厚生労働科学研究費補助金

障害者政策総合研究事業

大規模疫学研究データと診療報酬明細書（レセプト）データを用いた一般住民における入院外統合失調症及び統合失調症関連障害の有病率推定方法の開発に関する研究

令和 3 年度～令和 5 年度　総合研究研究報告書

研究代表者　太田　充彦

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研究代表者　　太田　充彦　藤田医科大学医学部公衆衛生学講座教授

研究要旨
大規模疫学研究データを用いて統合失調症を判別できるモデルを開発し、日本の一般住民サンプルに適用して日本の地域住民における統合失調症有病率が 1.59%であると推計した。健康保険組合のレセプトデータを利用し、統合失調症の受療率を 1.16%と推計した。これら元に推定した日本の一般住民における入院外の統合失調症有病率は 1.24%となった。この数値は生涯有病率を推計した可能性もあり、現時点で治療を必要とする者に限った有病率よりは高く推計された可能性も考えられる。

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A. 研究目的

本研究の目的は、日本における入院外統合失調症および統合失調症関連障害（短期精神病性障害、妄想性障害、統合失調感情障害、および統合失調症様障害）（以下、統合失調症等）の有病率を、大規模疫学研究や診療報酬明細書（以後、レセプト）のデータを用いて推定する方法を開発すること、および、これを用いて最終的に日本の一般住民における入院外の統合失調症等の有病率を推計することである。

Lancet Global Burden of Diseases, Injuries, and Risk Factors Study によれば、2019 年の統合失調症の年齢標準化済み有病率（以下、有病率は人口 10 万人当たり人数）は全世界では 287.4 人（男性：302.7 人、女性：272.0 人）、日本では 300.8 人とされた（*Lancet Psychiatry* 2022; **9**: 137-150.）。Moreno-Küstner らのシステマティックレビューでは、統合失調症を含む精神病性障害の時点・12 ヶ月・生涯有病率の中央値がそれぞれ 389 人、403 人、749 人であったことが報告されている（*PLoS One* 2018; **13**: e0195687.）。Simeone らのシステマティックレビューでは、12 ヶ月有病率の中央値

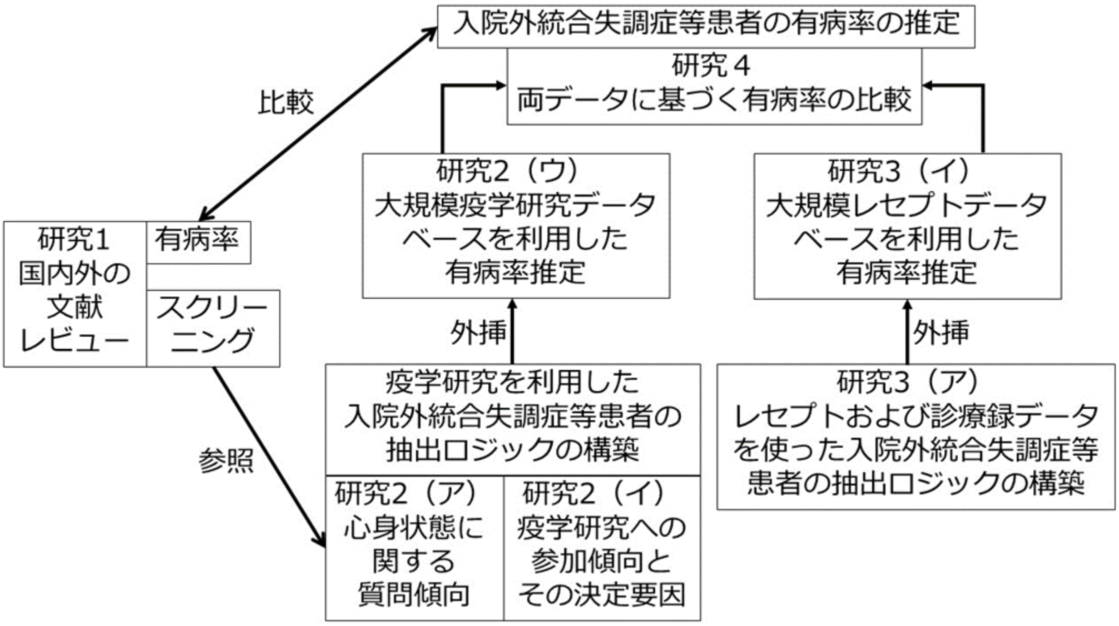


図１．研究スキーム

が全世界では 330 人、アジアでは 370 人であることが報告された（*BMC Psychiatry* 2015；15：193.）。アジアでの生涯有病率に関しては中国、韓国、マレーシア、タイからの報告があり、130～880 人と報告されていた。Okui は患者報告のデータを利用して、日本の平成 29 年（2017 年）の統合失調症の年齢調整済み有病率は男性で 765 人、女性で 766 人と推計した（*Soc Psychiatry Psychiatr Epidemiol* 2021；**56**：639-648.）。

日本では統合失調症の入院患者数が多く、入院期間が長い。統合失調症の推計入院患者数は 14.3 万人であった（令和 2 年患者調査）。これは、精神及び行動の障害の推計入院患者数 23.7 万人の 60%を占める。長期入院患者の割合は高く、入院期間が 6 か月以上の者が 81.9%、1 年 6 か月以上の者が 69.2%、3 年以上の者が 56.7%を占めた。入院の状況は、受け入れ条件が整えば退院可能な者が 13.5%存在しており、地域での受け皿づくりの必要性が示唆された。統合失調症等を含む精神障害者の地域移行・地域定着のためには、地域で精神障害者を支える体制が不可欠である。精神障害にも対応した地域包括ケアシステムは、精神障害者が地域の一員として安心して自分らしい暮らしをすることができるよう、医療、障害福祉・介護、住まい、社会参加、地域の助け合いが包括的に確保された地域の構築を目指している。この政策を実現するためには、入院外を含めた統合失調症等の有病率を明らかにしたうえで、退院後の医療・アウトリーチ等の継続支援、住まいの確保支援、家族への支援などに必要なニーズを算出し整備する必要がある。

Ｂ．研究方法

我々は日本における入院外の統合失調症等の有病率を、大規模疫学研究やレセプトデータを用いて推定するスキームを研究者間で協議し、作成した（図 1）。また、各年度末のマイルストーン（表 1）と研究のタイムライン（図 2）も策定した。これに従って研究を進めた。以下、各研究の方法の詳細を

表１．各年度末のマイルストーン

令和3年度	○ 研究１：レビューにより、国内外における統合失調者等患者の有病率および統合失調症のスクリーニングに有用な方法に関する既存の知見をまとめる。 ○ 研究２：疫学研究を用いた入院外（外来受診＋未受診）統合失調症等有病率を推定する研究計画の確定。 ○ 研究３：レセプトおよび診療録データを用いた入院外（外来受診）統合失調症等有病率を推定する研究計画の確定。
令和4年度	○ 研究２：(ア) 既存質問紙調査を利用した統合失調症患者を判別するロジックの開発、および(イ)統合失調症等患者が疫学研究に参加する割合と決定要因の探索の完了。 ○ 研究３：(ア) レセプト病名と処方薬を組み合わせた統合失調症等患者の抽出の妥当性検証の完了、および（イ）大規模レセプトデータベースによる入院外統合失調症等有病率の推計の着手。
令和5年度	○ 研究２：(ウ)大規模疫学研究データによる入院外統合失調症等有病率の推定の完了。 ○ 研究３：(イ) 大規模レセプトデータベースによる入院外統合失調症等有病率の推計の完了。 ○ 研究４：大規模疫学研究・大規模レセプトデータから推計した入院外統合失調症等有病率の比較の完了。

