patients who visited the cardiology department in a tertiary hospital and were initially screened for psychological disorders. Therefore, the current results may only reflect the somatization symptoms of patients suspected of psychological disorders. Second, the diagnosis of somatization symptoms in a few patients with somatic diseases was based on their descriptive accounts, rather than objective examinations. Besides, some patients were reluctant to disclose their personal or family financial situation because the medical expenses of most patients were borne by medical insurance; therefore, certain demographic data were unavailable for a more thorough analysis. Furthermore, this study did not incorporate the economic status of patients or the means of medical cost payment. A study by Xu *et al.*[33] found that whether outpatient expenses could be reimbursed was one of the factors influencing somatization symptoms.

5. Conclusion

Somatization symptoms are prevalent in cardiology outpatients with psychological disorders in Chinese general hospitals. The severity and occurrence of somatization symptoms are affected by anxiety, depression, and gender. Timely recognition and accurate diagnosis of these symptoms can lead to effective treatment and reduce medical expenses. We believe our findings provide a general guideline to cardiologists in general hospitals in identifying, diagnosing, and treating patients with psychological disorders.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Guolong Yu
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Writing–review and editing: Yali Ou, Guolong Yu

Ethics approval and consent to participate

Written consent and permission were obtained from each subject before their participation in this study.

Consent for publication

Written consent and permission were obtained from each subject for publishing their data.

Availability of data

Not available.

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ACCSCIENCE PUBLISHING

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BRIEF REPORT

The prevalence of skin disorders in patients with schizophrenia

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Abstract

There is ample evidence suggesting the presence of various multisystemic comorbidities in patients with schizophrenia. However, data on dermatological comorbidities in these patients are scarce. The present study aimed to analyze the profile of cutaneous conditions in patients with schizophrenia and contribute to the existing evidence in this area. A total of 102 consecutive adult patients with schizophrenia, who were attending the follow-up service at the outpatient clinic of the Department of Psychiatry in a tertiary hospital in North India, were evaluated by a dermatologist for the presence of any skin disorder. Dermatological findings were noted in 70% of patients and 38% had multiple skin conditions. Infections were the most prevalent diagnosis, with fungal infections being commonly observed. Other common dermatoses included nevi, age-related cutaneous changes, dyschromia, and drug-induced acne. The present study concluded that there is a high prevalence of dermatological diseases in patients with schizophrenia. Caregivers and psychiatrists managing these patients should familiarize themselves with these conditions, and dermatology consultation should be sought for prompt diagnosis and management.

Keywords: Schizophrenia; Psychosomatics; Dermatoses; Psychodermatology

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1. Introduction

Schizophrenia is a severe and chronic mental disorder, the exact etiology of which remains unknown. However, various strands of evidence point to the fact that schizophrenia is a brain disorder of neurodevelopmental origin[1].

Embryologically, the skin shares its origin with the central nervous system (CNS), and thus it stands to reason that neurodevelopmental pathologies are potentially associated with skin disorders[2]. The potential association is reflected in phenomena such as the faulty growth of skin fibroblasts sourced from patients with schizophrenia in culture media[3]. Second, immunological mechanisms that influence both the CNS and skin may contribute to skin pathology in schizophrenia[4]. Third, patients with schizophrenia may experience lower levels of self-care and impaired quality of life, which can lead to poor hygiene and subsequent skin disorders such as infections. The symptoms of schizophrenia, such as repetitive self-harming behaviors or hand washing,

may also contribute to the manifestation of skin disorders. Finally, many skin disorders in schizophrenia may be iatrogenic, as observed in the dermatological consequences associated with the use of drugs such as chlorpromazine and olanzapine[5,6]. The interface between schizophrenia, in particular, and skin disorders is important as both are chronic disorders. Patients with schizophrenia have higher all-cause mortality, and skin disorders may increase the risk. In addition, skin disorders can lead to greater disability and impairment in quality of life.

There is a high prevalence of non-communicable diseases and associated risk factors among patients with schizophrenia[7]. In a study on inpatients with psychiatric disorders, 69% were found to have some form of skin disorder[8]. Similar results were reported in two Indian studies[9,10], as well as a study conducted in Egypt that showed a high prevalence of skin disorders in psychiatric patients[11]. However, these studies were conducted in patients with various psychiatric disorders and were not exclusive to patients with schizophrenia. Consequently, studies specifically focusing on patients with schizophrenia are limited. A Taiwanese study examining 337 patients with schizophrenia reported a prevalence rate of approximately 50% for at least one skin disorder[12]. The literature review shows that studies have primarily focused on severely ill inpatients with schizophrenia. Therefore, the profile of skin disorders in community-living patients with schizophrenia may differ.

