the current study may hsve been influenced by psychosocial stress or mood change. At baseline in sub-chronic and chronic subjects, CA2-3, and DG volumes were decreased compared to healthy volunteers as well as left total hippocampus, supporting the hypothesis of trisynaptic pathway dysfunction in schizophrenia [2,38]. In non-schizophrenia subjects, the presence of newly generated neurons in the granule cell layer of the DG are thought to be a result of, or an indicator of neuroplasticity [39]. In contrast, similar neuroplastic-driven neuronal generation appeared suppressed in a postmortem study of schizophrenia [40]. Decreased volumes in DG may represent the lack of neurogenesis in schizophrenia.

Other studies of hippocampal subfields in schizophrenia using MRI also describe complementary findings to the present results. In a study of non-psychotic, first-degree relatives of patients with schizophrenia, the volume of the subiculum was smaller than controls with no family history of schizophrenia [18]. In patients with clinically stable, chronic schizophrenia, schizoaffective disorder, or bipolar disorder with psychosis, the CA2-3 subfield was most prominently affected, and an inverse correlation between subfield volumes and positive symptoms was noted [16]. In patients with approximately 8 years of illness, the severity of positive symptoms was inversely correlated with CA2-3 and CA1 subfield volumes [17]. Comparison of subfield volumes with healthy participants was not reported. Larger studies of patients with acute versus stable symptoms, and at first episode and chronic stages of illness will be needed before any definitive relationships between hippocampal subfield volumes and symptoms can be determined.

The CA4-DG subfield appeared sensitive to the effects of schizophrenia, as smaller volume was detected even at first episode. The increasing volume loss over time could relate to progression of schizophrenia [2]. Patients in our study were treated with antipsychotic drugs. Similar to the present observations, other investigators reported no statistically significant relationships between hippocampal subfield size or surface mapping and amount of antipsychotic drug treatment [12–14,17]. However, in other studies our group and others have reported that total hippocampal volumes and hippocampal shape may be sensitive to antipsychotic drug treatments, with some antipsychotics reducing volumes, and others ameliorating progressive, illness-related volume reduction [41,42]. The present study did not conclude the influence of antipsychotics on hippocampal volume and its subfield volume because duration and type of medication was not controlled. Further studies will be needed to investigate the possibility of antipsychotic drug contributions to subfield volume loss, and the possibility that non-pharmacological interventions such as aerobic exercise could ameliorate the progression of volume loss [43].

There are several limitations to our imaging approach. First, automated hippocampal subfield remains technically challenging. The Images we used were acquired with a 1.5T scanner, a strategy successfully applied in studies of Alzheimer's and Parkinson's diseases [19,28]. Although the mean subfield volumes we report in healthy volunteers and patients were similar to those reported in studies using 3T field strength [16,17], and demonstrated good reliability over time for healthy volunteers, higher resolution images would have been preferred. At this time, direct comparisons between hippocampal subfield volumes obtained at 1.5T and 3T are not available., Although higher field strength would theoretically improve image resolution and subsequently increase the accuracy of segmentation, this is not always the case due to the increased sensitivity to motion and magnetic susceptibility [44]. The image acquisition strategy used here was based on a T1 sequence, as in the original report of the subfield algorithm [15,17]. Other studies report advantages of T2 sequences [45,46], or combined high resolution T1 and T2 sequences to improve definition of hippocampal subfields [47]. The automatic segmentation approach was developed to apply manually delineated subfields from 3T images into a probablistic atlas or mask to be implemented across varying image sets. A direct

comparison of manually delineated subfields and the automatic segmentation approach was not feasible in our sample set, and this is a limitation of the study. However, as stated in [12], "manual delineations suffer from intra- and interobserver variability, which confounds subsequent statistical analyses of the results." Despite these difficulties, the representative images obtained in our study appeared similar to those reported by other groups [15,17,19,28]. Second, the small sample size in each group might not be sufficient to detect subtle volume changes. The effects of laterality, sex, and medications were difficult to interpret in this context. Analysis of larger numbers of patients will be required to characterize detailed volumetric change and to control for potential effects of modifying factors. Third, we did not examine the possible influence of factors such as IQ, BMI, and psychological stress on hippocampal total or subfield volumes. Additional anatomical information such as the anterior and posterior segment volumes would also add value.

In summary, data from this study provides empirical evidence of effects of illness, and of illness progression on volumes of hippocampal subfields. As imaging techniques continue to improve, study of hippocampal subfields in schizophrenia may provide important insights into the dynamic characteristics of the illness and of neuroplasticity related to treatment.

Acknowledgments

We thank the assistance of Dr. Mikako Fuji, Dr. Junko Uchiumi, Dr. Yasuhiko Sudo, and Dr. Yoichiro Takasaka. We also thank all the participants and all the staff of Atago Hospital, Tosa Hospital and Hosogi Unity Hospital.

Author Contributions

Conceived and designed the experiments: MK KS SS YO SK SI WGH. Performed the experiments: MK KS SS. Analyzed the data: MK KS DJL WGH. Contributed reagents/materials/analysis tools: SS YO SK SI. Wrote the paper: KS DJL WGH.

References

1. Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA (2006) Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry 188: 510–518. PMID: 16738340
2. Tamminga CA, Stan AD, Wagner AD (2010) The hippocampal formation in schizophrenia. Am J Psychiatry 167: 1178–1193. doi: 10.1176/appi.ajp.2010.09081187 PMID: 20810471
3. Vita A, De Peri L, Silenzi C, Dieci M (2006) Brain morphology in first-episode schizophrenia: a meta-analysis of quantitative magnetic resonance imaging studies. Schizophr Res 82: 75–88. PMID: 16377156
4. Benes FM (1999) Evidence for altered trisynaptic circuitry in schizophrenic hippocampus. Biol Psychiatry 46: 589–599. PMID: 10472413
5. Harrison PJ (2004) The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications. Psychopharmacology (Berl) 174: 151–162. PMID: 15205886
6. Sawada K, Barr AM, Nakamura M, Arima K, Young CE, et al. (2005) Hippocampal complexin proteins and cognitive dysfunction in schizophrenia. Arch Gen Psychiatry 62: 263–272. PMID: 15753239
7. Csernansky JG, Joshi S, Wang L, Haller JW, Gado M, et al. (1998) Hippocampal morphometry in schizophrenia by high dimensional brain mapping. Proc Natl Acad Sci U S A 95: 11406–11411. PMID: 9736749
8. Csernansky JG, Wang L, Jones D, Rastogi-Cruz D, Posener JA, et al. (2002) Hippocampal deformities in schizophrenia characterized by high dimensional brain mapping. Am J Psychiatry 159: 2000–2006. PMID: 12450948
9. Narr KL, Thompson PM, Szeszko P, Robinson D, Jang S, et al. (2004) Regional specificity of hippocampal volume reductions in first-episode schizophrenia. Neuroimage 21: 1563–1575. PMID: 15050580

10. Qiu A, Tuan TA, Woon PS, Abdul-Rahman MF, Graham S, et al. (2010) Hippocampal-cortical structural connectivity disruptions in schizophrenia: an integrated perspective from hippocampal shape, cortical thickness, and integrity of white matter bundles. Neuroimage 52: 1181–1189. doi: 10.1016/j.neuroimage.2010.05.046 PMID: 20573561

11. Shenton ME, Gerig G, McCarley RW, Szekely G, Kikinis R (2002) Amygdala-hippocampal shape differences in schizophrenia: the application of 3D shape models to volumetric MR data. Psychiatry Res 115: 15–35. PMID: 12165365

12. Wang L, Mamah D, Harms MP, Karnik M, Price JL, et al. (2008) Progressive deformation of deep brain nuclei and hippocampal-amygdala formation in schizophrenia. Biol Psychiatry 64: 1060–1068. doi: 10.1016/j.biopsych.2008.08.007 PMID: 18814865

13. Brambilla P, Perlini C, Rajagopalan P, Saharan P, Rambaldelli G, et al. (2013) Schizophrenia severity, social functioning and hippocampal neuroanatomy: three-dimensional mapping study. Br J Psychiatry 202: 50–55. doi: 10.1192/bjp.bp.111.105700 PMID: 23284150

14. Zierhut KC, Grassmann R, Kaufmann J, Steiner J, Bogerts B, et al. (2013) Hippocampal CA1 deformity is related to symptom severity and antipsychotic dosage in schizophrenia. Brain 136: 804–814. doi: 10.1093/brain/aws335 PMID: 23388407

15. Van Leemput K, Bakkour A, Benner T, Wiggins G, Wald LL, et al. (2009) Automated segmentation of hippocampal subfields from ultra-high resolution in vivo MRI. Hippocampus 19: 549–557. doi: 10.1002/hipo.20615 PMID: 19405131

16. Mathew I, Gardin TM, Tandon N, Eack S, Francis AN, et al. (2014) Medial Temporal Lobe Structures and Hippocampal Subfields in Psychotic Disorders: Findings From the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Study. JAMA Psychiatry.

17. Kuhn S, Musso F, Mobascher A, Warbrick T, Winterer G, et al. (2012) Hippocampal subfields predict positive symptoms in schizophrenia: First evidence from brain morphometry. Transl Psychiatry 2: e127. doi: 10.1038/tp.2012.51 PMID: 22692142

18. Francis AN, Seidman LJ, Tandon N, Shenton ME, Thermenos HW, et al. (2013) Reduced subicular subdivisions of the hippocampal formation and verbal declarative memory impairments in young relatives at risk for schizophrenia. Schizophr Res 151: 154–157. doi: 10.1016/j.schres.2013.10.002 PMID: 24144441

19. Li YD, Dong HB, Xie GM, Zhang LJ (2013) Discriminative analysis of mild Alzheimer's disease and normal aging using volume of hippocampal subfields and hippocampal mean diffusivity: an in vivo magnetic resonance imaging study. Am J Alzheimers Dis Other Demen 28: 627–633. doi: 10.1177/1533317513494452 PMID: 23813689

20. Okada N, Kasai K, Takahashi T, Suzuki M, Hashimoto R, et al. (2014) Brief rating scale of socioeconomic status for biological psychiatry research among Japanese people: A scaling based on an educational history. Japanese Journal of Biological Psychiatry 25: 115–117.

21. Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13: 261–276. PMID: 3616518

22. Guy W (2000) Clinical Global Impressions (CGI) Scale. In: Rush AJ, editor. Handbook of Psychiatric Measures. Washington DC: American Psychiatric Association.

23. Keefe RS, Poe M, Walker TM, Kang JW, Harvey PD (2006) The Schizophrenia Cognition Rating Scale: an interview-based assessment and its relationship to cognition, real-world functioning, and functional capacity. Am J Psychiatry 163: 426–432. PMID: 16513863

24. Kaneda Y, Ueoka Y, Sumiyoshi T, Yasui-Furukori N, Ito T, et al. (2011) Schizophrenia Cognition Rating Scale Japanese version (SCoRS-J) as a co-primary measure assessing cognitive function in schizophrenia. Nihon Shinkei Seishin Yakurigaku Zasshi 31: 259–262. PMID: 22256616

25. Woods SW (2003) Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 64: 663–667. PMID: 12823080

26. Inagaki A, Inada T (2006) Dose equivalence of psychotropic drugs. Part XVIII: dose equivalence of psychotropic drugs (in Japanese). Jpn J Psychopharmacol 9: 1443–1447.

27. American Psychiatric Association (1997) Practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry 154: 1–63. PMID: 9167537

28. Pereira JB, Junque C, Bartres-Faz D, Ramirez-Ruiz B, Marti MJ, et al. (2013) Regional vulnerability of hippocampal subfields and memory deficits in Parkinson's disease. Hippocampus 23: 720–728. doi: 10.1002/hipo.22131 PMID: 23553678

29. Reuter M, Schmansky NJ, Rosas HD, Fischl B (2012) Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 61: 1402–1418. doi: 10.1016/j.neuroimage.2012.02.084 PMID: 22430496

30. Huang Y, Hsu JC (2007) Hochberg's Step-Up Method: Cutting Corners Off Holm's Step-Down Method. Biometrika 94: 965–975.

31. Blakesley RE, Mazumdar S, Dew MA, Houck PR, Tang G, et al. (2009) Comparisons of methods for multiple hypothesis testing in neuropsychological research. Neuropsychology 23: 255–264. doi: 10.1037/a0012850 PMID: 19254098

32. Sheng G, Demers M, Subburaju S, Benes FM (2012) Differences in the circuitry-based association of copy numbers and gene expression between the hippocampi of patients with schizophrenia and the hippocampi of patients with bipolar disorder. Arch Gen Psychiatry 69: 550–561. doi: 10.1001/archgenpsychiatry.2011.1882 PMID: 22309971

33. Makris N, Meyer JW, Bates JF, Yeterian EH, Kennedy DN, et al. (1999) MRI-Based topographic parcellation of human cerebral white matter and nuclei II. Rationale and applications with systematics of cerebral connectivity. Neuroimage 9: 18–45. PMID: 9918726

34. Teicher MH, Anderson CM, Polcari A (2012) Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. Proc Natl Acad Sci U S A 109: E563–572. doi: 10.1073/pnas.1115396109 PMID: 22331913

35. Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, et al. (2002) Childhood trauma associated with smaller hippocampal volume in women with major depression. Am J Psychiatry 159: 2072–2080. PMID: 12450959

36. Driessen M, Herrmann J, Stahl K, Zwaan M, Meier S, et al. (2000) Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. Arch Gen Psychiatry 57: 1115–1122. PMID: 11115325

37. Vermetten E, Schmahl C, Lindner S, Loewenstein RJ, Bremner JD (2006) Hippocampal and amygdalar volumes in dissociative identity disorder. Am J Psychiatry 163: 630–636. PMID: 16585437

38. Tamminga CA, Southcott S, Sacco C, Wagner AD, Ghose S (2012) Glutamate Dysfunction in Hippocampus: Relevance of Dentate Gyrus and CA3 Signaling. Schizophr Bull.