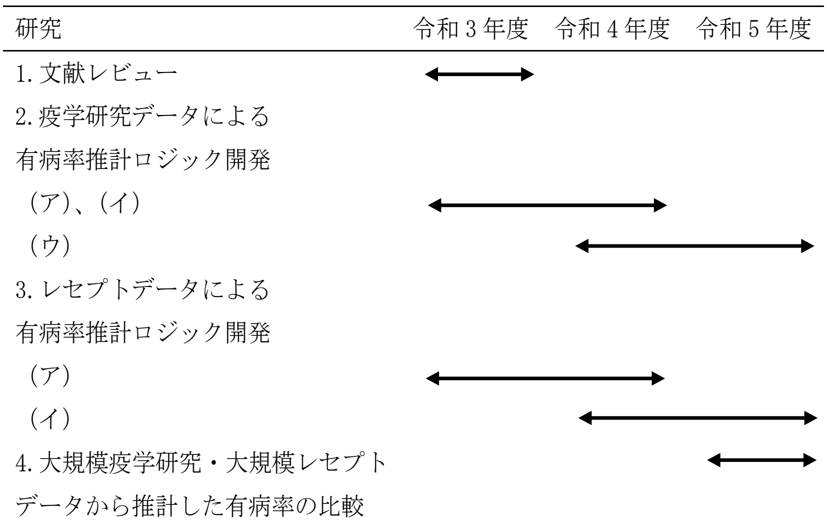


図2. 研究のタイムライン

示す。

1. 研究１：国内外の文献レビュー

統合失調症の有病率、主観的健康感・幸福感・生活満足度、身体的・精神的・社会的併存疾患を報告した論文を対象とした。身体的併存疾患として、過体重と肥満、口腔衛生、生活習慣病、便秘、食行動などを取り上げた。精神的併存疾患として、うつ病と睡眠障害、喫煙・アルコール・薬物摂取、問題のあるインターネットやスマートフォンの使用、ストレス知覚とアロスタティック負荷を取り上げた。社会的併存疾患として、健康リテラシーと行動、社会経済的状態（教育、雇用、収入、配偶者の有無、家族構成など）、社会的認知バイアス、サポート、ネットワークを取り上げた。これらの用語を用いて、関連する可能性のある論文を収集した。既存のシステマティックレビューやメタアナリシスの結果を優先して検索した。それらがない場合は、既存のコホート研究、症例対照研究、横断研究を参照した。2022 年 2 月までに発表された文献を PubMed で検索した。このレビューに採用した既存研究は、英語で書かれた臨床研究および疫学研究に限定した。

2. 研究 2（ア）（イ）：疫学研究を利用した入院外統合失調症等患者の抽出ロジックの構築

個人特性および身体的・精神的・社会的併存症状から統合失調症を有する者を判別できるモデルを作るために以下の方法で研究を行った。

まずは統合失調症を有する者に頻度が高い個人特性および身体的・精神的・社会的併存症状を明らかにするためのインターネット調査を 2022 年 2 月に実施した。対象者は 20～75 歳で、統合失調症を有すると自己申告した 223 人と精神障害を有さないと自己申告した 1776 人であった。それぞれの定義は図 3・4 に示す。個人特性として、性、年齢、身長、体重、喫煙状況、飲酒状況、食生活、便通、身体機能、主観的健康観、歯の残存数などを尋ねた。身体的併存症状として、過体重（body mass index（BMI）25 以上）・肥満（BMI30 以上）、がん、心血管疾患、心不全、高血圧、糖尿病、脂質異常症、痛風、睡眠時無呼吸症候群、骨折の有無を尋ねた。精神的併存症状として、うつ症状（Center for Epidemiological Studies Depression (CES-D) Scale にて評価）、不眠症状（睡眠時間、中途覚醒、早朝覚醒、入眠困難、睡眠の質）、認知ストレス（4 項目版 Perceived Stress Scale (PSS-4)にて評価）、生きがい、幸福感、インターネット使用時間を尋ねた。社会的併存症状として、健康診断受診状況、教育歴、就業状況、世帯収入、婚姻状況、家族構成、同居者の状況、ソーシャルサポート（ENRICHD Social Support Instrument (ESSI)にて評価）、ソーシャルキャピタルを尋ねた。精神障害を有さない者に比べて統合失調症を有する者がどの程度多く身体的・精神的・社会的併存症状を有しているかを、性・年齢を調整したオッズ比によって表した。

このインターネット調査の回答データを元に、機械学習を用いて統合失調症を有する者を判別できるモデルを作成した。インターネット調査の質問項目への回答は、1 つの回答変数（統合失調症と診断された）と特徴変数（個人特性、身体的・精神的・社会的併存症状）にフォーマットされた。機械学習モデルとして、人工ニューラルネットワー