The present study aimed to assess the prevalence of skin disorders in ambulatory community-living adult patients with schizophrenia.

2. Materials and methods

The study protocol was approved by the ethics committee of the Postgraduate Institute of Medical Education and Research. Adult patients of any gender diagnosed with International Classification of Diseases-10 schizophrenia who visited the outpatient clinic of the Department of Psychiatry of a tertiary hospital in North India were invited to participate in the study. Eligible participants had to meet the following criteria: Being clinically stable, living in the community, and receiving stable doses of antipsychotic medications (at least 3 months preceding the evaluation for the study). The sociodemographic information, anthropometric details, diastolic and systolic blood pressure readings[13], clinical global impression scores[14], and clinical profiles of patients who consented were recorded. Hypertension was defined as per norms (systolic ≥140 mmHg and/or diastolic ≥90 mmHg)[15]. Subsequently, they were examined by a dermatologist in the same hospital to diagnose the presence and type or absence of a skin disorder. All dermatological diagnoses were recorded and categorized for the purposes of analysis. Continuous variables were analyzed using means and standard deviations, with independent samples *t*-test applied, while discrete variables were reported as frequencies and compared using the Chi-square test. Patients who declined participation or exhibited severe active psychopathology were excluded from the study.

3. Results

A total of 102 participants (66 males and 36 females) were evaluated. The sociodemographic and clinical profiles of the participants are presented in Table 1. The most commonly prescribed antipsychotics was olanzapine in both males and females (28 and 16 patients, respectively), followed by risperidone (18 and 7 patients, respectively). Thus, 67.64% of the study population were on stable doses of these two antipsychotics. In addition, nine male and four female patients were prescribed typical antipsychotics (12.74%). Six patients were aware of their hypertension and were receiving treatment for it.

The prevalence of obesity (body mass index ≥25) was 54.90% (n = 56 [male = 32, female = 24]) in the study population. The prevalence of obesity was observed to be 56.81% among patients prescribed olanzapine, 48.00% among those prescribed risperidone, 85.71% among those prescribed clozapine, and 83.33% among patients on injectables. However, no statistically significant difference was found in the prevalence of obesity among patients prescribed different antipsychotics (P = 0.23).

A majority of patients were considered to be normal or borderline mentally ill at the time of assessment (51 males and 29 females). Furthermore, 60 males and 32 females were considered to be very much improved or much improved as a result of drug treatment, as per the clinical global impression[14]. The prevalence of any dermatological finding was 69.60% (n = 72 [male = 47, female = 25], P = 0.85), and 45 patients (63.38% of those with dermatological diagnosis) had more than one dermatological condition. A total of 136 diagnoses were made, encompassing 71 different diagnoses. All of the diagnoses were analyzed. Table 2 presents the most common dermatological diagnoses in the participants (>1 mention). Table 3 highlights the most common categories of diagnoses.

There was no statistically significant difference observed between those with dermatoses and those without dermatoses with regards to gender (P = 0.81), obesity (P = 0.83), clinical state (P = 0.32), or improvement due to psychotropic drugs (P = 0.51).

Table 1. Sociodemographic and clinical profile of the study population

Sociodemographic and clinical variables	Male (*n*=66)	Female (*n*=36)	*P*
Mean age in years (SD)	39.30 (12.12)	39.63 (10.60)	0.88*
Mean years of education (SD)	10.34 (3.79)	10.08 (5.22)	0.76*
Mean duration of schizophrenia in months (SD)	142.53 (108.79)	119.02 (92.67)	0.27*
Mean BMI (SD)	25.10 (4.57)	26.02 (5.34)	0.36*
Mean waist circumference in cm (SD)	93.87 (10.76)	94.67 (15.10)	-
No. of participants with hypertension (%)	19 (28.78)	9 (25)	0.68*

Notes: Statistically significant if $P<0.05$ for *Independent samples *t*-test.