39. Schmidt-Hieber C, Jonas P, Bischofberger J (2004) Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 429: 184–187. PMID: 15107864

40. Reif A, Fritzen S, Finger M, Strobel A, Lauer M, et al. (2006) Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Mol Psychiatry 11: 514–522. PMID: 16415915

41. Mamah D, Harms MP, Barch D, Styner M, Lieberman JA, et al. (2012) Hippocampal shape and volume changes with antipsychotics in early stage psychotic illness. Front Psychiatry 3: 96. doi: 10.3389/fpsyt.2012.00096 PMID: 23162479

42. Panenka WJ, Khorram B, Barr AM, Smith GN, Lang DJ, et al. (2007) A longitudinal study on the effects of typical versus atypical antipsychotic drugs on hippocampal volume in schizophrenia. Schizophr Res 94: 288–292. PMID: 17570643

43. Pajonk FG, Wobrock T, Gruber O, Scherk H, Berner D, et al. (2010) Hippocampal plasticity in response to exercise in schizophrenia. Arch Gen Psychiatry 67: 133–143. doi: 10.1001/archgenpsychiatry.2009.193 PMID: 20124113

44. Ho AJ, Hua X, Lee S, Leow AD, Yanovsky I, et al. (2010) Comparing 3 T and 1.5 T MRI for tracking Alzheimer's disease progression with tensor-based morphometry. Hum Brain Mapp 31: 499–514. doi: 10.1002/hbm.20882 PMID: 19780044

45. Das SR, Avants BB, Pluta J, Wang H, Suh JW, et al. (2012) Measuring longitudinal change in the hippocampal formation from in vivo high-resolution T2-weighted MRI. Neuroimage 60: 1266–1279. doi: 10.1016/j.neuroimage.2012.01.098 PMID: 22306801

46. Pluta J, Yushkevich P, Das S, Wolk D (2012) In vivo analysis of hippocampal subfield atrophy in mild cognitive impairment via semi-automatic segmentation of T2-weighted MRI. J Alzheimers Dis 31: 85–99. doi: 10.3233/JAD-2012-111931 PMID: 22504319

47. Winterburn JL, Pruessner JC, Chavez S, Schira MM, Lobaugh NJ, et al. (2013) A novel in vivo atlas of human hippocampal subfields using high-resolution 3 T magnetic resonance imaging. Neuroimage 74: 254–265. doi: 10.1016/j.neuroimage.2013.02.003 PMID: 23415948

Schizophrenia Research 159 (2014) 257–262

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Risk for suicidal problems in poor-help-seeking adolescents with psychotic-like experiences: Findings from a cross-sectional survey of 16,131 adolescents

Atsushi Nishida [a,b,*,1], Shinji Shimodera [c,1], Tsukasa Sasaki [d], Marcus Richards [a], Stephani L. Hatch [e], Syudo Yamasaki [b], Satoshi Usami [f,g], Shuntaro Ando [b], Nozomu Asukai [b], Yuji Okazaki [h]

[a] MRC Unit for Lifelong Health and Aging, University College London, London, UK
[b] Department of Psychiatry and Behavioural Science, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
[c] Department of Neuropsychiatry, Kochi Medical School, Kochi University, Kochi, Japan
[d] Department of Health Education, Graduate School of Education, University of Tokyo, Tokyo, Japan
[e] King's College London, Psychological Medicine, Institute of Psychiatry, London, UK
[f] Department of Psychology, University of Southern California, Los Angeles, CA, USA
[g] Faculty of Human Sciences, Department of Psychology, University of Tsukuba, Japan
[h] Tokyo Metropolitan Matsuzawa Hospital, Tokyo, Japan

ARTICLE INFO

Article history:
Received 25 February 2014
Received in revised form 1 September 2014
Accepted 20 September 2014
Available online 12 October 2014

Keywords:
Psychotic-like experiences
Suicidal ideation
Self-harm
Self-awareness of mental distress
Help seeking

ABSTRACT

Background: Recent evidence suggests that psychotic-like experiences (PLEs) in the general population are important markers of risk of suicidal problems. However, there have been no epidemiological studies investigating help-seeking status in individuals with PLEs and elevated risk of suicide.
Methods: Information on PLEs, self-awareness of mental distress (SAMD), help-seeking behaviours (HSBs), and suicidal problems was collected from 16,131 Japanese adolescents. Participants were divided into two groups, those with and without PLEs, and then both groups were further divided into three subgroups: a group without SAMD, who had no HSB by definition; a group with both SAMD and HSB; and a group with SAMD but without HSB (poor-help-seeking group), yielding a total of six groups.
Results: Adolescents with PLEs (14.3%) had significantly higher risk of suicidal problems than those without PLEs. Among the individuals with both PLEs and SAMD, 38.1% did not seek any help (poor-help-seeking status). Among the six groups, odds of suicidal ideation was the highest among poor-help-seeking adolescents with PLEs, with a 20-fold increase compared to those without PLEs, SAMD and HSB (adjusted for age and sex), while the odds was increased 10-fold in those with PLEs, SAMD and HSB. After adjusting for anxiety/depression level, the odds ratios remained significant in both poor-help-seeking adolescents with PLEs (OR = 3.8 [3.0–4.9 (95% CI)]) and those with PLEs, SAMD and HSB (OR = 2.5 [2.0–3.1]).
Conclusions: Adolescents with PLEs and self-awareness of mental distress are at high risk for suicidal problems, particularly those without help seeking.

1. Introduction

For suicide prevention, it is important to investigate help-seeking status in individuals who have elevated risk of suicide (Michelmore and Hindley, 2012). Several studies have highlighted that the risk of suicide is significantly higher for people with psychotic disorders compared to the general population (Caldwell and Gottesman, 1990; Radomsky et al., 1999; Palmer et al., 2005; Mitter et al., 2013), and recent evidence suggests that psychotic-like experiences (PLEs) in the general population are potentially important markers of risk for suicidal problems in adolescence (Nishida et al., 2010; Kelleher et al., 2012). For example, Kelleher et al. (2012) found that psychotic experiences in the general adolescent population were associated with 10-fold increased odds of suicidal behaviours. However, to our knowledge, there have been no population-based studies investigating whether this risk is modified by help-seeking behaviour due to self-awareness of mental distress.

In order to assess the risk of suicidal problems in the general population, it is important to consider two different types of non-help-seeking: (1) adolescents who do not have help-seeking behaviours (HSB) because they do not report self-awareness of mental distress (SAMD) and (2) adolescents who do not have HSB despite reporting

* Corresponding author at: Department of Psychiatry and Behavioral Science, Tokyo Metropolitan Institute of Medical Science, 2-1-6 Kamikitazawa, Setagayaku, Tokyo, 156-8506, Japan. Tel.: +81-3-6834-2296; fax: +81-3-5316-3150.
E-mail address: nishida-at@igakuken.or.jp (A. Nishida).
[1] AN and SS contributed equally to this work.

http://dx.doi.org/10.1016/j.schres.2014.09.030
0920-9964/

SAMD. Some studies have indicated that suicidal adolescents are less likely to engage in help-seeking strategies than their healthy counterparts (Gould et al., 2004; Fortune et al., 2008). This implies that there might be a 'poor-help-seeking' subgroup with severe mental distress in the general population, in which case. It is important to examine suicide risk in adolescents who *do not engage in help-seeking behaviours despite having self-awareness of mental distress.*

1.1. Aims of the study

The present study had the following goals: (1) to investigate the prevalence of poor help seekers with PLEs in a general population of adolescents and (2) to examine the risk of suicidal problems in relation to presence/absence of PLEs and help-seeking behaviours. We hypothesized that the risk of suicidal problems is positively associated with PLEs, and that this association is particularly strong in those who do not seek help despite self-awareness of mental distress (poor help seekers).

2. Methods

2.1. Study design and procedures

The present study was an anonymous cross-sectional survey in Japan of adolescent students in public junior high schools (7th–9th graders, age range 12–15 years) and public senior high schools (10th–12th graders, age range 15–18 years). The survey was conducted between 2008 and 2009 using a self-reported questionnaire. The principal investigators of the study asked all heads and administrators of public junior high schools in the city of Tsu and public junior high and senior high schools in Kochi Prefecture to participate the survey. Of the 138 junior and 36 senior high schools invited, 47 (34%) junior and 30 (83%) senior high schools participated.

Parents were informed of the research project by letter and asked to notify the school if they did not want their child to participate. On the day of the survey, students were also given the choice of opting out. Each teacher reported the total number of students present and absent on the day of the survey. The study was approved by the ethics committees of Tokyo Metropolitan Institute of Medical Science, Mie University School of Medicine and Kochi Medical School.

2.2. Participants

Of 19,436 students in the relevant classes, 18,250 agreed to participate. Of the remainder, 798 were absent on the day of the survey and 388 declined to participate. Among those agreeing, 1,973 were excluded from the analysis because of incomplete answers to questions regarding psychotic-like experiences, self-awareness of mental distress, help-seeking behaviours or demographic characteristics. Thus, responses from 16,131 students were analysed (83.3% of all students in the relevant classes). Of these students, 48.1% were male, and 51.9% were female. Their ages ranged from 12 to 18 years, with a mean age of 15.2 years (SD = 1.7 years).

2.3. Measures

The participants were asked to fill in an anonymous self-report questionnaire including questions about age, gender and the following variables:

Psychotic-like experiences

Psychotic-like experiences (PLEs) were assessed by four items adopted from the schizophrenia section of the Diagnostic Interview Schedule for Children (DISC-C) (Costello et al., 1982). These items were previously used in a birth cohort study and have been found to be good predictors of schizophrenia spectrum disorder in adulthood (Poulton et al., 2000). The items were (1) 'Some people believe that their thoughts can be read. Have other people ever read your thoughts?' (2) 'Have you ever had messages sent especially to you through the television or radio?' (3) 'Have you ever thought that people are following you or spying on you?' (4) 'Have you ever heard voices that other people cannot hear?' Possible responses were 'no', 'yes, probably' or 'yes, definitely (only once or more than once)'. We defined 'yes, definitely' as the presence of a hallucinatory and delusional experience and 'no' or 'yes, likely' as no experience. We defined 'adolescents with PLEs' as adolescents who reported at least one type of PLEs.

Help-seeking category: Self-awareness of mental distresses and help-seeking behaviours

Self-awareness of mental distress (SAMD) and help-seeking behaviours (HSB) were assessed by the following question: 'Are you currently consulting anyone to discuss your psychological stress or mental health problems?' Possible responses included 'No, I do not need to consult because I have no psychological stress or mental health problems' (No SAMD/No HSB); 'Yes, I am currently in discussion about my psychological stress or mental health problems' (SAMD/HSB); and 'No, I am not currently consulting anyone despite having some psychological stress or mental health problems' (SAMD/No HSB). The third response option (SAMD/No HSB) represented 'poor help-seeking'. HSB was defined as help seeking with professionals (i.e. general practitioners, psychiatrists, psychologists and school nurses) and/or non-professionals (i.e. friends, family members, and school teachers).

Suicidal ideation

Information about the presence or absence of current suicidal ideation was collected by asking the following question: 'Do you currently have thoughts that your life is no longer worth living?' The four possible responses were 'no', 'probably no', 'probably yes' and 'yes'. A response of 'yes' or 'probably yes' was regarded as the presence of suicidal ideation.

Self-harm

Self-harm behaviours in the previous 12 months were assessed by two questions. The first was 'Have you intentionally hurt yourself within the past year?' Response options were 'yes' and 'no'. Respondents who answered 'yes' were then asked to provide a written description of the actual act. Based on the definition used in a previous study (Hawton et al., 2002) and in a comparative study of seven countries (Madge et al., 2008), self-harm was defined as an act with a non-fatal outcome in which an individual deliberately did one or more of the following: initiated behaviour (e.g., self-cutting, jumping from a height), which was intended to cause self-harm; ingested a substance in excess of the prescribed or generally recognized therapeutic dose; or ingested a non-ingestible substance or object. Classification of the episode as self-harm or otherwise was based on independent ratings by two researchers using these criteria. The kappa value for agreement between the two raters was 0.83 (95% confidential interval [CI] 0.79–0.86). Any classification discrepancies between the two raters were resolved by discussion.