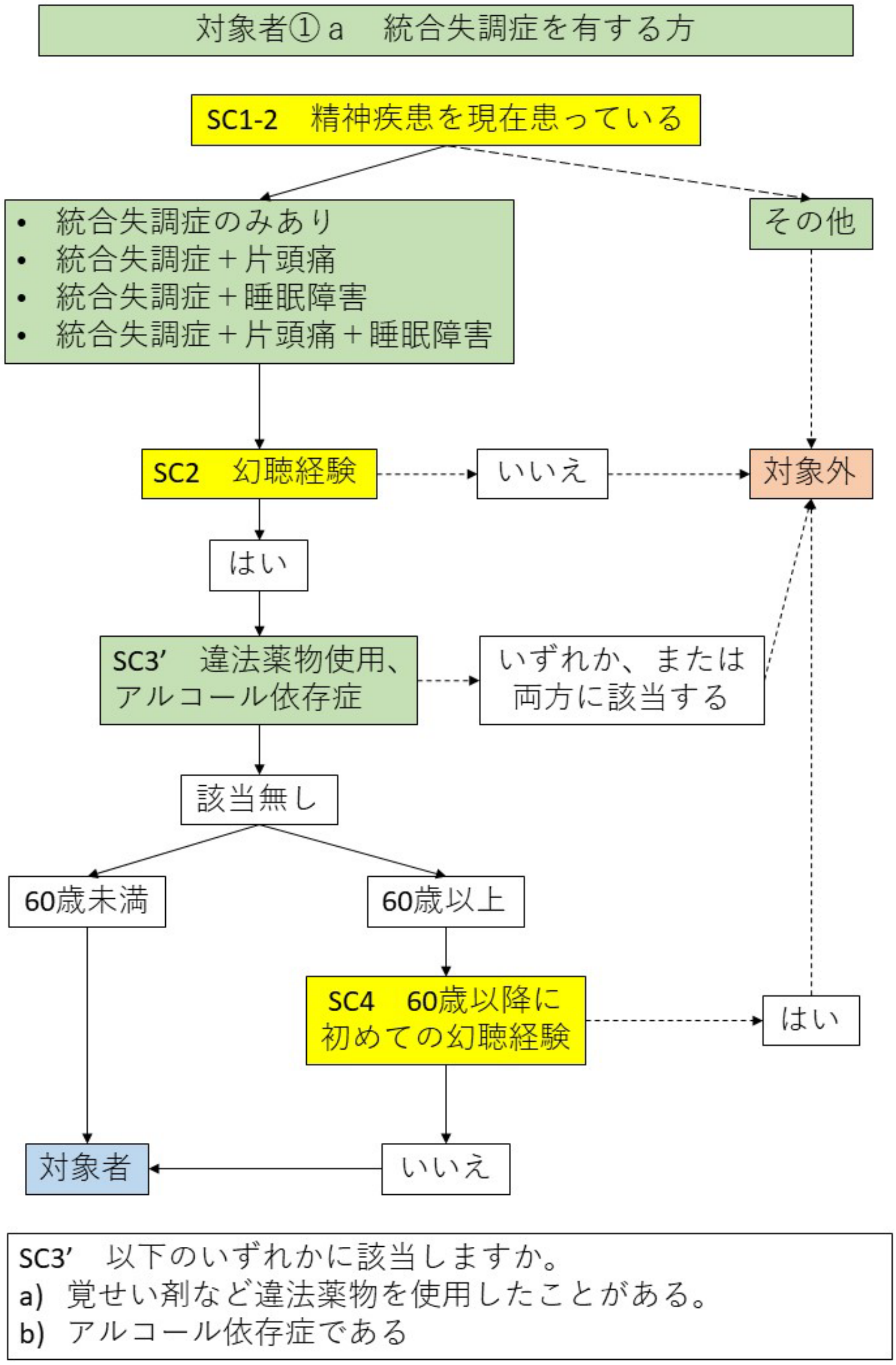


図 3．統合失調症を有する者の定義

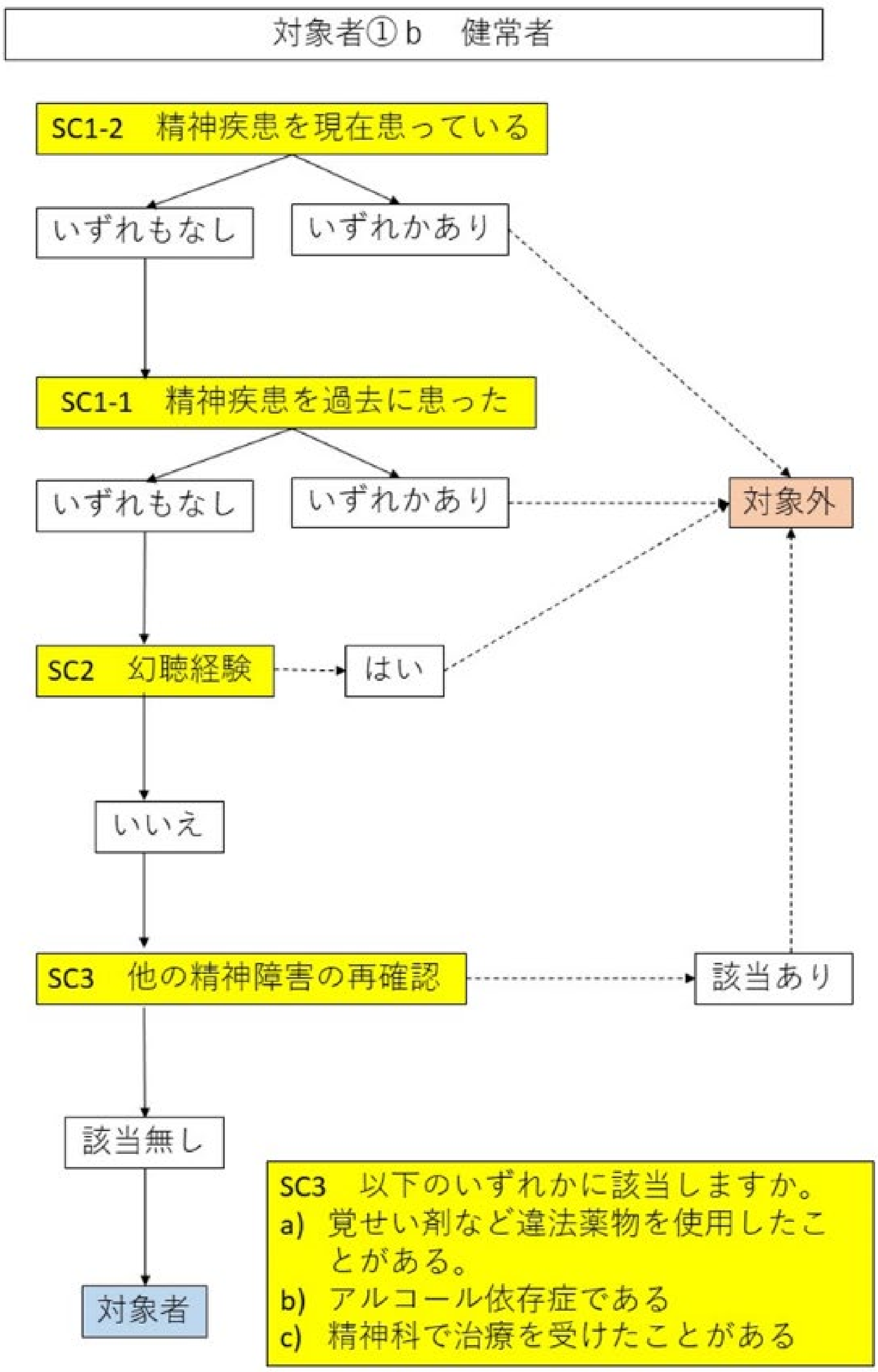


図 4．精神障害を有さない者の定義

ク

ク(artificial neural network: ANN) を適用して、統合失調症の症例を分類するためのモードを構築した。本研究では、5 つの隠れ層(各層のニューロン:128-64-32-16-8)、HeNormal 重み初期化器、隠れ層の ReLU 活性化関数、出力層の Sigmoid 活性化で ANN を構成した。多重ロジスティック回帰モデルを比較対照として適用した。作成した判別モデルの内的整合性の検証として、機械学習モデルと多重ロジスティック回帰モデルのそれぞれで、感度・特異度・陽性的中率・陰性的中率を算出し、比較した。受信者動作特性曲線下面積(AUC)と精度も算出した。

次いで、この判別モデルの外的妥当性を検証した。2022 年 1 月から 2023 年 5 月までに藤田医科大学病院精神神経科外来を受診した 20 歳以上 75 歳未満の患者で、熟練した精神科医によって統合失調症(61 人)、大うつ病性障害 (MDD: major depression disorder)(56 人)、双極性障害(BD: bipolar disorder)(32 人)、強迫性障害 (OCD: obsessive-compulsive disorder)(1 人)と診断された患者を対象者とした。対象者は、統合失調症判別モデルの作成で使用したものと同じ、個人特性と身体的・精神的・社会的併存症状を尋ねるアンケートに回答した。この回答内容を統合失調症判別モデルに当てはめ、回答者が統合失調症であるか否かを判別した。精神科医の診断をゴールデンスタンダードとした場合の統合失調症判別モデルの感度、特異度、誤診率を算出した。

3. 研究 2(ウ):大規模疫学研究データベースを利用した有病率推定

我々の統合失調症判別モデルを一般住民サンプルに当てはめ、統合失調症有病率を算出するためのインターネット調査を実施した。統合失調症の母比率(日本国民における有病率)を 0.5～2%と仮定し、誤差を 1%、信頼度を 95%とした場合にサンプルサイズは 750 あれば十分と算出された。対象者 750 人は、その年齢・性別・地域の分布が総務省・人口推計 2021 年(令和 3 年)10 月 1 日現在人口の全国人口構成比に合うように設定した。対象者は、統合失調症判別モデルの作成で使用したものと同じ、個人特性と身体的・精神的・社会的併存症状を尋ねるアンケートに回答した。この回答を統合失調症判別モデルに投入し、統合失調症と判別された人数を対象者数 750 で割った値を粗有病率とした。この粗有病率から、これまでの生涯にわたって精神障害を有してない者とうつ病・双極性障害を有する者で統合失調症と誤診される者が占める 7.1%を差し引いた。これらを除した残りを統合失調症を有する者とし、その 0.326 倍に相当する数の者が我々の判別モデルにおいては真に統合失調症を有しているが統合失調症ではないと誤診された者(偽陰性者)とした。この偽陰性者を追加した人数を対象者数 750 で除して、統合失調症有病率を算出した。

また、人工画像化と画像識別を用いて統合失調症判別モデルを作成できるかを検証した。統合失調症を有すると自己申告した成人 223 人と精神障害を有さないと自己申告した成人 1776 人の個人特性と身体的・精神的・社会的併存症状のデータ・76 項目から人工画像を作成し、統合失調症を判定するモデルとしての適性を AUC を算出して評価した。

4. 研究 3(ア):レセプトおよび診療録データを使った入院外統合失調症等患者

の抽出ロジックの構築

レセプトデータを用いて統合失調症受療率を算出するための基礎調査として、レセプトに含まれないが精神障害の有病率が高い集団である生活保護受給者が除外されることの影響を推計した。平成 26 年および 29 年の総務省推計人口（総人口、確定値）と同年の厚生労働省社会・援護局保護課「被保護者調査」月次調査による 6 月分の性・年齢階級別被保護実人員の比較を行った。具体的には、性別に 5 歳年齢階級別の人口（被保護実人員）割合を算出した。その後、平成 26～令和 2（2014～2019）年の被保護者調査より、6 月分の 1 か月平均被保護実人員あたりの統合失調症による医療扶助件数を算出した。また、各年 10 月 1 日時点の推計人口を用いて、人口一万人当たりの生活保護受給者かつ統合失調症による医療扶助を受けている者の割合を求めた。

次いで、大規模レセプトデータベースに収載されている傷病名に「統合失調」という文字列を含む傷病名の状況を検討し、レセプトデータから統合失調症の有病率を推計する方法論を検討する上で留意すべき点を明らかにする研究を実施した。株式会社 JMDC 社にデータ利用許諾を行った複数の医療機関における 2020 年 1 月～2021 年 12 月のレセプト 547,403 件（DPC30,989 件, 入院 13,158 件、入院外 347,895 件、不明 155,361 件）に記載された傷病名を分析の対象とした。レセプトは全て電子的に提出されたものであり、各医療機関において独自にテキストで入力された傷病名については、社会保険診療報酬支払基金による「傷病名マスター（レセプト電算処理システムマスターファイル）」における標準病名マスターの病名基本テーブルに基づいた標準化を行った。その後、傷病名の一部に「統合失調」という文字列を含む傷病名を全て抽出し、各傷病名の分布を検討した。

レセプト傷病名「統合失調症」は真に統合失調症を有さない患者にも付与されていることがあるため、レセプト情報から真に統合失調症を有する者を抽出する際の妥当性を検証した。某総合病院精神神経科に 2020 年 9 月～2022 年 8 月に入院した患者全員・987 人を対象者とした。調査項目として、レセプトデータにおける傷病名「統合失調症」の有無と抗精神病薬の処方の有無、および、統合失調症が真に存在するかの精神科専門医の最終診断をゴールデンスタンダードとして調べた。対象者に対しては、退院時までに複数の精神科専門医が協議して診断が確定し、退院時サマリーに最終診断病名として記載される。これを対象者が統合失調症を真に有していたかの評価とした。レセプトデータ（統合失調症の傷病名、および、統合失調症の傷病名かつ抗精神病薬の処方）と真に統合失調症であるかをもとに、陽性的中率、陰性的中率、感度、特異度を算出した。