Table 2. Most common diagnoses (>1 mention)

Diagnosis	n
Melasma	9
Acne vulgaris	9
Cherry angioma	8
Melanocytic nevi	8
Onychomycosis	6
Freckles	6
Acanthosis nigricans	4
Rosacea	3
Tinea cruris	3
Polymorphous light eruption	3
Beau's lines	3
Folliculitis	3
Melanonychia	3
Post varicella scarring	3
Xerosis	3
Androgenic alopecia	2
Dermatitis passivata	2
Tinea corporis	2
Post inflammatory hyperpigmentation	2
Lichen simplex	2
Seborrheic keratosis	2
Psoriasis	2

4. Discussion

Schizophrenia is known to be associated with a high degree of comorbidity with various non-communicable and communicable diseases. However, the comorbidity of schizophrenia with skin disorders remains relatively understudied. Thus, this study aimed to contribute to the existing literature in this area. The results of the present study should be discussed with reference to the participants being health-care-seeking patients in a tertiary hospital, the absence of a control group, the possibility of a selection bias where patients with skin complaints may have consented with greater alacrity, and the modest sample size. However, most participants did not volunteer any skin complaints, and the findings are a product of careful dermatological examination.

The sociodemographic information and clinical profile of the study group were fairly representative of the population of treatment-seeking, community-living, and stable patients with schizophrenia visiting the outpatient clinic of the Department of Psychiatry. Furthermore, the prevalence of hypertension, obesity, and abdominal obesity in the present study is consistent with previous reports from this center[16].

Our study reveals a high prevalence of skin disorders in patients with schizophrenia, similar to, although slightly lower than, the findings of a study conducted in Taiwan[12]. The prevalence of skin disorders in this population is higher than that observed in the general population in rural India[17] but lower than the prevalence reported in clinic-based studies of patient populations, such as those with diabetes[18]. As pointed out earlier, there is a paucity of systematic studies with regard to skin disorders in patients with schizophrenia, making direct comparisons challenging[19].

Our findings reveal several notable observations. The most common group of disorders observed in our study was photo-aggravated dermatoses (29.41%). While photosensitivity has been recognized as a side-effect of typical antipsychotics, there is increasing recognition of its frequency with the use of newer atypical antipsychotics as well[20]. Interestingly, the study conducted in Taiwan did not report any instances of photosensitivity reactions in their sample[12]. Photosensitivity reactions can have various manifestations and severities. Our study demonstrates that in an Indian population with schizophrenia receiving antipsychotics, photosensitivity reactions are common. Early identification and treatment of these disorders are needed, as facial pigmentary disorders associated with photosensitivity can significantly impair quality of life and require long-term management.

Table 3. Most common classes of dermatoses

Class	Diagnosis	*n*
Photo-aggravated dermatoses	Polymorphous light eruption, photosensitive dermatitis, melasma, freckles, generalized hyperpigmentation, Favre-Racouchot syndrome, and tanning	30
Benign skin growth	Melanocytic naevi, dermal naevi, seborrheic keratosis, cherry angiomas, syringomas, and verrucous epidermal naevi	25
Others	Keloid, acne scars, post-varicella scars, linear focal elastosis, mucosal vitiligo, angular cheilitis, papular scars, leukoplakia, geographic tongue, nevus depigmentosus, xerosis, and excoriation marks	19
Fungal infections	Tinea, onychomycosis, pityriasis versicolor, and paronychia	16
Pilosebaceous disorders	Acne and rosacea, erythema, and telangiectasias	14
Inflammatory skin diseases associated with itching	Psoriasis, sebopsoriasis, lichen simplex chronicus, annular lesions, seborrhea capitis, keratosis pilaris, papular urticaria, and amyloidosis	10
Hair and nail disorders	androgenetic Alopecia, nail pigmentation, Beau's lines, and melanonychia	9
Obesity/metabolic related	Acanthosis nigricans, skin tags, and striae alba	6
Other infections	Folliculitis, warts, and trichomycosis	5
Dermatitis passivata	-	2

Benign skin growths refer to non-cancerous lesions that are frequently observed in both clinical and non-clinical populations. In our study population, benign skin growths ranked as the second most prevalent group of skin disorders. These growths can occur across all age groups and in individuals from different cultural backgrounds. Therefore, it is essential to differentiate benign skin growths from malignant lesions[21]. Other disorders such as keloids, acne scars, post varicella scars, linear focal elastosis, mucosal vitiligo, angular cheilitis, papular scars, leukoplakia, geographic tongue, nevus depigmentosus, xerosis, and excoriation marks were also observed in our study population. Furthermore, patients with inflammatory skin diseases, hair disorders and nail disorders were commonly observed in the study group. These conditions are likely to be incidental and unrelated to the effects of schizophrenia or its treatment[12].