GHQ-12

The GHQ-12 is one of the most widely used self-report measures for assessing anxiety and depression (Goldberg et al., 1976). It has been used and validated in younger samples as well as in adults (Kaneita et al., 2007). Additionally, previous studies have established the

validity and reliability of the Japanese version of the instrument (Doi and Minowa, 2003). A four-point scale recoded into binary scoring (0011) was used for the 12 GHQ items. Responses for each question were added together to form a total score, with a range between 0 (best possible) and 12 (worst possible).

2.4. Statistical analysis

First, participants were divided into two groups, those with and without PLEs. Second, both groups were further divided into three subgroups: a group without SAMD (and not having HSB by definition), a group with both SAMD and HSB and a group with SAMD but without HSB, yielding a total of six groups. Group 1 included those *without* PLEs who did not have SAMD or HSB, Group 2 included those *without* PLEs who had SAMD and HSB, Group 3 included those *without* PLEs who had SAMD but not HSB, Group 4 included those *with* PLEs who did not have SAMD or HSB, Group 5 included those *with* PLEs who had SAMD and HSB and Group 6 included those *with* PLEs who had SAMD but not HSB ('poor help-seeking with PLEs').

We examined whether there was any statistically significant difference in frequency of suicidal ideation and self-harm between the two clusters defined by the presence or absence of PLEs. We also investigated whether there was any statistical difference in the prevalence of suicidal ideation and self-harm among the three help-seeking categories within each of the two groups with and without PLEs. Tests were carried out using logistic regression analysis based on two different models. In the first model, only the main effect of the PLE factor on suicidal ideation or self-harm was tested. The second model set Group 1 (those with no PLEs, SAMD or HSB) as a reference group, and five dummy variables indicating group membership were included to evaluate the effects of PLEs and help-seeking factors on suicidal ideation and self-harm. We additionally adjusted for three covariates, age, sex and depression/anxiety assessed by GHQ-12. There were 32 incomplete answers to questions about suicidal ideation and 284 concerning self-harm behaviours. Thus, we used the data of 16,099 adolescents for suicidal ideation and 15,847 for self-harm in the logistic analyses. We confirmed that the frequency of missing data about suicidal ideation was equal in the two sexes and not related to age. In the case of self-harm, the frequency of missing data was not related to age, but it was higher among male participants. All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS), version 20.0 for Windows (SPSS Inc., Tokyo, Japan). A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Prevalence of poor help seekers with PLEs

The distribution of 16,131 adolescents in the six groups defined by the presence of PLEs, SAMD and HSB is shown in Fig. 1. Demographic characteristics for each group are reported in Table 1. Regardless of the presence of PLEs, more girls than boys reported SAMD (in Group 2, Group 3, Group 5 and Group 6) and HSB (in Group 2 and Group 5).

The prevalence of PLEs in the total sample was 14.3% [$n = 2{,}313$: 941 boys (40.7%) and 1,372 girls (59.3%)]. Of the 2,313 adolescents with PLEs, 660 (28.5% of adolescents with PLEs) answered 'I am not currently consulting anyone despite having some psychological stress or mental health problems' (Group 6). Among the adolescents with PLEs and SAMD, 38.1% (660 out of 1,731) did not seek any help.

3.2. Risk for suicidal ideation and self-harm in each group

Table 2 shows the prevalence of suicidal ideation and self-harm in each group defined by psychotic-like experiences and conditions of self-awareness of mental distress and help-seeking behaviours. Analysis based on the first regression model showed that the frequency of suicidal ideation ($p < .001$) and self-harm ($p < .001$) were significantly higher in those with PLEs than in those without. These significant differences

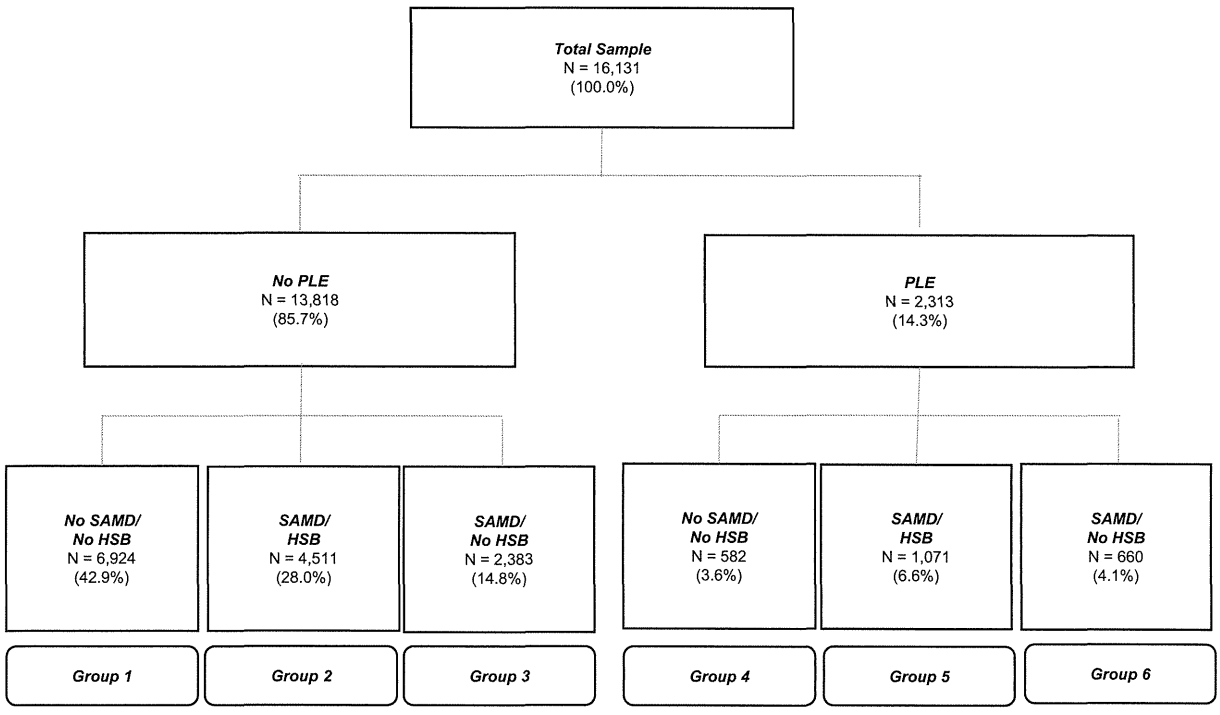


Fig. 1. Participants were divided into two clusters and six groups defined by psychotic-like experiences and condition of self-awareness of mental distress/help-seeking behaviours. Abbreviations: PLEs, psychotic-like experiences; SAMD, self-awareness of mental distress; HSB, help-seeking behaviour.

Table 1
Demographic characteristics and GHQ-12 total score in each group defined by psychotic-like experiences and conditions of self-awareness of mental distress and help-seeking behaviours (n = 16,131).

Group (n)	Condition in each group		Demographic Characteristics		GHQ-12 total score
	PLEs	Self-awareness/help-seeking	Age	Female	Mean (SD)
			Mean (SD)	n (%)	
Group 1 (6,924)	No PLEs	No SAMD/No HSB	15.1 (1.7)	2,667 (38.5)	1.77 (2.04)
Group 2 (4,511)	No PLEs	SAMD/HSB	15.4 (1.7)	3,015 (66.8)	4.39 (2.95)
Group 3 (2,383)	No PLEs	SAMD/No HSB	15.4 (1.7)	1,293 (54.3)	5.55 (3.04)
Group 4 (582)	PLEs	No SAMD/No HSB	14.8 (1.7)	261 (44.8)	2.75 (2.53)
Group 5 (1,071)	PLEs	SAMD/HSB	15.2 (1.7)	742 (69.3)	5.96 (3.08)
Group 6 (660)	PLEs	SAMD/No HSB	15.0 (1.7)	391 (59.2)	7.07 (3.11)

Abbreviations: GHQ-12, 12-Item General Health Questionnaire; PLEs, psychotic-like experiences; SD, standard deviation; SAMD, self-awareness of mental distress; HSB, help-seeking behaviours.

Table 2
Prevalence of suicidal problems in each group defined by psychotic-like experiences and conditions of self-awareness of mental distress and help-seeking behaviours.

Group	Condition in each group		Suicidal ideation (SI)		Self-harm (SH)	
	PLEs	Self-awareness of mental distress/help-seeking	Without SI, n (%)	With SI, n (%)	Without SH, n (%)	With SH, n (%)
Group 1	No PLEs	No SAMD/ No HSB	6704 (96.9)	211 (3.1)	6793 (99.1)	62 (0.9)
Group 2	No PLEs	SAMD/ HSB	3999 (88.8)	504 (11.2)	4249 (95.9)	181 (4.1)
Group 3	No PLEs	SAMD/ No HSB	1791 (75.3)	588 (24.7)	2193 (94.7)	123 (5.3)
Group 4	PLEs	No SAMD/ No HSB	531 (91.2)	51 (8.8)	560 (98.1)	11 (1.9)
Group 5	PLEs	SAMD/ HSB	796 (74.7)	269 (25.3)	895 (86.0)	146 (14.0)
Group 6	PLEs	SAMD/ No HSB	392 (59.8)	263 (40.2)	538 (84.9)	96 (15.1)
Total			14213 (88.3)	1886 (11.7)	15228 (96.1)	619 (3.9)

Abbreviations: PLEs, psychotic-like experiences; SD, standard deviation; SAMD, self-awareness of mental distress; HSB, help-seeking behaviours.

remained even after controlling for the effects of age, sex and level of depression and anxiety [suicidal ideation ($p < .001$) and self-harm ($p < .001$)]. The second logistic regression analysis showed that frequencies of suicidal ideation and self-harm were significantly different among the six groups, with the exception of self-harm behaviours between Group 5 (those with PLEs, SAMD and HSB) and Group 6 (those with PLEs and SAMD but without HSB) ($p = 0.57$). Regarding this point, Tables 3 and 4 summarize results of group differences among six groups in suicidal ideation and self-harm. The group of adolescents with PLEs who had SAMD but not HSB (Group 6: 'poor help-seeking') had the highest risk of suicidal ideation as well as self-harm among all six groups, at nearly 21-fold increased odds of suicidal ideation (OR, 21.3; 95% CI, 17.3–26.2) and self-harm (OR, 19.6; 95% CI, 14.0–27.2) compared with Group 1 (the reference group of adolescents without PLEs who did not have SAMD and did not engage in HSB). Odds in Group 6 were 16–20 times higher than in the reference group for suicidal ideation and self-harm even after controlling for age and sex. These ORs were attenuated after additional adjustment for affective symptoms, but they remained statistically significant (Tables 3 and 4). All groups except Group 4 (self-harm behaviours in those with PLEs but without SAMD) reported significantly raised odds of suicidal problems in comparison to the reference group, even after adjusting for sex, age and level of affective symptoms. On the whole, the highest odds of suicidal problems were found in those with PLEs and SAMD, regardless of HSB (Group 5 and Group 6); those with PLEs and SAMD without HSB (Group 6) had higher odds of suicidal ideation than those with this combination with HSB (Group 5), although odds of this outcome in the latter group were still over double those of the reference group. Furthermore, the odds of self-harm was equally high in those with PLEs and SAMD, whether with HSB (OR = 4.6, 95% CI 3.3–6.5) or without HSB (OR = 4.3, 95% CI 3.0–6.3).

4. Discussion

This large general population survey is the first to investigate the prevalence of poor help seekers with PLEs in a general population of adolescents, and the association between risk of suicidal problems and help-seeking condition in adolescents with PLEs. It should be noted that over a third (38%) of adolescents with both PLEs and self-awareness of mental distress, with significantly elevated risk of suicidal problems, did not seek any help (poor-help-seeking status). The risk of both suicidal ideation and self-harm among poor help seekers with PLEs was elevated by nearly 20-fold compared to the reference group of adolescents who did not have PLEs, recognized no mental distresses, and

Table 3
Risk for current suicidal ideation in each group.

Groups (n)	Condition in each group		Risk for current suicidal ideation								
	PLEs	Self-awareness/help-seeking	Unadjusted OR			OR, adjusted for sex and age			OR, adjusted for sex, age and GHQ score		
			OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Group 1 (6,915)	No PLEs	No SAMD/No HSB	1.0			1.0			1.0		
Group 2 (4,503)	No PLEs	SAMD/HSB	4.0	3.4–4.7	<0.001	3.7	3.1–4.4	<0.001	1.4	1.2–1.7	<0.001
Group 3 (2,379)	No PLEs	SAMD/No HSB	10.4	8.8–12.3	<0.001	9.9	8.4–11.7	<0.001	2.8	2.3–3.4	<0.001
Group 4 (582)	PLEs	No SAMD/No HSB	3.1	2.2–4.2	<0.001	3.1	2.2–4.2	<0.001	2.1	1.5–2.9	<0.001
Group 5 (1,065)	PLEs	SAMD/HSB	10.7	8.8–13.0	<0.001	10.0	8.3–12.3	<0.001	2.5	2.0–3.1	<0.001
Group 6 (655)	PLEs	SAMD/No HSB	21.3	17.3–26.2	<0.001	20.1	16.8–25.5	<0.001	3.8	3.0–4.9	<0.001

Abbreviations: SAMHD, self-awareness of mental health distress; HSB, help-seeking behaviours; PLEs, psychotic-like experiences; GHQ-score, total score of 12-Item General Health Questionnaire; OR, odds ratio; CI, confidence interval.