5. 研究 3（イ）：大規模レセプトデータベースを利用した有病率推定

健保組合データベースを用いて統合失調症等の受療率を算出した。2020 年 4 月～2022 年 3 月診療分レセプトより、文字列に「統合失調」を含む標準病名が少なくとも一度記載されたレセプトを期間中に少なくとも 1 件有する者を統合失調症を有する者とした。同期間に被保険者本人・家族であった者の性・年齢階級別人口を分母として、期間受療率を算出した。

6.　研究 4：両データに基づく有病率の比較

大規模疫学研究データを用いて推計した統合失調症有病率とレセプトデータを用いて推定した統合失調症受療率を利用した。我々はレセプト傷病名「統合失調症」の陽性的中率は 41.3%であることを明らかにしている（参照：令和 4 年度岸研究分担者の分担研究報告書)。このデータを掛け合わせて、レセプトデータを用いて推定した統合失調症受療率を再計算した。最新の令和 2 年患者調査における「統合失調症、統合失調症型障害及び妄想性障害」の受療率は入院:外来＝2.83：1 であった。この比を、大規模疫学研究データを用いて推定した統合失調症有病率およびレセプトデータを用いて推定した統合失調症受療率に当てはめ、それぞれにおいて入院・外来が占める割合を推計した。最終的に日本の一般住民における入院外の統合失調症有病率は以下の計算式にて求めた。

日本の一般住民における入院外の統合失調症有病率
＝大規模疫学研究データを用いて推計した統合失調症有病率
－レセプトデータを用いて推定した統合失調症受療率の入院部分

（倫理面への配慮）

本研究はヘルシンキ宣言および人を対象とする生命科学・医学系研究に関する倫理指針（文部科学省、厚生労働省、経済産業省）に則って実施した。研究にあたっては、研究代表者・分担研究者が所属する機関において倫理審査を受け、承認を得た。この審査を受け、所属機関長の承認を得て実施した。利益相反管理は研究代表者・分担研究者が所属する藤田医科大学利益相反委員会および久留米大学利益相反マネジメント委員会へ申請を行い、適切に各大学にて管理した。

C. 研究結果

1.　研究 1：国内外の文献レビュー

本レビューの結果の結果の概要は表 2 に示す。詳細は論文報告しており（He Y, et al. *Neuropsychopharmacology Reports* 2022; **42**: 430-436)、本論文を総合研究報告書の資料として別添する。

〇有病率

Simeone ら(2015)のシステマティックレビューでは、過去 12 ヶ月および生涯の有病率の中央値は 0.33%と 0.48%と報告された。Moreno-Küstner ら(2018)のシステマティックレビューでは、時点、過去 12 ヶ月、および生涯の有病率の中央値はそれぞれ 0.39%、0.40%、0.75%であると報告された。これらには日本において行われた研究結果は利用されていない。日本では、Okui(2021)が患者調査のデータを用いて、統合失調症と妄想性障害の有病率を約 0.7%と推定した。

〇主観的健康感、幸福感、生活満足度

Fervaha ら(2016)はカナダでの横断的研究で、統合失調症を有する者とそうでない若年成人の主観的健康感、幸福感、生活満足度を比較した。全体的には、統合失調症を有する者は健康対象者よりも主観的健康感、幸福感、生活満足度の平均点が低かった。同様の知見はスペインの成人を対象とした別の研究でも確認された(Gutiérrez-Rojas et al., 2021)。なお、Fervaha らは主観的健康感、幸福感、生活満足度の個人の得点のばら

表 2. 文献レビュー結果の要約

Subjective well-being, happiness, and life satisfaction
• Worsened subjective well-being, happiness, and life satisfaction at a group level but varied by individual.
Overweight and obesity
• High prevalence of obesity but varied by race.
• Consequence of antipsychotics.
Oral health
• Poor oral health: the greater number of missing and decayed teeth.
Non-communicable diseases
• High prevalence of chronic obstructive pulmonary disease, metabolic syndrome, type 2 diabetes, hypertension, and hypertriglyceridemia.
Constipation
• Constipation and ileus caused by psychotropic medications, especially clozapine.
Eating behaviors
• High dietary energy, sodium, and saturated fat.
• Poor diet in fiber, fruit, and unsaturated fatty acids.
Depression and sleep disorders
• High prevalence of comorbid major depressive disorder and sleep disturbances.
Smoking, alcohol, and drug consumption
• High prevalence of smoking, drinking, and drug consumption.
Problematic internet and smartphone use
• Problematic internet and smartphone use reported in South Korea.
Stress perception and allostatic load
• Inconsistent evidence on whether to perceive more stress.
• Related to greater allostatic load.
Health literacy and behaviors
• Low health literacy and poor understanding of preventive behaviors.
Socioeconomic status: education, employment, income, marital status, and family structure
• Low employment rate and income.
• Less educated and likely to be unmarried/unattached.
Social cognitive bias, support, and network
• Low ability to navigate social cues and behaviors.
• Deficits in building relationships; lack of social support, community integration, and friends; and small size of social network.

つきが広く、統合失調症を有する者とそうでない若者の間でかなり重なっていることも指摘した。

〇身体的併存症

・過体重と肥満

Mitchell ら(2013)によるメタアナリシスでは統合失調症を有する者のほぼ半数が肥満であると報告された。統合失調症を有する者が過体重・肥満であるかは、受けている治療によって異なる可能性があった。Shar ら(2019)によるシステマティックレビューでは、健常対照者と比較して抗精神病薬を投与されていない統合失調症患者と最小限の治療しか受けていない統合失調症患者では、body mass index (BMI)が低く、腹囲に差がないことが示された。抗精神病薬は統合失調症を有する者の過体重・肥満の原因となっていた。Tariicone ら(2010)によるメタアナリシスでは、抗精神病薬未使用の患者の体重と BMI が抗精神病薬の投与開始後に増加することが示された。Tek ら(2016)らのメタアナリシスでは、初発精神病患者において、ジプラシドンを除くハロペリドール、オランザピン、クエチアピン、リスペリドンなどの抗精神病薬が体重や BMI の増加と関連があった。彼らは抗精神病薬の服用期間が長いほど、体重増加が多いことも示された。これらの知見は抗精神病薬の副作用として体重超過や肥満があることを示している。

統合失調症を有する患者における体重増加は人種によって異なる可能性がある。Tek ら(2016)らのメタアナリシスでは、欧米における体重増加とは対照的に、アジアでは体重増加が少なかったと報告された。統合失調症を有する患者の低体重に焦点を当てた Sugawara ら(2018)のメタアナリシスによれば、日本の統合失調症を有する入院患者の低体重の有病率は 17.6%で、世界の統合失調症を有する患者に比べて 3 倍近く高かった。

・口腔衛生

統合失調症を有する者の口腔内の健康状態が悪いことを報告した 2 つのメタアナリシスがあった(Yang et al., 2018; Sun et al., 2021)。いずれの研究も、統合失調症を有する者は健常対照群と比較して、Decayed, Missing, and Filled Teeth (DMFT)指数が高いことを明らかにした。この指数は、虫歯、欠損、充填歯の合計数が多いほど、欠損歯や虫歯の数が多いほど、充填歯の数が少ないほど高い値となる。この結果は、口腔衛生状態が悪く、歯科治療、予防、治療の機会が少ないことを示唆している。

・生活習慣病

統合失調症を有する者において生活習慣病が高い割合で併存することが報告されていた。Zareifopoulos ら(2018)のシステマティックレビューによれば、統合失調症患者が慢性閉塞性肺疾患(COPD)を併発する可能性は一般集団の約 1.5 倍であった。統合失調症を有する者におけるメタボリックシンドロームの有病率は 30%以上と高いことを指摘したメタアナリシスがあった(Mitchell et al., 2013; Vancampfort et al., 2015)。Mamakou ら(2018)のレビューでは、統合失調症を有する者における 2 型糖尿病の有病率は 8%～23.3%と報告された。Mitchell ら(2013)のメタアナリシスでは、統合失調症を有する者の約 19%が高血糖、38.7%が高血圧、39.3%が高トリグリセリド血症を有していることが示された。

・便秘

統合失調症を有する者は便秘になることが多い。クロザピンと便秘やイレウスとの関連が多く調べられてきた。Shirazi ら(2016)のメタアナリシスでは、クロザピンを服用している統合失調症患者の約 3 分の 1 が便秘を経験していると推定された。このメタアナリシスでは、クロザピンを服用している者においては他の抗精神病薬を服用している患者よりも有意に便秘が起こることが報告された。Nielsen ら(2012)は、クロザピン服用中の統合失調症を有する者は、他の向精神薬服用中の者と比較してイレウスになるリスクが 2 倍高いことを報告した。クロザピンは他の向精神薬に比べて致死的なイレウスを引き起こす頻度が高かった。