Infections (fungal and non-fungal) were common in our patient population (24.50%). The prevalence of infections in this population can be influenced by various interacting etiologies. These may include immune abnormalities, metabolic syndrome, altered glycemic control, altered skin microbiome, and lack of general hygiene due to the effects of the illness[22]. Furthermore, tinea or onychomycosis must be treated, as they are associated with significant morbidity and can be transmitted to family members. Systemic antifungal treatment is expensive, and if the condition is not promptly and adequately treated, it may become more severe, requiring a longer duration of treatment.

The prevalence of obesity-associated skin disorders was 10.71% in the population diagnosed with obesity. As previously mentioned, obesity is a common comorbidity in schizophrenia and has a multifactorial origin[16]. Our study underscores the importance of assessing this particular group of dermatoses in patients with schizophrenia who are also obese.

The association between pilosebaceous disorders, particularly acne, and antipsychotics is well-established[12]. This relationship is complex and multifactorial. In the context of schizophrenia, these disorders are especially troublesome due to their propensity to cause disfigurement[23].

We identified two patients with dermatitis passivata[24]. This finding may reflect the overall clinical status of the study group, as most patients had well-controlled schizophrenia and were on stable doses of medication. It is possible that patients with more severe or poorly controlled schizophrenia may exhibit different and possibly more severe dermatological manifestations.

5. Conclusion

Our study emphasizes the importance of psychiatrists being aware of the high comorbidity between schizophrenia and skin disorders. Limitations of the study, as mentioned above, include the absence of a control group, the use of a cross-sectional design, and a modest sample size. In addition, we did not conduct testing for common comorbidities such as diabetes or assess the association between specific medication use and dermatological manifestations. These limitations may limit the generalizability of the findings.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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Ethics approval and consent to participate

Ethical approval was obtained (Approval ID: INT/IEC/2019/002190) and informed consent was taken from patients.

Consent for publication

Informed consent was taken from patients to publish their data.

Availability of data

The data that support the findings of this study are available on request from the corresponding author.

Further disclosure

The preprint of this paper can be accessed at: https://www.medrxiv.org/content/10.1101/2022.09.07.22279578v1

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ACCSCIENCE PUBLISHING

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LETTER TO THE EDITOR

The development and practice of psychosomatic digestive medicine: An innovative and successful treatment model in China

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Functional gastrointestinal disorders (FGID) are prevalent worldwide, affecting approximately 40% of the population, with a higher incidence in females than males[1]. In China, the morbidity of FGID ranges from 27.3% to 39.2%[2,3]. Psychosomatic diseases of the digestive system rank first in terms of incidence and the number of types among all internal psychosomatic diseases. Among the patients with FGID, approximately 32.1% have comorbid anxiety symptoms and 25.2% have comorbid depressive symptoms[4].

Patients with FGID often spend additional resources due to frequent visits to gastroenterology outpatient clinics, leading to a higher economic burden[5,6] — several gaps toward possible resolution. Gastroenterologists may have difficulty identifying the psychosocial factors behind gastrointestinal symptoms. Consequently, symptoms often become chronic and persistent, with limited treatment outcomes affecting the patient's quality of life. Therefore, there is an urgent need to develop a more effective treatment model for patients with FGID.

Psychosomatic digestive medicine was increasing important in the clinical practice of FGID. In 2006, Rome III was published, and gastroenterologists reached a consensus that social-psycho factors played an important role in the entire course of FGID. This was < 20 years since the diagnostic criteria, Rome I, was published for irritable bowel syndrome in 1989. In 2016, Rome IV was published, further strengthening the psychosocial components of FGID. Over the last decade, gastroenterologists in China have progressively carried forward the holistic model of medicine, incorporating research achievements from Western psychosomatic medicine and forming related academic groups (Table 1). In 2011, the academic committee of psychosomatic digestive medicine was established under the Western Psychiatric Association in China, marking the first academic group on the platform of psychiatric medicine in the country. Before long, the psychosomatic digestive group of Zhengzhou was established. In 2014, the cooperation committee of psychosomatic medicine was established under the Chinese Medical Association of Gastroenterology. Subsequently, in 2015, the book titled "Expert Opinions of Digestive Psychosomatic Health Problems in China" was published. In 2016, the book titled "Theory and Practice on the Management of Mind-body Problems of Gastroenterology" was published. In 2017, the Chinese Digestive Psychosomatic Union was established. In 2021, the book "Foundation and Clinical Practice of Digestive Psychosomatic Disorder" was published. In the same year, China's first and only psychosomatic digestive ward was established.