Table 4
Risk for self-harm behaviours in each group.

Groups (*n*)	Condition in each group		Risk for self-harm behaviour in previous 12 months								
	PLEs	Self-awareness/help-seeking	Unadjusted OR			OR, adjusted for sex and age			OR, adjusted for sex, age and GHQ-score		
			OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Group 1 (6,855)	No PLEs	No SAMD/No HSB	1.0			1.0			1.0		
Group 2 (4,430)	No PLEs	SAMD/HSB	4.7	3.5–6.2	<0.001	3.3	2.5–4.5	<0.001	1.6	1.2–2.2	0.002
Group 3 (2,316)	No PLEs	SAMD/No HSB	6.1	4.5–8.4	<0.001	5.0	3.7–6.9	<0.001	1.9	1.3–2.6	<0.001
Group 4 (571)	PLEs	No SAMD/No HSB	2.1	1.1–4.1	<0.001	2.1	1.1–3.9	0.03	1.6	0.8–3.1	0.164
Group 5 (1,041)	PLEs	SAMD/HSB	17.9	13.2–24.2	<0.001	13.0	9.5–17.7	<0.001	4.6	3.3–6.5	<0.001
Group 6 (634)	PLEs	SAMD/No HSB	19.6	14.0–27.2	<0.001	16.1	11.5–22.4	<0.001	4.3	3.0–6.3	<0.001

Abbreviations: SAMD, self-awareness of mental distress; HSB, help-seeking behaviours; PLEs, psychotic-like experiences; GHQ-score, total score of 12-Item General Health Questionnaire; OR, odds ratio; CI, confidence interval.

therefore did not engage in help-seeking behaviours. Suicidal problems were significantly elevated in those with PLEs, regardless help-seeking status, which is consistent with several studies in the general population (Nishida et al., 2008, 2010; Saha et al., 2011; Kelleher et al., 2012). In the present study, the associations between PLEs and suicidal problems remain significant after controlling for the level of anxiety and depression.

We observed a heightened risk of suicidal ideation in the poor-help-seeking groups regardless of PLEs (Group 3 and Group 6). Previous studies have reported the 'help-negation effect' of suicidal ideation, referring to help avoidance or refusal (Wilson et al., 2011). Recent research has suggested that suicidal thoughts and feeling may act as barriers to resource utilization, thus serving as significant obstacle to effective suicide prevention (Barnes et al., 2001). The poor help seekers with PLEs who have elevated risk of suicide and been help-negation status are more likely to be left unsupported and untreated (Evans et al., 2005; Michelmore and Hindley, 2012), which would predict poorer social and mental health outcome including the onset of clinical psychosis.

Risk of self-harm was high in the groups of adolescents with both PLEs and SAMD regardless of HSB in our current study (Group 5 and Group 6). One previous study focusing on help-seeking young people who met ultra-high risk (UHR) criteria for psychosis demonstrated that nearly 20% of that group had engaged in serious self-harm during the time they were in contact with a specialized service (Hutton et al., 2011). As the majority of help-seeking individuals who are at high risk of developing psychosis have psychotic-like symptoms (Fusar-Poli et al., 2014), they might be a similar population to Group 5 in our study. Our result indicated that the risk of self-harm was also very high in poor-help seekers (Group 6) with PLEs, who might be less likely to engage in such a professional services.

In terms of prevention for suicide and clinical psychosis, our results suggest the need for increased attention for the individuals with poor help seekers with PLEs in the community. As the poor help seekers with PLEs have already had a self-awareness of mental distress, it might be appropriate to make the best efforts to attenuate "help-negation" (Yakunina et al., 2010), rather than to have a public campaign to increase vigilance in the community for psychotic-like symptoms. However, given our finding that those with PLEs but without self-awareness of mental distress are also a high-risk group for suicidal ideation, it will be important to investigate strategies that could provide help-seeking opportunities in this group, as well as in those with poor-help-seeking.

Several methodological limitations should be noted. First, despite endeavouring to recruit as many adolescents as possible from the target population, we cannot rule out effects of absenteeism and non-responding on frequency of suicidal problems, psychotic-like experiences, and help-seeking behaviours. It is known that suicidal problems are more common in those with truant behaviour (Bjarnason and Thorlindsson, 1994). Second, while we had good compliance among high schools (83%) in Kochi Prefecture, this was less the case in Tsu City and Kochi prefecture, where 47 (34%) of the 138 junior high schools agreed to participate. This was due to a rejection decision by the Educational Committee in Kochi Central City, which supervises most junior high schools in our targeted regions. Third, information was not available about further confounding factors which may be associated suicidal problems, such as socioeconomic status, family circumstances (Fergusson et al., 2000; Agerbo et al., 2002; Aschan et al., 2013) and personality (Portzky et al., 2005; Blasco-Fontecilla et al., 2009). Finally, we used a cross-sectional sample and, therefore, were not able to identify causal relationships between suicidal problems and PLEs, SAMD and HSB. Hence, in the future, follow-up studies will need to address these issues.

Role of funding source

This work was supported by the Ministry of Health, Labour and Welfare of Japan Scientific Research Grant (#H19-kokoro-ippan-012), the Ministry of Education, Culture, Sports, Science and Technology of Japan Scientific Research Grant on Innovative Area (23118004; Adolescent Mind & Self-Regulation), the Japanese Society for the Promotion of Science Scientific Research Grant (Strategic Young Researcher Overseas Visits Program for Accelerating Brain Circulation) and the Tokyo Metropolitan Institute of Medical Science Project Grant (Kokoronokenko H21-H26). SLH receives salary support from the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King's College London.

Contributors

AN, SS, TS and YO conceptualized the study and wrote the first draft of the manuscript. SU, SA and SY conducted the statistical analyses. MR, SLH and NA helped in the design of the study and edited the manuscript. All authors have approved the final manuscript.

Conflict of interest

None.

Acknowledgments

We are grateful to all the adolescents who took part in this study as well as the Board of Education of Tsu City and Kochi Prefecture for their cooperation and assistance in conducting this research.

References

Agerbo, E., Nordentoft, M., Mortensen, P.B., 2002. Familial, psychiatric, and socioeconomic risk factors for suicide in young people: nested case-control study. BMJ 325 (7355), 74.
Aschan, L., Goodwin, L., Cross, S., Moran, P., Hotopf, M., Hatch, S.L., 2013. Suicidal behaviours in South East London: prevalence, risk factors and the role of socio-economic status. J. Affect. Disord. 30 (13) (00338-00338).
Barnes, L.S., Ikeda, R.M., Kresnow, M.J., 2001. Help-seeking behavior prior to nearly lethal suicide attempts. Suicide Life Threat. Behav. 32 (1 Suppl.), 68–75.
Bjarnason, T., Thorlindsson, T., 1994. Manifest predictors of past suicide attempts in a population of Icelandic adolescents. Suicide Life Threat. Behav. 24 (4), 350–358.
Blasco-Fontecilla, H., Baca-Garcia, E., Dervic, K., Perez-Rodriguez, M.M., Saiz-Gonzalez, M.D., Saiz-Ruiz, J., Oquendo, M.A., de Leon, J., 2009. Severity of personality disorders and suicide attempt. Acta Psychiatr. Scand. 119 (2), 149–155.
Caldwell, C.B., Gottesman, I.I., 1990. Schizophrenics kill themselves too: a review of risk factors for suicide. Schizophr. Bull. 16 (4), 571–589.
Costello, A.J., E.C., Kalas, R., Kessler, M.K., Klaric, S.A., 1982. NIMH Diagnostic Interview Schedule for Children: Child Version. National Institute of Mental Health, Rockville, MD.
Doi, Y., Minowa, M., 2003. Factor structure of the 12-item General Health Questionnaire in the Japanese general adult population. Psychiatry Clin. Neurosci. 57 (4), 379–383.
Evans, E., Hawton, K., Rodham, K., 2005. In what ways are adolescents who engage in self-harm or experience thoughts of self-harm different in terms of help-seeking, communication and coping strategies? J. Adolesc. 28 (4), 573–587.

Fergusson, D.M., Woodward, L.J., Horwood, L.J., 2000. Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. Psychol. Med. 30 (1), 23–39.
Fortune, S., Sinclair, J., Hawton, K., 2008. Help-seeking before and after episodes of self-harm: a descriptive study in school pupils in England. BMC Public Health 8 (369), 1471–2458.
Fusar-Poli, P., Yung, A.R., McGorry, P., van Os, J., 2014. Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention. Psychol. Med. 44 (1), 17–24.
Goldberg, D.P., Rickels, K., Downing, R., Hesbacher, P., 1976. A comparison of two psychiatric screening tests. Br. J. Psychiatry 129, 61–67.
Gould, M.S., Velting, D., Kleinman, M., Lucas, C., Thomas, J.G., Chung, M., 2004. Teenagers' attitudes about coping strategies and help-seeking behavior for suicidality. J. Am. Acad. Child Adolesc. Psychiatry 43 (9), 1124–1133.
Hawton, K., Rodham, K., Evans, E., Weatherall, R., 2002. Deliberate self harm in adolescents: self report survey in schools in England. BMJ 325 (7374), 1207–1211.
Hutton, P., Bowe, S., Parker, S., Ford, S., 2011. Prevalence of suicide risk factors in people at ultra-high risk of developing psychosis: a service audit. Early Interv. Psychiatry 5 (4), 375–380.
Kaneita, Y., Ohida, T., Osaki, Y., Tanihata, T., Minowa, M., Suzuki, K., Wada, K., Kanda, H., Hayashi, K., 2007. Association between mental health status and sleep status among adolescents in Japan: a nationwide cross-sectional survey. J. Clin. Psychiatry 68 (9), 1426–1435.
Kelleher, I., Lynch, F., Harley, M., Molloy, C., Roddy, S., Fitzpatrick, C., Cannon, M., 2012. Psychotic symptoms in adolescence index risk for suicidal behavior: findings from 2 population-based case–control clinical interview studies. Arch. Gen. Psychiatry 69 (12), 1277–1283.
Madge, N., Hewitt, A., Hawton, K., de Wilde, E.J., Corcoran, P., Fekete, S., van Heeringen, K., De Leo, D., Ystgaard, M., 2008. Deliberate self-harm within an international community sample of young people: comparative findings from the Child & Adolescent Self-harm in Europe (CASE) Study. J. Child Psychol. Psychiatry 49 (6), 667–677.
Michelmore, L., Hindley, P., 2012. Help-seeking for suicidal thoughts and self-harm in young people: a systematic review. Suicide Life Threat. Behav. 42 (5), 507–524.
Mitter, N., Subramaniam, M., Abdin, E., Poon, L.Y., Verma, S., 2013. Predictors of suicide in Asian patients with first episode psychosis. Schizophr. Res. 151 (1–3), 274–278.
Nishida, A., Tanii, H., Nishimura, Y., Kajiki, N., Inoue, K., Okada, M., Sasaki, T., Okazaki, Y., 2008. Associations between psychotic-like experiences and mental health status and other psychopathologies among Japanese early teens. Schizophr. Res. 99 (1–3), 125–133.
Nishida, A., Sasaki, T., Nishimura, Y., Tanii, H., Hara, N., Inoue, K., Yamada, T., Takami, T., Shimodera, S., Itokawa, M., Asukai, N., Okazaki, Y., 2010. Psychotic-like experiences are associated with suicidal feelings and deliberate self-harm behaviors in adolescents aged 12-15 years. Acta Psychiatr. Scand. 121 (4), 301–307.
Palmer, B.A., Pankratz, V.S., Bostwick, J.M., 2005. The lifetime risk of suicide in schizophrenia: a reexamination. Arch. Gen. Psychiatry 62 (3), 247–253.
Portzky, G., Audenaert, K., van Heeringen, K., 2005. Suicide among adolescents. A psychological autopsy study of psychiatric, psychosocial and personality-related risk factors. Soc. Psychiatry Psychiatr. Epidemiol. 40 (11), 922–930.
Poulton, R., Caspi, A., Moffitt, T.E., Cannon, M., Murray, R., Harrington, H., 2000. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. Arch. Gen. Psychiatry 57 (11), 1053–1058.
Radomsky, E.D., Haas, G.L., Mann, J.J., Sweeney, J.A., 1999. Suicidal behavior in patients with schizophrenia and other psychotic disorders. Am. J. Psychiatry 156 (10), 1590–1595.
Saha, S., Scott, J.G., Johnston, A.K., Slade, T.N., Varghese, D., Carter, G.L., McGrath, J.J., 2011. The association between delusional-like experiences and suicidal thoughts and behaviour. Schizophr. Res. 132 (2–3), 197–202.
Wilson, C.J., Bushnell, J.A., Caputi, P., 2011. Early access and help seeking: practice implications and new initiatives. Early Interv. Psychiatry 1, 34–39.
Yakunina, E.S., Rogers, J.R., Waehler, C.A., Werth Jr., J.L., 2010. College students' intentions to seek help for suicidal ideation: accounting for the help-negation effect. Suicide Life Threat. Behav. 40 (5), 438–450.