・食行動

統合失調症を有する者の食行動・栄養摂取に焦点を当てたシステマティックレビューが 2 編あった。Teasdale ら(2019)は、統合失調症を有する者は健常者と比較してエネルギーと食塩の摂取量が多いことを明らかにした。Dipasquale ら(2013)は、統合失調症を有する者は飽和脂肪を多く摂取し、食物繊維、果物および不飽和脂肪酸の接種が少ないことを指摘した。

〇精神的併存症

・うつ病と睡眠障害

統合失調症を有する者には、うつ病の併存が多くみられた。Etchecopar-Etchart ら(2021)のメタアナリシスでは、大うつ病性障害の併存有病率の推定値は 32.6%と報告された。Crespo-Facorro ら(2021)のシステマティックレビューでは、健康対照者と比べて初発の統合失調症を有する患者はより頻繁にうつ症状を示していることが示唆された。この研究では、初期の統合失調症を有する者と慢性期の統合失調症を有する者のどちらがより重度の抑うつ状態を示すかについては、既存の知見に一貫性がないことも示された。Cotton ら(2013)によれば、初発の統合失調症を有する者と分裂感情障害を有する者の間で大うつ病性障害の併存有病率に有意差は認められなった。

睡眠障害は統合失調症でしばしば認められる。Meyer ら(2020)のメタアナリシスでは、寛解した統合失調症を有する者では睡眠時間が長く、全睡眠時間、在床時間、睡眠潜時が長いと報告された。Waite ら(2020)は、不眠症（50%）および悪夢障害（48%）が統合失調症を有する者の最も一般的な睡眠問題であることを報告した。

・喫煙、アルコール、薬物摂取

アメリカで行われた多施設研究では、統合失調症を有する者では喫煙者、飲酒者、薬物使用者の割合が一般人口集団よりも高かった(Hartz et al., 2014)。喫煙が統合失調症発症の危険因子であることがメタアナリシス(Hunter et al., 2020)やメンデルランダム化解析(Wootton et al., 2020)において示されていた。

・問題のあるインターネットやスマートフォンの使用

インターネット中毒とも呼ばれる問題あるインターネットの利用（PIU: problematic internet use)は、日常生活に支障をきたすような持続的なインターネットの強迫的利用と特徴づけられる。Lee ら(2018)が韓国で行った横断研究では、統合失調症スペクトラム障害を有する者の約 22%が PIU を持っていることが示された。これらの者では知覚ストレスが高く、コー

ピング戦略が機能不全になっている傾向があった。近年スマートフォンの普及に伴い、PIU は次第に問題的スマートフォン使用(PSU: problematic smartphone use)という形で現れている。韓国の研究(Lee et al., 2019)では、PSU の重症度は不安の高さと同意性の低さの両方と有意に関連していた。これらの研究の対象者には健常対照者が含まれていないため、統合失調症を有する者においてインターネット中毒が健常対照者よりも高い割合で見られたかは不明である。

・ストレス知覚とアロスタティック負荷

ストレスは統合失調症のさまざまな病期において重要な役割を担っていることから、統合失調症の病因病態生理と関連づけられている(Nugent et al., 2015)。Gutiérrez-Rojas ら(2021)は統合失調症を有する者が健常対照群と比べてストレスを知覚しやすいことを見いだしたが、Nugent ら(2015)はこの関連を確認できなかった。Nugent ら(2015)はアロスタティック負荷、すなわち、外的ストレス因子に反応した後に身体が経験する消耗に注目した。Nugent ら(2015)は、統合失調症を有する者は健常対照者と比較してアロスタティック負荷が大きく、初期と慢性期の統合失調症を有する者の両方でアロスタティック負荷が大きいことを報告した。

〇社会的併存症

・健康リテラシー/行動

Degan ら(2021)のシステマティックレビューによれば、統合失調症を有する者では健康に関するリテラシーが低い傾向にある。Kim ら(2019)の横断研究によれば、精神病を有する者（うち 85%が統合失調症）は予防行動に対する理解や身体的疾患に対する知識が低く、健常対照者と比べて、定期的な健康診断や運動をすること、がんの早期発見や生活習慣病のコントロールの重要性を認識することが少なかった。

・社会経済的要因（教育、雇用、収入、婚姻状況、家族構成）

既存のシステマティックレビューやメタアナリシスでは、統合失調症を有する者は健常対照者と比べて学歴(Dickson et al., 2020)や就業率(Crespo-Facorro et al., 2021)が低いことが示された。中国の研究では、低収入と統合失調症の関連が個人レベルで確認された(Ding et al., 2020)。デンマークの人口ベースのデータを用いた研究では、統合失調症を有する者は独身であることが多いことが明らかになった(Agerbo et al., 2004; Hakulinen et al., 2019)。中国の統合失調症を有する者においては、社会的機能不全と婚姻状況との間に関連があった(Li et al., 2015)。日本においては、ホームレスの約 10%が統合失調症などの精神病性障害と診断されていることが報告されている(Nishio et al., 2017)。

・社会的認知の偏り、社会的支援、ネットワーク

Savla ら(2013)のメタアナリシスでは、健常対照者と比較して、統合失調症を有する者は社会的認知、すなわち、知識ベースと一連のスキルに本質的に依存する社会的手がかりと行動を支配する能力が低いことが示された。心理学的研究により、社会的認知バイアスは統合失調症を有する者の対人葛藤に関連する認知、症状、機能についての情報をもたらすことが明らかになった(Buck et al., 2016)。

統合失調症の人は孤独であることが多く、

人間関係の構築、社会的支援、地域社会への溶け込みがうまくいかず、友人がいないことが指摘されている(Perese & Wolf, 2005)。Megnanら(2018)らのシステマティックレビューによれば、ソーシャルネットワークの規模が小さいことと統合失調症の人の精神症状が重いことが関連していた。オーストラリアの全国規模の調査では、精神病を有する成人（うち47%は統合失調症、16%は統合失調感情障害）は孤独を感じる頻度が高く(80.1%)、より多くの友人を欲するものが48.1%いたことが示された(Stain et al., 2012)。

2.　研究2（ア）（イ）：疫学研究を利用した入院外統合失調症等患者の抽出ロジックの構築

精神障害がない者に比べて統合失調症を有する者ではいくつかの身体的・精神的・社会的併存症状が統計学的に有意に多くみられた。身体的併存症状としては、骨折（性・年齢調整済みオッズ比：7.17)、睡眠時無呼吸(4.04)、過体重・肥満(BMI25以上)(3.85)、糖尿病(3.25)、脂質異常症(2.60)が多くみられた（図 5)。精神的併存症状としては、うつ症状(7.54)、長時間睡眠(3.95)、認知ストレスの自覚(3.60)、中途・早朝覚醒(3.57)、入眠困難(2.98)、幸福感の欠如(2.58)、生きがいの欠如(2.26)、不良な睡眠の質(2.07)、長時間のインターネット使用(1.50)が多く見られた(図6)。社会的併存症状としては、非就労(6.25)、非正規雇用(6.24)、親との同