The psychosomatic digestive ward was established in Chengdu, Sichuan Province, and it consisted of 40 beds. The doctors in the ward operated on a bio-psycho-social medical model and created a mind-body holistic treatment model of FGID. The medical team in

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Table 1. The organizations and hallmark events in the development of psychosomatic digestive medicine in China

Year	The organizations and hallmark events
2011	Establishment of an academic committee of psychosomatic digestive medicine under the Western Psychiatric Association in China
2014	Establishment of a cooperation committee of psychosomatic medicine under the Chinese Medical Association (CMA) of Gastroenterology
2015	Publication of the book titled "Expert Opinions of Digestive Psychosomatic Health Problems in China"
2016	Publication of the book titled "Theory and Practice on the Management of Mind-body Problems of Gastroenterology"
2017	Establishment of the Chinese Digestive Psychosomatic Union (CDPU)
2021	Publication of the book titled "Foundation and Clinical Practice of Digestive Psychosomatic Disorder"
2021	Establishment of a psychosomatic digestive ward in Chengdu, China

a p sychosomatic digestive ward comprised psychiatrists, gastroenterologists, psychotherapists, physiotherapists, traditional Chinese medicine (TCM) physiotherapists, and nurses, forming an integrative treatment model of psychosomatic medicine in Chengdu, China.

In a psychosomatic-digestive clinic, patients suffering from various digestive symptoms, potentially indicative of "functional gastrointestinal symptoms," are advised for hospitalization in a psychosomatic-digestive ward. On admission, a series of medical tests, such as blood tests, abdomen ultrasound or computer tomography scan, and gastrointestinal endoscopy, are performed as necessary to rule out organic disease. Psychiatrists and gastroenterologists collaborate and undergo extensive training to exchange professional knowledge and skills, in the aspects of disease identification, diagnosis, differential diagnosis, and treatment. Working together, they gather detailed medical history, conduct comprehensive physical examinations, and perform psychiatric interviews to determine appropriate drug selection and dose adjustment. Patients will receive extensive health education from both psychiatrists and gastroenterologists, covering admission and discharge instructions, medication side effects and precautions, the significance of various therapies, and basic knowledge and management of FGID. During daily ward rounds, doctors not only adjust medication doses but also provide positive psychological support, which help patients enhance adherence to treatment and rebuild confidence in their recovery. Finally, doctors formulate follow-up plans, and patients receive follow-up phone calls from the ward, visit outpatient clinics at regular intervals, and can contact their attending doctor online through a mobile-health app. If necessary, the staff can deliver medications to the patients.

Patients with FGID often underestimate the significance of individual psychotherapy and do not seek psychological help before being admitted to the ward. They tend to focus on their gastrointestinal symptoms, spending considerable time, money, and energy on medical examinations and consulting numerous gastroenterologists. However, they are repeatedly informed that there are no organic diseases in their digestive systems and are prescribed medications to take home. These patients usually lack awareness of the emotional problems underlying their gastrointestinal symptoms, resulting in prolonged symptoms. To address this issue, in addition to the collaboration between psychiatrists and gastroenterologists, psychotherapists in the ward provide individual psychotherapy and group psychotherapy for patients with FGID, which plays an important role in their recovery. Psychotherapists arrange initial psychological assessments for each patient and work together with psychiatrists to create a treatment plan for individual and group psychotherapy.

The consultation settings for individual psychotherapy are once or twice a week for 1 h per session in a specific counseling room. After being discharged from the ward, patients can make appointments for individual psychotherapy in the clinic if needed. Initially, psychotherapists will establish a reliable and safe counseling relationship with the patients and reach a consensus on the counseling goal. Psychotherapists use various psychological techniques, such as cognitive-behavioral therapy, psychoanalysis, or humanism, to help patients identify psychosocial factors behind gastrointestinal symptoms, explore their inner conflicts, recognize the influence of their emotional problems on symptoms, and discuss possible and proper ways to deal with their inner conflicts and negative emotions.