NEW RESEARCH

JCSM
Journal of Clinical Sleep Medicine

http://dx.doi.org/10.5664/jcsm.3624

Change in Quality of Life after Brief Behavioral Therapy for Insomnia in Concurrent Depression: Analysis of the Effects of a Randomized Controlled Trial

Shinji Shimodera, M.D., Ph.D.[1]; Norio Watanabe, M.D., Ph.D.[2,3]; Toshi A. Furukawa, M.D., Ph.D.[4]; Fujika Katsuki, R.N., Ph.D.[5]; Hirokazu Fujita, M.D., Ph.D.[1]; Megumi Sasaki, Ph.D.[6]; Michael L. Perlis, Ph.D.[7]

[1]Department of Neuropsychiatry, Kochi Medical School, Kochi University, Kochi, Japan; [2]Department of Clinical Epidemiology, Translational Medical Center, National Center of Neurology & Psychiatry, Tokyo, Japan; [3]Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [4]Departments of Health Promotion and Human Behavior and of Clinical Epidemiology, Kyoto University Graduate School of Medicine / School of Public Health, Kyoto, Japan; [5]Department of Psychiatric and Mental Health Nursing, Nagoya City University School of Nursing, Nagoya, Japan; [6]Health Care Center, Japan Advanced Institute of Science and Technology, Ishikawa, Japan; [7]Behavioral Sleep Medicine Program, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA

Study Objectives: The efficacy of cognitive behavioral therapy for insomnia (CBT-I) has been suggested for insomnia concomitant with depression, but its impact on quality of life (QoL) has not been adequately evaluated. The study aimed to determine which aspects of QoL could be affected by CBT-I and how any changes in QoL were mediated by changes in insomnia and depression.

Methods: We conducted a 4-week randomized controlled trial with 4-week follow-up in outpatient clinics in Japan. Thirty-seven patients with DSM-IV diagnosis of major depressive disorder concomitant with chronic insomnia were randomly assigned to the treatment-as-usual (TAU) alone arm or the TAU with brief behavioral therapy for insomnia (TAU plus psychotherapy) arm using modified CBT-I consisting of 4 weekly individual sessions. We evaluated QoL using norm-based scoring of the Short Form-36 at baseline and at 8 weeks. We also examined associations between QoL subscales and remission in insomnia or depression while controlling for baseline scores of the entire sample.

Results: We tested group effects while controlling for baseline scores. TAU plus psychotherapy resulted in significantly better scores on physical functioning ($p = 0.006$), social functioning ($p = 0.002$), and mental health ($p = 0.041$) subscales than TAU alone at 8 weeks. Patients with either remitted insomnia or depression showed higher QoL scores than non-remitted patients; scores approximated those within the normal range.

Conclusions: For patients with insomnia in depression, adding CBT-I to TAU can produce substantive benefits in some aspects of QoL.

Trial Registration: ClinicalTrials.gov Identifier: NCT00610259, http://www.clinicaltrials.gov/

Keywords: Depressive disorder, sleep initiation and maintenance disorders, behavior therapy, quality of life

Citation: Shimodera S; Watanabe N; Furukawa TA; Katsuki F; Fujita H; Sasaki M; Perlis ML. Change in quality of life after brief behavioral therapy for insomnia in concurrent depression: analysis of the effects of a randomized controlled trial. *J Clin Sleep Med* 2014;10(4):433-439.

SCIENTIFIC INVESTIGATIONS

Insomnia occurs comorbidly with many, if not most, Axis I disorders. Estimated concordance rates for depression are as high as 80% to 90% in untreated patients.[1,2] Even after achieving remission from depression, half of these patients still suffer from residual insomnia.[3] Moreover, persistent insomnia might be a risk factor for depression relapse.[4]

Insomnia is not only associated with difficulty initiating and maintaining sleep, but also a variety of daytime sequelae including fatigue, sleepiness, poor concentration and memory, mood disturbance, and impaired interpersonal functioning and work performance, all of which lead to deterioration in quality of life (QoL). QoL refers to both subjective life satisfaction and objective indicators such as health status and external life situations.[5] Assessment of QoL is important for any psychiatric or medical disorder because impaired QoL is typically cited as the impetus for seeking treatment.[6] QoL is severely impaired in patients with depression, as well as in those with comorbid insomnia.[7] According to a study on QoL outcomes, insomnia in depression is associated with increasing problems with daily living and role functioning.[8]

Pharmacological and psychological therapies have been used in the treatment of insomnia. Although benzodiazepines have not been formally studied for their impact on QoL,[7] benzodiazepine receptor agonists (BZRAs) appear to be efficacious

BRIEF SUMMARY

Current Knowledge/Study Rationale: The efficacy of cognitive behavioral therapy for insomnia (CBT-I) has been suggested for insomnia concomitant with depression. However, its impact on quality of life (QoL) has not been adequately evaluated.

Study Impact: For patients with insomnia in depression, adding CBT-I to TAU can produce substantive benefits in some aspects of QoL. Patients with either remitted insomnia or depression showed higher QoL scores than non-remitted patients.

for patients with primary insomnia given the QoL outcomes of previous randomized controlled trials (RCTs).[9,10] In addition, several RCTs have investigated the QoL outcomes of psychotherapy for primary insomnia. Various psychotherapy interventions have been tested including problem-solving therapy,[11] but cognitive behavioral therapy for insomnia (CBT-I) has been a frequently selected intervention strategy, with reported post-intervention improvements in not only sleep quality but also QoL outcomes.[12]

In regard to insomnia concurrent with depression specifically, QoL outcomes from RCTs employing BZRAs in combination with antidepressants have been reported.[13,14] As for psychotherapy, several previous trials including ours have confirmed the efficacy of CBT-I in insomnia in depression.[15,16] However, to the best of our knowledge, no previous trials on psychotherapy for insomnia in depression have reported QoL outcomes, and which aspects of QoL can be changed by psychotherapy are as yet unknown. Moreover, even if QoL outcomes were found to be improved after psychotherapy, questions would still remain as to whether improvement in insomnia or improvement in depression led to better QoL.

Against this background, this study aimed to examine which aspects of QoL changed among patients with insomnia in depression treated with psychotherapy. To do so, we analyzed data obtained in an RCT on brief behavioral therapy for insomnia in depression, using a modified standardized form of CBT-I consisting of 4 weekly individual sessions.[16] We also explored the degree to which changes in depression and sleep outcomes contributed to changes on the QoL subscales.

METHODS

Participants

We recruited patients from February 18, 2008, to April 9, 2009, at 3 psychiatric outpatient departments in Japan. The entry criteria were as follows: (1) refractory depression, defined as currently partially remitted, mild, or moderate major depressive disorder (diagnosed with DSM-IV), even after being on maximum doses of 2 types of antidepressants ≥ 4 weeks each for the index episode; (2) chronic comorbid insomnia; (3) a score between 8 and 23 on the 17-item GRID-HAMD[17]; and (4) a score ≥ 8 on the Insomnia Severity Index (ISI).[18-20] Patients were allowed to continue any psychotropic medications other than methylphenidate or modafinil (due to their probable stimulating effects), including antidepressants and hypnotics and prescriptions for medical conditions.

Study Design and Interventions

Participants were individually randomized to 2 arms: treatment-as-usual (TAU) alone (control) and TAU plus brief behavioral therapy for insomnia (TAU plus psychotherapy). The psychotherapy, based on CBT-I, consisted of 4 weekly individual sessions of approximately 50 min each.[21] Although the number of sessions in this study were fewer than the 6 to 8 offered in traditional CBT-I, previous trials have indicated the efficacy of brief versions of CBT-I in patients with primary insomnia, older adults with chronic insomnia, and patients with alcoholism and insomnia.[22-26] The treatment regimen was highly structured and included modules on sleep hygiene education, an introduction to the behavioral model of insomnia, sleep restriction, stimulus control, sleep titration, and relapse prevention.[16] Five psychiatrists and a psychiatric nurse provided the psychotherapy, and they received a written manual describing the regimen. Before the study began, they participated in a 2-day intensive training course on the psychotherapy, and thereafter received ongoing monthly supervision. Patients assigned to TAU plus psychotherapy arm were asked to self-administer these skills after intervention sessions ended at 4 weeks until the final assessment conducted at 8 weeks.

In the TAU-alone sessions, patients met individually with a psychiatrist once every 2 weeks to discuss their depressive symptoms and insomnia and to obtain medication. Each session typically lasted 10 minutes. We prohibited changes in type and dosage of medication during the first 4 weeks of the study unless depression rapidly worsened. Physicians were allowed to discuss sleep hygiene (as defined in the study handout) with the patients but not sleep restriction or stimulus control for insomnia.

Assessment Measures

We assessed patients at baseline and at 4 and 8 weeks, but collected QoL data only at baseline and at 8 weeks. Patients who discontinued the intervention were still asked to complete the assessments.

We evaluated QoL using Short Form 36 (SF-36), which consists of 8 subscales (physical functioning, role limitations due to physical health problems [role physical], bodily pain, general health perception, vitality, social functioning, role limitations due to emotional health problems [role emotional], and mental health).[27,28] We did not calculate 2 global scales (mental health and physical health subscales), based on research that QoL assessment should comprise at least the following 4 domains: physical functional status, disease and treatment-related physical symptoms, psychological functioning, and social functioning.[29] For all the SF-36 subscales, we used norm-based scoring for the general Japanese population (mean, 50; SD, 10). The scale has no units, and scores can theoretically range from 0 to 100. Higher scores indicate better health. We assessed insomnia using the ISI. For depression, the GRID-HAMD was evaluated through face-to-face semi-structured interviews by raters at each assessment. For these 2 variables, higher scores indicated worse status. Patients were considered insomnia remitters when their ISI score was < 8, and depression remitters when their 17-item HAMD score was < 8.[30,31]

Data Management and Analysis

Before the study began, we calculated the number of patients who should be included in the study based on a power analysis conducted on the ISI scores.[16] The dependent outcomes of this study were the 8 SF-36 subscales. For all these subscales, we used analysis of covariance to test group effects between TAU plus psychotherapy and TAU alone while controlling for baseline scores. Moreover, we tested mean differences in QoL subscales between non-remitters (no remission in either insomnia or depression) and remitters (remission in insomnia and/or depression) while controlling for baseline scores of the entire sample. For subscales where significant superiorities

Table 1—Clinical characteristics of participants at baseline

Characteristic	Psychotherapy + TAU (n = 20)	TAU alone (n = 17)	All Patients (N = 37)
Age, mean (SD), year	52.9 (11.6)	47.8 (10.1)	50.5 (11.1)
Sex, No. (%)			
Female	15 (75.0)	8 (47.1)	23 (62.2)
Male	5 (25.0)	9 (52.9)	14 (37.8)
Occupation, No. (%)			
Employed, full time	3 (15.0)	6 (35.3)	9 (24.3)
Employed, part time	3 (15.0)	3 (17.6)	6 (16.2)
Homemaker	11 (55.0)	5 (29.4)	16 (43.2)
Unemployed	3 (15.0)	3 (17.6)	6 (16.2)
Duration of treatment for index episode, mean (SD), month	18.1 (11.1)	27.8 (46.5)	22.5 (32.4)
Insomnia Severity Index, mean (SD)	15.3 (4.7)	17.4 (3.3)	16.3 (4.2)
Hamilton Depression Rating Scale, mean (SD)	15.0 (3.6)	16.8 (4.2)	15.8 (3.9)
SF-36: Norm-based Scoring			
Physical functioning, mean (SD)	41.2 (13.2)	40.6 (15.4)	41.0 (14.1)
Role-physical, mean (SD)	37.1 (16.3)	32.2 (16.4)	34.9 (16.3)
Bodily pain, mean (SD)	46.0 (10.0)	43.1 (13.9)	44.7 (11.9)
General health perception, mean (SD)	40.2 (5.8)	33.6 (9.5)	37.2 (8.3)
Vitality, mean (SD)	39.0 (9.4)	31.2 (7.6)	35.4 (9.4)
Social functioning, mean (SD)	40.3 (15.9)	32.3 (19.2)	36.7 (17.7)
Role-emotional, mean (SD)	37.6 (15.6)	31.1 (14.7)	34.6 (15.4)
Mental health, mean (SD)	38.9 (11.5)	29.9 (9.5)	34.7 (11.4)

TAU, treatment as usual.

were observed in remitters, we used a multiple linear regression model to determine if changes in the ISI and HAMD scores (baseline to 8 weeks) mediated changes in the QoL subscales by entering both scores into the model. We set a p-value < 0.05 to test the null hypothesis without correcting for multiple tests to avoid β (type II) rather than α (type I) errors because this was the first study to investigate QoL outcomes in psychotherapy for insomnia concomitant with depression. To avoid multiple tests, we did not conduct statistical tests to detect baseline differences between the two arms. Also, our decision to adjust for baseline data in RCTs should not depend upon statistical significance of baseline differences.[32] We computed inferential statistics using SPSS for Windows 21.0.