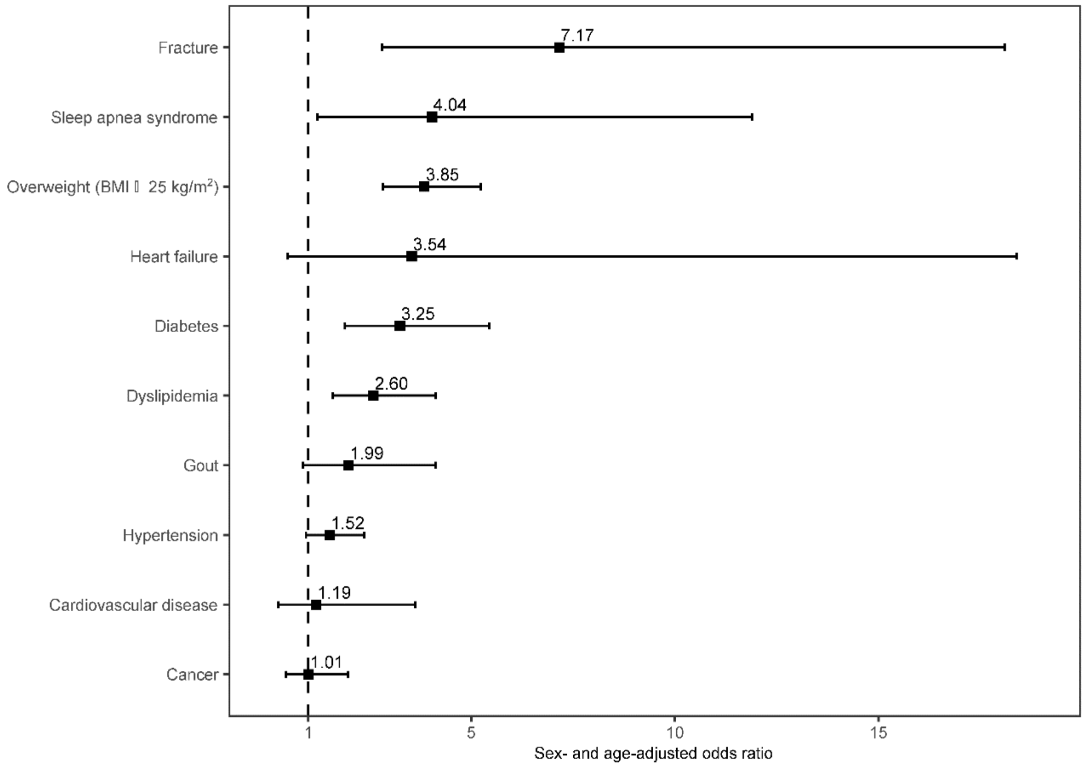


図 5.統合失調症を有する者において頻度の高い身体的併存症状：：精神障害がない者における有病率を 1 とした場合の性・年齢調整済みオッズ比

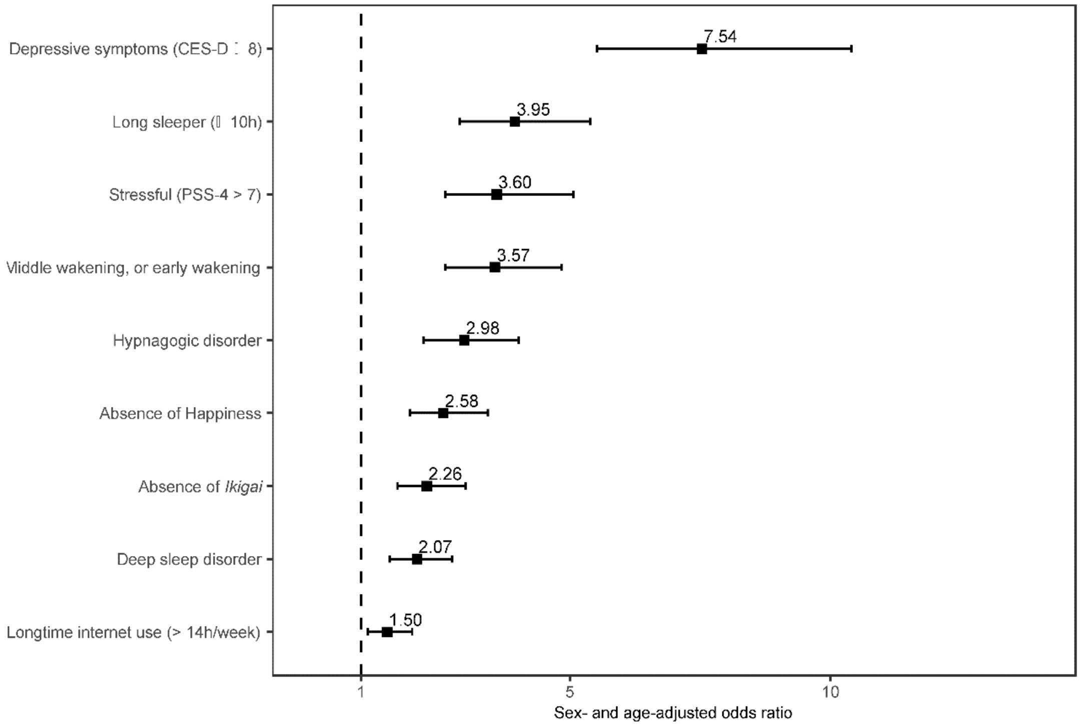


図 6. 統合失調症を有する者において頻度の高い精神的併存症状：：精神障害がない者における有病率を 1 とした場合の性・年齢調整済みオッズ比

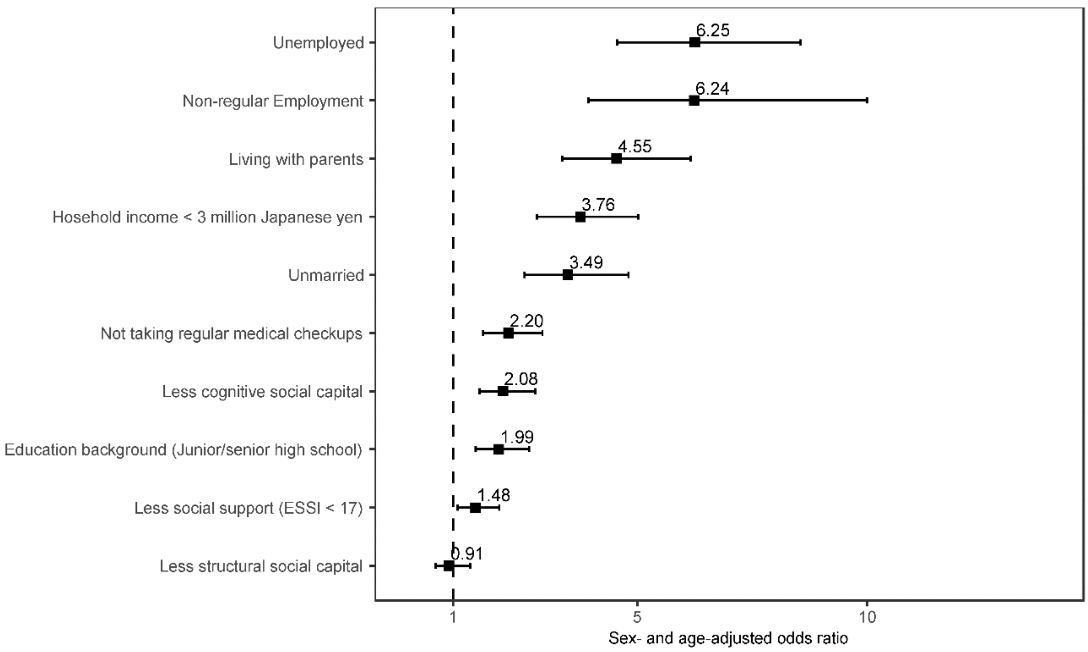


図 7.統合失調症を有する者において頻度の高い社会的併存症状：：精神障害がない者における有病率を 1 とした場合の性・年齢調整済みオッズ比

表 3.統合失調症例の予測値と観察値：機械学習とロジスティック回帰式の比較

		機械学習		ロジスティック回帰式	
観察値（統合失調症）	あり	19	24	16	27
	なし	346	11	337	20
		なし	あり	なし	あり
		予測値（統合失調症）		予測値（統合失調症）	
		感度	0.56	感度	0.63
		特異度	0.97	特異度	0.94
		陽性的中率	0.69	陽性的中率	0.57
		陰性的中率	0.95	陰性的中率	0.95

居(4.55)、世帯収入 300 万円未満(3.76)、未婚(3.49)、定期健康診断未受診(2.20)、低い認知的ソーシャルキャピタル(2.08)、高校・短期大学卒以下の学歴(1.99)、低いソーシャルサポート(1.48)が多く見られた（図7)。詳細は論文報告しており(Matsunaga M, et al. *International Journal of Environmental Research and Public Health* 2023; **20**: 4336.)、本論文を総合研究報告書の資料として別添する。

機械学習モデルの感度、特異度、陽性的中率、陰性的中率は、それぞれ 0.56、0.97、

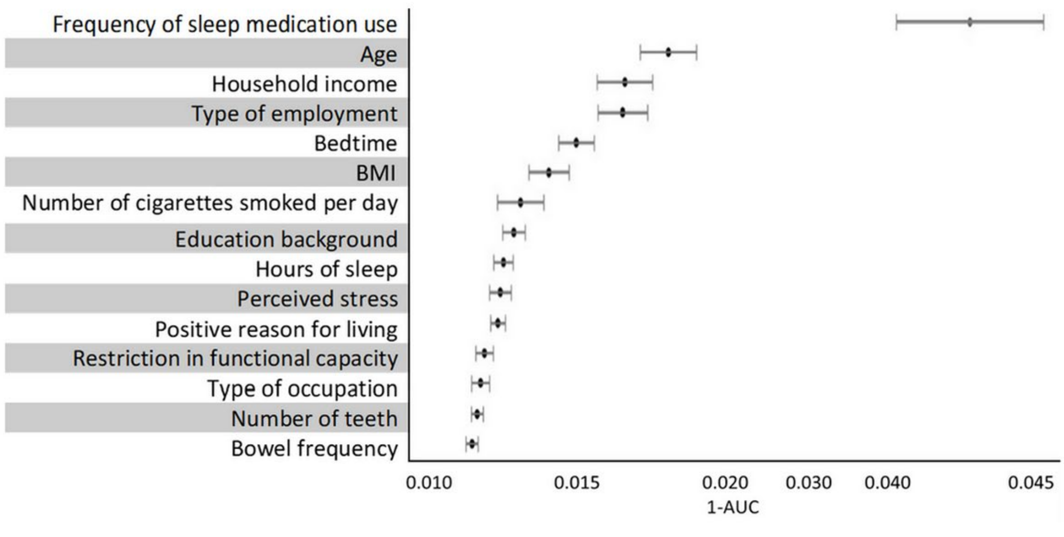


図 8. 判別モデルにおける変数の重要度（1-AUC)
AUC：ROC 曲線（受信者操作特性曲線)下の面積 area under the receiver operating characteristic curve.