Group psychotherapy is conducted every workday, typically lasting 1 – 1.5 h, with different themes and topics for each session, such as disease education group, perception of happiness group psychotherapy, emotional chessboard, somatic symptom group, mindfulness meditation group, emotion regulation group, and relaxation group. During these sessions, patients learn to understand the relationship between their gastrointestinal symptoms and negative moods and gut-brain interactions and learn the ways of expressing emotions properly and coping with stress. It is noteworthy that the perception of happiness group psychotherapy, an innovative psychotherapy first introduced in the treatment of patients with FGID in China, has proven successful in terms of its creativity and effectiveness.

Finally, technicians in the ward also play a role in the treatment of patients with FGID. These technicians include TCM physiotherapists and physical technicians. The physical technicians are responsible for administering neuroregulatory therapies, such as applying repetitive transcranial magnetic stimulation (rTMS) and using gastrointestinal biofeedback therapy apparatus on patients. Physiotherapists provide therapies involving auricular electrostimulation, acupuncture, and massage. The neuroregulatory therapies of rTMS and transcranial direct current stimulation are applied every workday, with each session lasting 60 min and 10 sessions making up a complete course of treatment. Similarly, TCM therapy is conducted for 30 min each session and consists of 10 sessions in a complete course of treatment.

It is worth mentioning that TCM therapies have largely promoted the recovery of patients with FGID. One such therapy is massage, an important practice in TCM known for its ease of operation, high safety, and minimal invasiveness. In short, massage involves the rubbing and pressing of specific regions of a person's body with specific hand techniques. Through massage, the function of viscera, Qi and blood, and meridians can be regulated, leading to the prevention and treatment of diseases. A great number of research studies and clinical practices have proven that massage can be an effective method for relieving gastrointestinal symptoms in both children and adults. In addition, acupuncture, another TCM method, involves the insertion of special thin needles into the skin on specific parts of the body to treat pain and illnesses. The previous studies have demonstrated that acupuncture can regulate the internal environment of the human body and play an important role in treating various illnesses, including gastrointestinal symptoms. Acupuncture holds promise as a potential treatment method for FGID.

After over 1 year of exploration, we have created a unique model for the treatment of FGIDs in China. The average length of stay in the ward was 12 days, and approximately 100 patients were discharged from the ward every month. Common types of FGIDs treated in the ward included functional constipation, functional diarrhea, functional dyspepsia, functional esophageal disorders, and chronic nausea and vomiting syndrome. Depression and anxiety were highly comorbid with FGIDs. With systematic treatment in the ward, more than 80% of the patients showed significant improvement not only in somatic symptoms and negative mood but also in psychological distress. Patients followed up regularly at the outpatient clinic, with the first clinic follow-up taking place 2 weeks after discharge from the hospital. Nurses regularly made follow-up telephone calls to patients within 1 year.

The establishment of the psychosomatic digestive ward in China is a successful demonstration of implementing the concept of body-mind integrity. After 1 year of careful exploration, a localized treatment model for FGID in the psychosomatic digestive ward in China was established, benefitting a large number of patients who were facing tough recoveries. The psychosomatic digestive ward is an innovative practice model that should be gradually implemented in more hospitals, so that patients with FGID can receive more effective and timely treatment, significantly reducing the wastage of medical resources, and ultimately improving the quality of life for these patients.

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None.

Conflict of interest

The authors declare that there are no conflicts of interest in this study.

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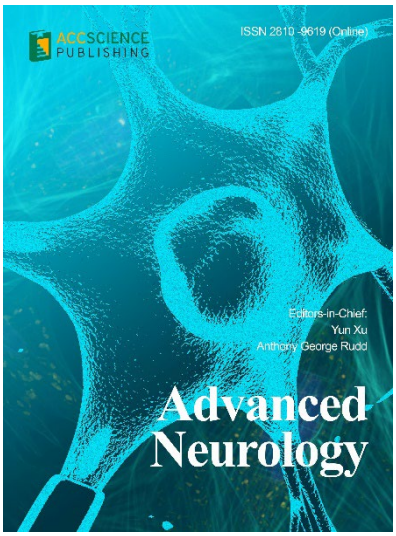

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