The ethics committees of all the recruiting centers approved the protocol in this study. Study staff introduced the purpose, procedures, and potential risks or discomforts of the study to those who satisfied eligibility criteria by using the standard informed consent form which emphasized that all potential participants who declined to participate or otherwise did not participate were eligible for usual treatment, and were not disadvantaged in any other way by not participating in the study. Following this explanation, all participants in the study provided written informed consent.

RESULTS

Thirty-seven patients satisfied the eligibility criteria, among whom 20 were randomly assigned to TAU plus psychotherapy arm and 17 to TAU alone arm. **Table 1** summarizes the participants' clinical characteristics at baseline. During the study, antidepressant dosage was changed for 2 participants in each of the 2 groups. Hypnotic dosage was changed for 2 participants in TAU plus psychotherapy group, and none in the TAU alone group. We observed no statistically significant between-group differences in defined daily doses[33] of either drug for either class of medication. One subject in TAU plus psychotherapy arm and one in TAU alone arm were admitted to the hospital due to exacerbation of depression. Nevertheless, no data were missing because all participants completed all the study assessments at 8 weeks.

Although we did not intend to perform any statistical tests to compare pre- and post-scores, data for all subjects were available at baseline and at 8 weeks. Mean scores of all SF-36 subscales increased in the psychotherapy plus TAU group at the 8-week follow-up, whereas mean scores in 3 subscales decreased in the TAU alone group: physical functioning, role physical, and social functioning. At 8 weeks, psychotherapy plus TAU resulted in significantly higher subscale scores for physical functioning ($p = 0.006$), social functioning ($p = 0.002$), and mental health ($p = 0.041$) than TAU alone (**Figure 1**). The other subscales tended to favor the psychotherapy plus TAU arm, but differences were not statistically significant.

Among all 37 participants, 13 remitted at 8 weeks (2 [10%] in the psychotherapy plus TAU group and 0 in the TAU alone group for insomnia only, 2 [10%] and 1 [6%] for depression only, and 8 [40%] and 0 for both insomnia and depression, respectively). Aggregated remitters in insomnia and/or depression showed significantly higher QoL subscale scores for physical functioning ($p = 0.033$), role physical ($p = 0.003$), general health perception ($p = 0.008$), vitality ($p = 0.001$),

social functioning ($p < 0.0005$), role emotional ($p = 0.027$), and mental health ($p = 0.005$) than those in non-remitters, except the bodily pain subscale ($p = 0.067$) (**Figure 2**). Mean scores of all QoL subscales in remitters were around 50 (equivalent to mean scores of a normal sample in Japan). In analyses exploring mediation of insomnia and depression symptoms to QoL, changes in ISI scores contributed to changes on the vitality subscale ($p = 0.027$), and changes in HAMD scores contributed to changes on subscales for role emotional ($p = 0.031$) and mental health ($p = 0.021$) (**Table 2**). No other changes in insomnia or depression outcomes contributed to the significant changes on these subscales.

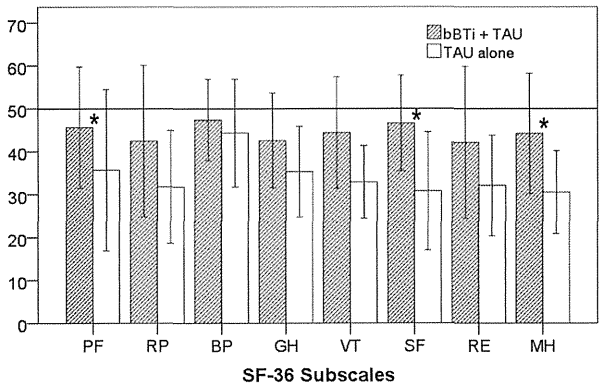
DISCUSSION

To our knowledge, this study is the first to report QoL outcomes based on an RCT with CBT-I in treatment refractory patients with depression. We found that, although not all SF-36 components were affected, insomnia treatment improved functioning in both physical and social situations and mental health status. Associations between remission and QoL subscales in the entire sample ($N = 37$) indicated significantly better QoL scores in remitters than those in non-remitters, and were within the normal range on almost all subscales. The bodily pain subscale revealed no significant difference because the mean score even at baseline was most likely not far from the normal range in both arms. For some of QoL, improvement was associated with improvement in insomnia or in depression. These aspects included vitality associated with insomnia, and role emotional and mental health with depression.

As for primary insomnia, a previous trial[12] investigated changes in various QoL aspects by examining the efficacy of CBT-I in patients with primary insomnia and long-term hypnotic drug use, and found that those treated with CBT-I had better outcomes than those without this additional treatment in SF-36 dimensions of vitality at 3 months and physical functioning and mental health at 6 months. For pharmacotherapy, patients treated with BZRAs had significantly better QoL scores than those with placebo at 6 months in SF-36 domains of role physical, bodily pain, general health perception, vitality, and social functioning.[10] Similarly, the same drug led to better QoL scores than a placebo during a 2-week study on the domains of the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[34] including physical health, mood, household activities, leisure time activities, and medication.[9] As mentioned above, no psychotherapy trials reported QoL outcomes for insomnia concomitant with depression. The efficacy of pharmacotherapy on QoL outcomes remains controversial, given that one trial has been for BZRAs and antidepressants[13] and the other against them.[14] Our results and those of previous studies lead us to conclude that adding psychotherapy to usual clinical care could produce statistically significant and clinically substantive added benefits in some aspects of QoL in patients with insomnia in depression, as shown in previous trials on primary insomnia. Above all, the present study is the first randomized trial investigating the efficacy of CBT-I in Japan. We believe our results will contribute to further dissemination of the therapy in Japan.

As for associations between QoL improvements in insomnia and depression, the recovery process was initially hypothesized to occur in the following order: (1) psychotherapy alleviated insomnia, (2) better sleep reduced severity of depression, and (3) better mood improved physical and mental functioning in daily life. Behind these assumptions, we speculated that improvement in QoL was better explained by changes in

Figure 1—SF-36 Norm-Based Subscales and Allocation Status at 8 weeks



*p < 0.05. A bar and an error bar indicate a mean and a standard deviation, respectively. bBTi, brief behavioral therapy for insomnia; BP, bodily pain; GH, general health perception; MH, mental health; PF, physical functioning; RE, role emotional: RP, role physical; SF, social functioning; TAU, treatment as usual; VT, vitality

Table 2—SF-36 subscales and regression coefficients for insomnia and depression variables

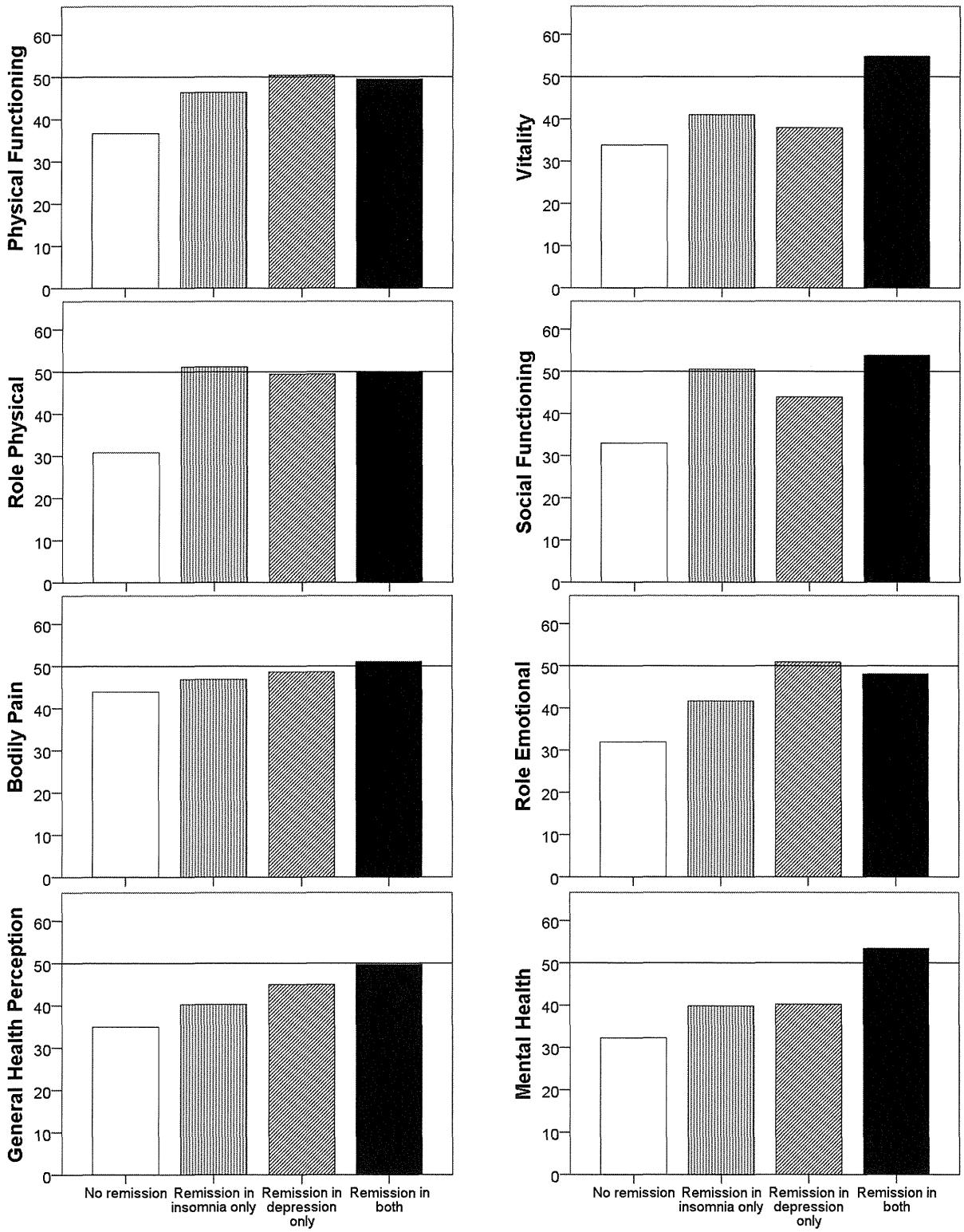
		ISI		HAMD	
SF-36 subscales	**Adjusted R^2**	**B (SE)**	**beta**	**B (SE)**	**beta**
Physical functioning	22.2%	-0.37 (0.35)	-0.21	-0.44 (0.24)	-0.36
Role physical	0.5%	0.30 (0.56)	0.12	-0.53 (0.38)	-0.30
Bodily pain	NA				
General health perception	14.4%	-0.23 (0.29)	-0.17	-0.30 (0.19)	-0.31
Vitality	37.4%	-0.62 (0.27)	-0.40*	-0.32 (0.18)	-0.30
Social functioning	5.8%	-1.15 (0.63)	-0.39	0.20 (0.42)	0.10
Role emotional	8.9%	0.43 (0.47)	0.19	-0.71 (0.32)	-0.47*
Mental health	16.3%	0.08 (0.36)	0.05	-0.60 (0.25)	-0.49*

*p < 0.05. HAMD, Hamilton Depression Rating Scale; ISI, Insomnia Severity Index; NA, not applicable.

depression severity, and that a time lag might exist between improvements in insomnia or depression and improvements in QoL. However, considering the results of the present study and of our previous study on insomnia and depression outcomes,[16] it now seems more likely that insomnia, depression and QoL almost simultaneously improve to a normal range when a patient responds successfully to treatment.

Although the findings of this study are very promising, there were some methodological limitations. First, sample sizes were small enough to raise concerns about the generalizability of

Figure 2—SF-36 Norm-Based Subscales and Remission Status at 8 weeks



A bar indicates a mean.

the results. Moreover, long-term consequences remain unclear because we evaluated patients for no more than 8 weeks. Further replication studies with a larger sample and longer follow-up period are needed to evaluate outcomes with more confidence. Second, we cannot state whether psychotherapy itself or careful patient monitoring was responsible for improvement in QoL outcomes. However, our aim was to examine the added value of psychotherapy to usual clinical care, not the efficacy of psychotherapy itself. Third, we set a significance level of p-values at 0.05, although this definition was applied many times during analysis and might have led to errors in multiple comparisons. Although we did this to avoid β (type II) rather than α (type I) errors, again, a further replication study with a larger sample and an appropriate threshold for statistical significance is needed.

On the other hand, the strengths of our study include our patient follow-ups in which there were no missing data, which produced robust results. Moreover, we reported eight subdomains of QoL even though previous reports often aggregated QoL into one[13] or two scales (mental health and physical health subscales).[35] Studies have indicated that QoL assessments should comprise at least four domains, as we stated in the Methods section.[29] We believe that our decision to employ eight subdomains is in line with this recommendation. All of these strengths should contribute to the greater applicability and feasibility of our findings.