0.69、0.95であった（表3）。AUC(0.86 vs. 0.78)、精度（0.93 vs. 0.91)、特異度(0.97 vs. 0.94)、陽性的中率(0.69 vs. 0.57)においてロジスティック回帰モデルよりも優れていた。ロジスティック回帰モデルは感度（0.63 vs. 0.56)において機械学習モデルより優れていた。睡眠薬の使用、年齢、世帯収入、雇用形態が、変数の重要度の上位4位を占めた（図8）。詳細は論文報告しており(He Y, et al. JMIR Formative Research 2024; **7**: e50193.)、本論文を総合研究報告書の資料として別添する。

外的妥当性検証の結果として、統合失調症、MDD、BDと診断された者と、これらの者に統合失調症判別モデルを適用した際の判別結果を表4・5に示す。感度は0.75、特異度は0.44であった。誤診率については、MDDを有する者56人のうち31人（55%)、BDを有する者32人のうち19人（59%）が誤って統合失調症と分類された。詳細は論文報告しており(He Y, et al. *Journal of Clinical Medicine* 2024; **13**: 2970.)、本論文を総合研究報告書の資料として別添する。

3. 研究2（ウ）：大規模疫学研究データベースを利用した有病率推定

一般住民に対しての統合失調症判別モデルの適用については、対象者750人の回答を判別モデルに投入したところ、62人が統合失調症と判別された。粗有病率は8.3% (=62/750)となった。これまでの生涯にわたって精神障害を有してない者とうつ病・双極性障害を有する者において統合失調症と誤診される者が占める7.1%を差し引くと

表4. 統合失調症判別モデルの感度と特異度

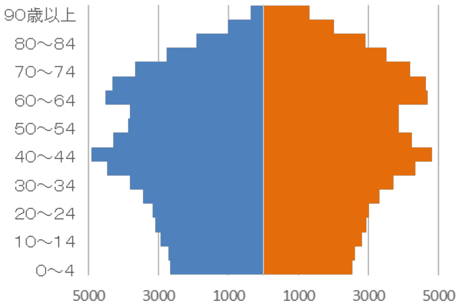
		観測値（精神科医の診断）	
		SZ	MDD + BD + OCD
予測値	SZ (+)	46	50
（判別モデルの結果）	SZ (-)	15	39
合計		61	89
感度		0.75	-
特異度		-	0.44

SZ：統合失調症、MDD：大うつ病性障害、BD：双極性障害、OCD：強迫性障害

表5. 統合失調症判別モデルの誤診率

		観測値（精神科医の診断）		
		MDD	BD	OCD
予測値	SZ (+)	31	19	0
（判別モデルの結果）	SZ (-)	25	13	1
合計		56	32	1
誤診率		0.55	0.59	0

SZ：統合失調症、MDD：大うつ病性障害、BD：双極性障害、OCD：強迫性障害



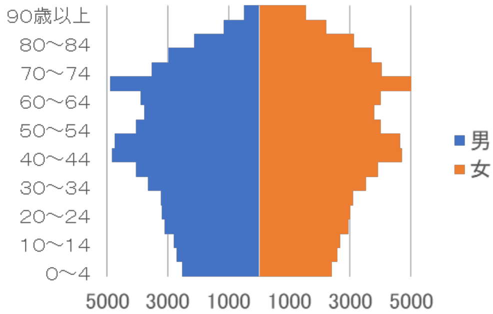


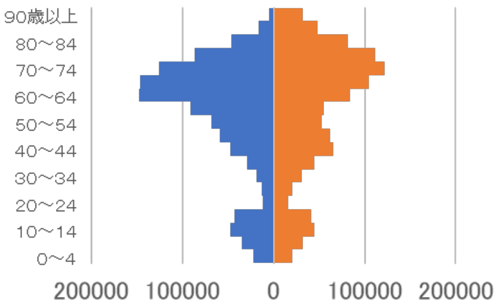
図 9. 平成 26 年（左）と 29 年（右）の推計人口（単位・1000 人）

1.2%となり、その人数は 9.0 人 （= 750 × 0.012）であった。これを元に算出した統合失調症の偽陰性者数は 2.9 人 （= 9.0× 0.326）であった。この 2 者の合計 11.9 人 （= 9.0 + 2.9）を 750 で割った値である 1.59%（95%信頼区間：0.69 - 2.48%）が日本の地域住民における統合失調症等有病率であると推計した。

人工画像化と画像識別を用いて統合失調症判別モデルを作成できるかについては、10,000 回の実験にわたる AUC スコア分布の大半は約 0.88 であり、総じて優れた識別能力が示された。詳細は論文報告しており（He Y, et al. *JAMIA Open* 2024; **7**: ooae012.）、本論文を総合研究報告書の資料として別添する。

4. 研究 3（ア）：レセプトおよび診療録データを使った入院外統合失調症等患者の抽出ロジックの構築

生活保護受給者を統合失調症の有病率推計から除外することの影響は大きくないとする結果が得られた。平成 26 年と 29 年の総務省推計人口（総人口、確定値）では（図 9）、いずれの年も男女ともに 65-74 歳と 40-54 歳の 2 つの年齢階級にピークが認められた。また 39 歳以下の年齢階級では 20-24 歳の年齢階級にわずかな山を認めるものの、おおむね年齢が下がるにつれて人口が減少していた。「被保護者調査」による 6 月の性・年齢別被保護人員数では（図 10）、男では 65-69 歳、女では 75-79 歳の年齢階級が最も多くなっていた。90 歳以上の男を除けば、男女とも 20-24 歳がもっとも少なくなっていた。男では 20-24 歳から最大である 65-69 歳までは単調に増加していたが、女では 20-24 歳から最大である 75-79 歳の中間の 45-49 歳の年齢階級にピークが認められた。0-19 歳の年齢階級では男女とも 10-14 歳が



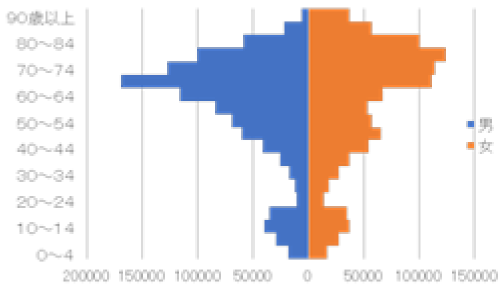


図 10. 平成 26 年（左）と 29 年（右）の被保護者数（単位・人）

もっとも多くなっていた。

平成 26〜令和 2（2014〜2019）年 6 月審査分の生活保護受給者かつ統合失調症による医療扶助の件数が最小だったのは令和 2（2020）年の 42,486 件、最大だったのは平成 26（2014）年の 45,996 件であり、最大と最小の格差は 1.08 倍であった。また、1 か月平均被保護実人員あたりの統合失調症による医療扶助件数の最小値は平成 29(2017) 年の 0.0209、最大値は平成 28（2016）年の 0.0217 であり、最大と最小の格差は 1.04 倍であった。さらに、人口一万人当たり生活保護受給者かつ統合失調症による医療扶助を受けている者の割合の最小値は令和 2(2020) 年の 3.37 人、最大値は平成 28（2016）年の 3.62 人であり、最大と最小の格差は 1.07 倍であった。本研究の結果から、生活保護被保護実人員の 2%強が統合失調症による医療扶助件数を受けていると推定できた。先行研究では統合失調症の有病率は 0.7〜1%程度とされており、生活保護対象者における統合失調症の有病率は一般人口より高いと言える。しかしながら、しかし、人口一万人当たりの生活保護受給者かつ統合失調症による医療扶助を受けている者の人数は 3.37〜3.62 の範囲と推計された。先行研究から人口一万人当たりの統合失調症の患者数を推計すると 70〜100 人（有病率：0.7〜1.0%）となり、これに生活保護受給者かつ統合失調症による医療扶助を受けている者が占める割合は 3〜5%程度と推定され、生活保護受給者を統合失調症の有病率推計から除外することの影響は大きくないと結論づけた。