In conclusion, adding psychotherapy to usual clinical care can produce clinically substantive benefits in some aspects of QoL in treating patients with insomnia in depression.

REFERENCES

1. Carney CE, Segal ZV, Edinger JD, Krystal AD. A comparison of rates of residual insomnia symptoms following pharmacotherapy or cognitive-behavioral therapy for major depressive disorder. *J Clin Psychiatry* 2007;68:254-60.
2. Sunderajan P, Gaynes BN, Wisniewski SR, et al. Insomnia in patients with depression: a STAR*D report. *CNS Spectr* 2010;15:394-404.
3. Nierenberg AA, Keefe BR, Leslie VC, et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. *J Clin Psychiatry* 1999;60:221-5.
4. Reynolds CF 3rd, Frank E, Houck PR, et al. Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? *Am J Psychiatry* 1997;154:958-62.
5. Dimenas ES, Dahlof CG, Jern SC, Wiklund IK. Defining quality of life in medicine. *Scand J Prim Health Care Suppl* 1990;1:7-10.
6. Morin CM, LeBlanc M, Daley M, Gregoire JP, Merette C. Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep Med* 2006;7:123-30.
7. Ishak WW, Bagot K, Thomas S, et al. Quality of life in patients suffering from insomnia. *Innov Clin Neurosci* 2012;9:13-26.
8. McCall WV, Reboussin BA, Cohen W. Subjective measurement of insomnia and quality of life in depressed inpatients. *J Sleep Res* 2000;9:43-8.
9. Scharf M, Erman M, Rosenberg R, et al. A 2-week efficacy and safety study of eszopiclone in elderly patients with primary insomnia. *Sleep* 2005;28:720-7.
10. Walsh JK, Krystal AD, Amato DA, et al. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. *Sleep* 2007;30:959-68.
11. Pech M, O'Kearney R. A randomized controlled trial of problem-solving therapy compared to cognitive therapy for the treatment of insomnia in adults. *Sleep* 2013;36:739-49.
12. Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M. Psychological treatment for insomnia in the regulation of long-term hypnotic drug use. *Health Technol Assess* 2004;8:iii-iv, 1-68.
13. McCall WV, Blocker JN, D'Agostino R Jr., et al. Treatment of insomnia in depressed insomniacs: effects on health-related quality of life, objective and self-reported sleep, and depression. *J Clin Sleep Med* 2010;6:322-9.
14. Fava M, Asnis GM, Shrivastava RK, et al. Improved insomnia symptoms and sleep-related next-day functioning in patients with comorbid major depressive disorder and insomnia following concomitant zolpidem extended-release 12.5 mg and escitalopram treatment: a randomized controlled trial. *J Clin Psychiatry* 2011;72:914-28.
15. Manber R, Edinger JD, Gress JL, San Pedro-Salcedo MG, Kuo TF, Kalista T. Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. *Sleep* 2008;31:489-95.
16. Watanabe N, Furukawa TA, Shimodera S, et al. Brief behavioral therapy for refractory insomnia in residual depression: an assessor-blind, randomized controlled trial. *J Clin Psychiatry* 2011;72:1651-58.
17. Furukawa T, Akechi T, Ozaki N, et al. GRID-HAMD-17. Tokyo: The Japanese Society of Clinical Neuropsychopharmacology, 2003.
18. Bastien CH, Vallieres A, Morin CM Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2:297-307.
19. Morin CM, Espie CA. Insomnia: A clinical guide to assessment and treatment. New York: Guilford Press, 2004.
20. Munezawa T, Morin CM, Inoue Y, Nedate K. Development of the Japanese version of the Insomnia Severity Index (ISI-J). *Jap J Psychiatr Treat* 2009;24:219-25.
21. Perlis ML, Jungquist C, Smith MS, Posner D. Cognitive Behavioral Treatment of Insomnia: A Session-By-Session Guide. New York: Springer Science, 2005.
22. Edinger JD, Wohlgemuth WK, Radtke RA, Coffman CJ, Carney CE. Dose-response effects of cognitive-behavioral insomnia therapy: a randomized clinical trial. *Sleep* 2007;30:203-12.
23. McCrae CS, McGovern R, Lukefahr R, Stripling AM. Research Evaluating Brief Behavioral Sleep Treatments for Rural Elderly (RESTORE): a preliminary examination of effectiveness. *Am J Geriatr Psychiatry* 2007;15:979-82.
24. Germain A, Moul DE, Franzen PL et al. Effects of a brief behavioral treatment for late-life insomnia: preliminary findings. *J Clin Sleep Med* 2006;2:403-6.
25. Buysse DJ, Germain A, Moul DE, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Arch Intern Med* 2011;171:887-95.
26. Currie SR, Clark S, Hodgins DC, El-Guebaly N. Randomized controlled trial of brief cognitive-behavioural interventions for insomnia in recovering alcoholics. *Addiction* 2004;99:1121-32.
27. Ware JE Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
28. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. *J Clin Epidemiol* 1998;51:1037-44.
29. Aaronson NK, Bullinger M, Ahmedzai S. A modular approach to quality-of-life assessment in cancer clinical trials. *Recent Results Cancer Res* 1988;111:231-49.
30. Morin CM, Vallieres A, Guay B, et al. Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. *JAMA* 2009;301:2005-15.
31. Furukawa TA, Akechi T, Azuma H, Okuyama T, Higuchi T. Evidence-based guidelines for interpretation of the Hamilton Rating Scale for Depression (HAM-D). *J Clin Psychopharmacol* 2007;27:531-34.
32. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663-94.
33. Guidelines for ATC classification and DDD assignment. ATC/DDD (Defined Daily Dose) Index 2009. Oslo, Norway: WHO Collaborating Centre for Drug Statistics Methodology, 2009.
34. Endicott J, Nee J, Harrison W, Blumenthal R. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull* 1993;29:321-6.
35. Van Houdenhove L, Buyse B, Gabriels L, Van den Bergh O. Treating primary insomnia: clinical effectiveness and predictors of outcomes on sleep, daytime function and health-related quality of life. *J Clin Psychol Med Settings* 2011;18:312-21.

ACKNOWLEDGMENTS

The authors thank all the assessors and the therapists (Nao Shiraishi, M.D., Yoshie Murata, MSc, Jun Mayumi, M.D., Mako Morikawa, M.D., Yumi Nakano, M.D., Ph.D. at Nagoya City University Graduate School of Medical Sciences, and Ryosuke Fujito, M.D. at Kochi Medical School) and the administrative staff (Kozue Maki at Nagoya City University Graduate School of Medical Sciences) for their contribution to this study. We also thank Mitsuhiko Yamada, M.D., Ph.D., Naohiro Yonemoto, MSc, Masatoshi Inagaki, M.D., Ph.D., at National Center of Neurology and Psychiatry, Japan, for their

advice regarding the design and statistical issues, and Izuru Miyoshi, M.D., Ph.D. at National Center of Neurology and Psychiatry, for providing the central allocation.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication August, 2013
Submitted in final revised form November, 2013
Accepted for publication December, 2013
Address correspondence to: Norio Watanabe, M.D., Ph.D., Department of Clinical Epidemiology, Translational Medical Center, National Center of Neurology & Psychiatry, 4-1-1 Ogawa-higashi, Kodaira, Tokyo 187-8551, Japan; Tel: +81-42-341-2711; Email: noriow@ncnp.go.jpx

DISCLOSURE STATEMENT

This was not an industry supported study. Shinji Shimodera and Norio Watanabe contributed equally to this work as the first authors. This study was funded by a Grant-in-Aid for Scientific Research (No. 19230201) from the Ministry of Health, Labor and Welfare, Japan, and Intramural Research Grant (25-8) for Neurological and Psychiatric Disorders of National Center of Neurology and Psychiatry, Japan. The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The work for this study was performed at Nagoya City University Graduate School of Medical Science, Kochi University, and National Center of Neurology & Psychiatry. All institutions are located in Japan. Dr. Shimodera has received research funds from the Japanese Ministry of Education, Science, and Technology. He has also received speaking fees from Asahi Kasei, Dai-Nippon Sumitomo, GlaxoSmithKline, Astellas, Eli Lilly, Janssen, Meiji, Otsuka, Pfizer, and Schering-Plough. Dr. Watanabe has research funds from the Japanese Ministry of Health Labor and Welfare and the Japanese Ministry of Education, Science, and Technology. He has also received speaking fees and research support from Asahi Kasei, Dai-Nippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Otsuka, Pfizer and Schering-Plough. Dr. Furukawa has received honoraria for speaking at CME meetings sponsored by Astellas, Dai-Nippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Kyorin, MDS, Meiji, Otsuka, Pfizer, Shionogi and Yoshitomi. He is on advisory board for Sekisui Chemicals and Takeda Science Foundation. He has received royalties from Igaku-Shoin, Seiwa-Shoten, Nihon Bunka Kagaku-sha and American Psychiatric Publication. The Japanese Ministry of Education, Science, and Technology and the Japanese Ministry of Health, Labor and Welfare have funded his research. The other authors have indicated no financial conflicts of interest.

PLOS ONE

Relationship between Violent Behavior and Repeated Weight-Loss Dieting among Female Adolescents in Japan

Nao Shiraishi[1], Atsushi Nishida[2], Shinji Shimodera[3]*, Tsukasa Sasaki[4], Norihito Oshima[5], Norio Watanabe[6], Tatsuo Akechi[1], Toshiaki A. Furukawa[7], Yuji Okazaki[8]

1 Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya, Japan, **2** Department of Psychiatry and Behavioral Science, Tokyo Metropolitan Institute of Medical Science, Setagaya-ku, Tokyo, Japan, **3** Department of Neuropsychiatry, Kochi Medical School, Kochi University, Nanngoku, Kohchi, Japan, **4** Laboratory of Health Education, Graduate School of Education, the University of Tokyo, Bunkyo, Tokyo, Japan, **5** Office for Mental Health Support, Division for Counseling and Support, The University of Tokyo, Bunkyo, Tokyo, Japan, **6** Department of Clinical Epidemiology, Translational Medical Center, National Center of Neurology & Psychiatry, Kodaira, Tokyo, Japan, **7** Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Yoshida Konoe-cho, Sakyo-ku, Kyoto, Japan, **8** Tokyo Metropolitan Matsuzawa Hospital, Setagaya, Tokyo, Japan

Abstract

Purpose: To examine whether interpersonal violence perpetration and violence toward objects are associated with body mass index (BMI), body weight perception (BWP), and repeated weight-loss dieting in female adolescents.

Methods: A cross-sectional survey using a self-report questionnaire was performed evaluating interpersonal violence perpetration, violence toward objects, the number of diets, BMI, BWP, the 12-item General Health Questionnaire (GHQ-12), victimization, substance use, and other psychosocial variables among 9,112 Japanese females aged between 12–18 years. Logistic regression analysis was conducted to analyze the contribution of BMI, BWP, and weight-control behavior to the incidence of violent behavior, while controlling for potential confounding factors.

Results: The number of diets was associated with both interpersonal violence perpetration (OR = 1.18, 95% CI 1.08–1.29, $p<0.001$) and violence toward objects (OR = 1.34, 95% CI 1.24–1.45, $p<0.001$), after adjusting for age, BMI, BWP, the GHQ-12 total score, victimization, and substance use. In terms of BMI and BWP, the "overweight" BWP was associated with violence toward objects (OR = 1.29, 95% CI 1.07–1.54, $p<0.05$). On the other hand, the "Underweight" and "Slightly underweight" BMI were related to violence toward objects [(OR = 1.28, 95% CI 1.01–1.62, $p<0.05$) and (OR = 1.27, 95% CI 1.07–1.51, $p<0.05$), respectively]. The "Underweight" BWP was related to interpersonal violence perpetration (OR = 2.30, 95% CI 1.38–3.84, $p<0.05$).

Conclusions: The cumulative number of diets is associated with violent behavior in female adolescents. In addition, underweight BMI and extreme BWP are associated with violent behavior.

Citation: Shiraishi N, Nishida A, Shimodera S, Sasaki T, Oshima N, et al. (2014) Relationship between Violent Behavior and Repeated Weight-Loss Dieting among Female Adolescents in Japan. PLoS ONE 9(9): e107744. doi:10.1371/journal.pone.0107744

Editor: James G. Scott, The University of Queensland, Australia

Received July 2, 2013; **Accepted** July 8, 2014; **Published** September 11, 2014

Funding: This study was funded by a grant-in-aid for scientific research (#H19-kokoro-ippan-012) from the Ministry of Health, Labor, and Welfare of Japan and a grant-in-aid from the Research Group for Schizophrenia in Japan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: NS has a research fund from Aichi Health Promotion Foundation. NS has also received a speaking fee from Eli Lilly. AN has research funds from the Japanese Ministry of Health, Labor, and Welfare and the Japanese Ministry of Education, Science, and Technology. He has also received research grants from the Japanese Society for the Promotion of Science and Research Group for Schizophrenia Research in Japan. SS has received research funds from the Japanese Ministry of Education, Science, and Technology. He has also received speaking fees from Asahi Kasei, Dai-Nippon Sumitomo, GlaxoSmithKline, Astellas, Eli Lilly, Janssen, Meiji, Otsuka, Pfizer, and Schering-Plough. TS has research funds from the Japanese Ministry of Education, Science, and Technology. NO has no conflict of interest to declare. NW has research funds from the Japanese Ministry of Health, Labor, and Welfare and the Japanese Ministry of Education, Science, and Technology. He has also received speaking fees and research funds from Asahi Kasei, Dai-Nippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Otsuka, Pfizer and Schering-Plough. TA has received speaking fees and/or research funds from Astellas, Astra-Zeneca, Dainippon-Sumitomo, GlaxoSmithKline, Meiji, MSD, Otsuka, Pfizer, Sanofi-Aventis, and Shionogi. He has received royalties from Igaku-Shoin, Nanzando and Chugai-igakusya. The Japanese Ministry of Education, Science, and Technology and the Japanese Ministry of Health, Labor, and Welfare have funded his research projects. TAF has received honoraria for speaking at CME meetings sponsored by Asahi Kasei, Eli Lilly, GlaxoSmithKline, Mochida, MSD, Otsuka, Pfizer, Shionogi and Tanabe-Mitsubishi. He is diplomate of the Academy of Cognitive Therapy. He has received royalties from Igaku-Shoin, Seiwa-Shoten and Nihon Bunka Kagaku-sha. He is on the advisory board for Sekisui Chemicals and Takeda Science Foundation. The Japanese Ministry of Education, Science, and Technology, the Japanese Ministry of Health, Labor, and Welfare, and the Japan Foundation for Neuroscience and Mental Health have funded his research projects. YO has no conflict of interest to declare. TAF is a PLOS ONE Editorial Board member. However, this does not alter the authors' adherence to PLOS ONE Editorial policies and criteria. In addition, these competing interests do not alter the authors' adherence to PLOS ONE policies on sharing data and materials.

* Email: shimodes@kochi-u.ac.jp

Introduction

Violence among young people is a major social issue around the world [1,2]. In the United Sates, 32% of high school students are involved in a physical fight and no fewer than 19% of female students physically abused someone at least once in the previous year [3]. The annual statistical survey for problematic behaviors of Japanese students shows that the incidence of violent behavior, such as interpersonal violence perpetration and property destruction, has risen approximately 1.5 times in the past decade [4]. Physical violence is likely to impair the quality of life of adolescents in family environment, peer relationships, and school perceptions [5]. The risk factors behind violence may include low academic performance [6,7], parent–child and peer relationship [8–10], victimization [7,10], illegal drug use [6,7,9,10], smoking [11], illegal alcohol consumption [6,8,10], and adolescent psychiatric disorders such as depression [8], attention-deficit/hyperactivity disorder (ADHD) and conduct disorder [9,12].

Weight-loss dieting is a frequent behavior among adolescents in industrialized countries, regardless of their race or nationality [2,3]. The prevalence of dieting is positively associated with a higher BMI [13]. More females than males have frequent experiences of dieting, across junior and senior high school students of all ages [2,13,14]. The reason for the difference between genders is that female adolescents commonly have much greater body-image dissatisfaction than their male counterparts [14–16]. Moreover, 13% of female dieters engage in maladaptive weight-loss behaviors (self-induced vomiting and binge eating) in the United States [13]. Exposure to violence, especially during childhood [17,18], and several adolescent psychiatric disorders (e.g., depression [13,19] or ADHD [20,21]) also influence BMI, BWP or weight-control behavior negatively.

Chronic dieting can cause negative effects on physical and mental health [22]. It can result in delayed growth [23], electrolyte imbalance, cardiac dysfunction [24], and morbidity due to nutritional deficiencies such as iron deficiency anemia [22,25]. Furthermore, chronic dieting can affect mental health because it is related to persistent irritability [26], emotional dysregulation, poor impulse control [27,28], low self-esteem [24], depression, and anxiety [22,29,30]. Similarly, physical violence is associated with increased irritability and a bad temperament [31]. These findings led us to hypothesize that frustration resulting from repeated dieting is associated with an increased probability of violence. It is known that perceived weight status and disordered eating including self-induced vomiting are related to violent behavior [32]. However, it has not yet been reported whether there is an association between violent behavior and repeated dieting. Thus, we aimed to examine the contribution of BMI, BWP, and weight-control behavior to the incidence of violent behavior in adolescents. Since the distribution of the number of diets was different between the sexes, the present study was performed only among females. Our hypothesis is that interpersonal violence perpetration and violence toward objects are associated with BMI, BWP, and repeated weight-loss dieting in female adolescents.

Methods

Ethics statement

The study was approved by the ethics committees of the Tokyo Institute of Psychiatry, the Kochi Medical School, and the Mie University School of Medicine and was conducted in accordance with the principles of the Helsinki Declaration. We complied with Japan's Ethical Guidelines for Epidemiological Research.

Subjects and procedures

We conducted a cross-sectional survey between 2008 and 2009 that investigated the psychopathology in adolescence. A detailed description of our sampling method has previously been reported and is only briefly discussed here [33]. For the survey, students were recruited from 45 public junior high schools (7^{th}–9^{th} grade) and 28 public high schools (10^{th}–12^{th} grade) in Kochi Prefecture and Tsu City, Japan. The populations of Kochi Prefecture and Tsu City are approximately 750,000 and 290,000, respectively; both of these areas are located in the mid-west part of Japan. Kochi Prefecture has urban and rural regions that surround a centrally located prefectural capital. Tsu City, which is the prefectural capital of Mie Prefecture, is a typical medium-size city in Japan. Therefore, these two areas are representative for general adolescent population. According to the Japanese law, junior high school is a part of the compulsory education system, whereas high school is not.

Our survey followed a standard procedure. School principals were approached about participating in the study. The principals discussed participation with teachers and parents. For schools that agreed to participate, teachers distributed questionnaires and envelopes to their students. At the time of distribution, the teachers explained to the students (1) that participation in the study was anonymous and voluntary, and (2) that strict confidentiality would be maintained. The teachers also explained that the completed questionnaire should be sealed in the provided envelope. Finally, survey staff members went to each school and collected the sealed questionnaires.

Measures

The self-report questionnaire included the following items: (1) cognitive and behavioral problems including interpersonal violence perpetration, violence toward objects, number of diets, body weight perception (BWP), and self-induced vomiting for the purpose of dieting; (2) the Japanese version of the 12-item General Health Questionnaire (GHQ-12); and (3) other variables including demographical characteristics, height, and weight.

Interpersonal violence perpetration and violence toward objects. Interpersonal violence perpetration and violence toward objects that occurred in the previous year were assessed using two questions: "Have you physically abused someone in your family or your friends within the past year?" and "Have you been extremely frustrated and damaged something within the past year?" Each student had a choice of two answers: "yes" or "no." Self-harm was not included in violent behavior in this study.

Number of diets. Dieting experience was assessed with the question: "Have you ever gone on a weight-loss diet?" Students could select "yes" or "no." "No" was defined as "never," and "yes" indicated the number of diets: "How many times have you ever gone on a weight-loss diet?" The response to this question was then categorized into one of the following groups: "1–3 times," "4–7 times," "8–12 times," and "more than 13 times."

Body Mass Index. BMI was calculated from a student's weight (kg) divided by their height (m^2), which were based on a self-reported height and weight. Evidence shows that self-reported BMIs are highly correlated with their measured counterparts in female adolescents aged 12–18 years ($r = 0.85$) [34]. Investigators (NS and NW) determined the exclusion of unlikely height and weight from the analyses by reference to the annual school health statistical surveys of the Ministry of Education, Culture, Sports, Science, and Technology in Japan [35].

The BMI was classified into five categories: "underweight" ($\leq 5^{th}$ percentile), "at risk of being underweight" (5^{th}–15^{th} percentile), "normal weight" (15^{th}–85^{th} percentile), "at risk of being

overweight" (85^{th}–95^{th} percentile), and "overweight" ($\geq 95^{th}$ percentile). The calculation of BMI percentiles for age and sex was based on the standard growth charts developed from the Japanese national survey conducted in 2000 [36].

Body Weight Perception. BWP was assessed with the question: "What do you think of your current body weight?" Students could respond by selecting "very underweight," "slightly underweight," "about the right weight," "slightly overweight," or "very overweight."

Self-induced vomiting for the purpose of dieting. The prevalence of self-induced vomiting for the purpose of dieting was assessed with the question: "Have you ever intentionally vomited (thrown up) after eating in order to lose weight?" Students could select "yes" or "no."

The 12-item General Health Questionnaire. GHQ-12 is widely used as a self-report psychiatric screening test for depression and anxiety [37]. The binary scoring method applied to four-point scale (0011) is used for each of the 12 questions. A total score, which is the sum of all the "1" responses, ranges from 0 (best possible) to 12 (worst possible). GHQ-12 was originally developed for adult populations and was later used and validated for younger populations [38,39]. The validity and reliability of the Japanese version of GHQ-12 have been confirmed [40]. Adolescents with a total GHQ-12 score ≥ 4 were considered to have poor mental health [38].

Other variables. Previous studies indicate that violence and frequent dieting in adolescents may be influenced by other confounding factors such as victimization [7,8,26] and substance use [6,9–11,26]. In our questionnaire, students were asked about their experiences of being bullied (within the past year), violence from adults at home (within the past month), tobacco use (within the past month), alcohol use (within the past month), and recreational drug use (ever). The questions regarding victimization ("being bullied" and "violence from adults in the home") and substance use (tobacco and alcohol use and recreational drug use) were answered with either "yes" or "no." Other variables also included demographic characteristics such as "only child" and "family type."

Statistical analysis

Logistic regression analyses were used to estimate associations between violent behavior and the number of diets. Dependent variables were interpersonal violence perpetration and violence toward objects. Multiple-variable analyses were conducted, adjusting for age, the BMI and BWP categories, the GHQ-12 total score, victimization by "being bullied" and "violence from adults in the home," tobacco and alcohol use, and recreational drug use. In the logistical regression analyses, odds ratios (OR) and 95% confidence intervals (95% CI) were calculated, setting the 15^{th}–85^{th} percentiles of the BMI category and the "about the right weight" response of the BWP category as references. For all statistical tests, a two-tailed p-value of <0.05 was considered statistically significant. For background information, the rates of the BMI and BWP categories were calculated by interpersonal violence perpetration and violence toward objects, respectively. All statistical analyses, including the descriptive statistics, were conducted using PASW Statistics version 20 for Windows (IBM Software Japan, Tokyo, Japan).

Results

Of 19,436 students from 45 of the 138 junior high schools and 28 of the 36 high schools, 798 (4.1%) were absent on the survey days and 388 (2.0%) did not agree to participate in the study. Of these 18,250 students (93.9%) that returned the questionnaire, 18,104 (93.1%) gave available responses. Their mean age was 15.3 (SD = 1.7) and ranged 12–18 years. Two investigators on the study team (NS and NW) classified ten cases with unlikely height and weight (e.g., 15.5 cm and 4.5 kg) as having missing values. Consequently, 9,112 females (50.3%) of the 18,104 students were analyzed.

Table 1. Percentages for demographics and psychological and behavioral problems in adolescent females by violence.

	Uninvolved[a]		Interpersonal violence perpetration[a]		Violence toward objects[a]	
	n	(%)	n	(%)	n	(%)
Total (aged 12–18 years)	5218	(100)	1776	(100)	3167	(100)
Junior high school (aged 12–15 years)	2179	(41.8)	1065	(60.0)	1552	(49.0)
High school (aged 15–18 years)	3039	(58.2)	711	(40.0)	1615	(51.0)
Only child	396	(7.6)	109	(6.1)	245	(7.7)
Living with both parents	4030	(77.2)	1335	(75.2)	2343	(74.0)
Living with one parent	978	(18.7)	375	(21.1)	689	(21.8)
Living apart from parents	210	(4.0)	66	(3.7)	135	(4.3)
Experience of dieting (ever)	1601	(32.0)	703	(41.6)	1375	(45.7)
Self-induced vomiting for the purpose of dieting (ever)	147	(2.8)	132	(7.5)	273	(8.7)
GHQ-12 total score (≥ 4)	2272	(43.5)	1213	(68.3)	2287	(72.2)
Being bullied (within one year)	214	(4.1)	231	(13.2)	347	(11.1)
Violence from adults in the home (within one month)	81	(1.6)	198	(11.2)	220	(7.0)
Tobacco use (within one month)	48	(0.9)	77	(4.5)	138	(4.5)
Alcohol use (within one month)	500	(9.7)	372	(21.3)	671	(21.6)
Use of recreational drugs (ever)	12	(0.2)	23	(1.3)	27	(0.9)

[a]The number of the missing values in each variable was 64 for uninvolved, 47 for interpersonal violence perpetration and 44 for violence toward objects.
Abbreviations: GHQ-12, 12-item General Health Questionnaire.
doi:10.1371/journal.pone.0107744.t001