全体では 44,982,671 件の傷病名が確認され、傷病名の一部に「統合失調」を含む傷病名は 107,568 件（0.24%）であった。入院では 2,708,284 件の傷病名の内、16,488 件が該当し、入院外では 40,156,540 の傷病名の内、84,701 件が該当した。

大規模レセプトデータベースに収載されている傷病名における「統合失調」という文字列を含む傷病名の状況については以下の通りであった。傷病名の一部に「統合失調」を含む傷病名で最も多かったのは「統合失調症」の 100,743 件（93.7%）であった。入院も同様に「統合失調症」の 15,601 件（94.6%）が最多であり、入院外も同様に「統合失調症」の 79,134 件（93.4%）が最多であった。傷病名の一部に「統合失調」を含む傷病名の内、14,092 件（13.1%）が主傷病であった。その中では「統合失調症」の 13,027 件（92.4%）が最多であった。「統合失調」を含む標準病名で、おそらく統合失調症を有すると考えられる傷病名として、「統合失調症」以外に、偽神経症性統合失調症、急性統合失調症、境界型統合失調症、緊張型統合失調症、型分類困難な統合失調症、残遺型統合失調症、小児期型統合失調症、潜在性統合失調症、前駆期統合失調症、体感症性統合失調症、単純型統合失調症、遅発性統合失調症、破瓜型統合失調症、妄想型統合失調症がデータベース上で確認できた。「統合失調」を含む標準病名だが、統合失調症以外の疾病の可能性も考えられる傷病名として、うつ病型統合失調感情障害、急性統合失調症性エピソード、急性統合失調症様精神病性障害、混合型統合失調感情障害、短期統合失調症様障害、統合失調感情障害、統合失調症型パーソナリティ障害、統合失調症型障害、統合失調症後抑うつ、統合失調症症状を伴う急性錯乱、統合失調症性パーソナリティ障害、統合失調症性反応、統合失調症様状態、

躁病型統合失調感情障害がデータベース上で確認できた。「統合失調」を含む標準病名だが、統合失調症以外の疾病の可能性も考えられる傷病名は合計で 4,452 件（4.2%）確認できた。

レセプト傷病名「統合失調症」の妥当性に関して、対象者 987 人中のうち、レセプトに傷病名「統合失調症」の記載があった者は 235 人、真に統合失調症を有していた者は 97 人であった。レセプトに傷病名として記載された「統合失調症」のいずれも「疑い病名」ではなかった。レセプトの傷病名「統合失調症」がなかった者においては、真に統合失調症を有していた者はいなかった。処方された薬のうち、統合失調症に保険適用がある抗精神病薬はシクレスト、エビリファイ、ジプレキサ、セロクエル、クロザリル（以上、第 2 世代抗精神病薬）およびレボトミン（第 1 世代抗精神病薬）の 6 種類であった。対象者における陽性的中率、陰性的中率、感度、特異度を表 9 に示す。レセプトのデータを傷病名「統合失調症」だけに絞って計算した場合、陽性的中率は 41.3%、陰性的中率は 100%、感度は 100%、特異度は 84.5%であった。統合失調症を有さなかった 890 人のうち 138 人（15.5%）のレセプトに傷病名「統合失調症」が付けられていた。これらの者の中で多かった真の病名はうつ病（47 人、34.1%）、双極性障害（31 人、22.5%）、妄想性障害（7 人、5.1%）、神経性食思不振症（6 人、4.3%）であった。いずれかの第 2 世代抗精神病薬の処方情報を加えた場合、陽性的中率は 54.2%と上がったが、感度は 66.0%と大きく下がった。陰性的中率と特異度も下がったが、感度のような大きな低下ではなかった。抗精神病薬の処方を単剤で加えた場合、感度はさらに大きく下がった。

5. 研究 3（イ）：大規模レセプトデータベースを利用した受療率推定

当該期間に少なくとも 1 か月以上被保険者本人あるいは家族であった者の総数は 1156 万 3008 人であった。解析対象条件に該当する者の総数は、 13 万 4013 人で、統合失調症の受療率は 1.16%と推定された。受療率は被保険者本人においては 1.00%、被扶養者においては 1.37%であった。

表9. 陽性的中率、陰性的中率、感度、特異度：2020年9月～2022年8月に入院した患者987人（うち、真に統合失調症を有していた者は97人）のデータから算出

	該当者	うち、真に統合失調症を有する者	陽性的中率（%）	陰性的中率（%）	感度（%）	特異度（%）
1. レセプト傷病名「統合失調症」	235	97	41.3	100	100	84.5
レセプト傷病名+第2世代抗精神病薬						
2. 1+シクレスト	28	18	64.3	91.8	18.6	98.9
3. 1+エビリファイ	63	35	55.6	93.3	36.1	96.9
4. 1+ジプレキサ	28	18	64.3	91.8	18.6	98.9
5. 1+セロクエル	19	5	26.3	90.5	5.2	98.4
6. 1+クロザリル	15	15	100	91.6	15.5	100
7. 1+第2世代のいずれか1つ以上	118	64	54.2	96.2	66.0	93.9
レセプト傷病名+第1世代抗精神病薬						
8. 1+レボトミン	5	3	60.0	60.0	3.1	99.8

6.　研究 4：両データに基づく有病率の比較

大規模疫学研究データを用いて推計した統合失調症有病率は 1.59%であった。これに統合失調症等の受療率の比である入院：外来＝2.83：1 を当てはめると、入院部分は 1.17%、外来部分は 0.42%となった。レセプトデータを用いて推定した統合失調症受療率は 1.16%であった。これにレセプト傷病名「統合失調症」の陽性的中率である 41.3%を掛けると 0.48%となった。さらに統合失調症等の受療率の比である入院：外来＝2.83：1 を当てはめると、入院部分は 0.35%、外来部分は 0.13%となった。以上の結果を元に推定した日本の一般住民における入院外の統合失調症有病率は 1.24%(= 1.59% － 0.35%)となった。

D．考察

我々は、大規模疫学研究データを用いて推定した統合失調症有病率およびレセプトデータを用いて推定した統合失調症受療率を利用して、日本の一般住民における入院外の統合失調症有病率を推定した。得られた 1.24%という数値は、過大評価されている可能性も考えられる。

大規模疫学研究データを用いた一般住民における入院外統合失調症等の有病率推計については、我々は健康に関連する情報と身体的・精神的・社会的併存症状のデータと機械学習を用いて構築した統合失調症の症例を判別するモデルを利用し、有病率を 1.59％と推計した。この数字は、過去に統合失調症を発症し、現在は治療を必要としないまでに回復している者が含まれた生涯有病率であった可能性がある。我々の構築した統合失調症判別モデルでは、睡眠薬の使用、年齢、世帯収入、雇用形態が変数の重要度の上位 4 位を占めていた。統合失調症を発症した後に治療が必要ないまで回復した者においても、世帯収入や雇用形態と言った社会経済的要因は発症前の状態に戻らず悪いままであることがある。このような者が含まれた有病率は時点有病率というよりも生涯有病率に近く、有病率が高めに推計された可能性がある。

レセプトデータに基づく統合失調症受療率の推計において利用したのは健康保険組合のレセプトデータである。被用者が加入する健康保険であるため、労働者ではない者が含まれる一般住民に比べて統合失調症の有病率が低く過小評価された可能性がある。家族が本人より受療率が高くなっていたのは、統合失調症を有する場合には常勤として健保組合を有するような企業に就労し続けることが困難であるためと考えられる。

大規模疫学研究データで利用したサンプルおよびレセプトデータの対象者において発生している統合失調症の重症度の分布は、母集団（日本国民全体）と同じではない可能性がある。本研究では、大規模疫学研究データを用いて推定した統合失調症有病率およびレセプトデータを用いて推定した統合失調症受療率の入院・外来比は、患者調査で得られた受療率の入院・外来比と同じと仮定した。しかし、この仮定が正しくない可能性も考えられる

過去に統合失調症を有していた者は、いったん寛解した後に再発して精神保健・医療・福祉サービスを必要とする可能性を潜在的に抱えている者であるとも考えられる。

医療・保健・福祉サービスの適切な供給量を考える上では、現に統合失調症の治療を受けている者だけの有病率ではなく、このような過去に統合失調症を発症した者も含めた有病率が必要ではないだろうか。我々の構築した統合失調症判別モデルはそのような者を含めた有病率を推計したという点で一定の価値を有すると考える。

Ｅ．結論

疫学的手法と機械学習を利用して開発した統合失調症判別モデルを日本の一般住民サンプルに適用し、日本の地域住民における統合失調症等有病率が 1.59%であると推計した。健康保険組合のレセプトデータを利用して、健康保険組合のレセプトデータを用いて受療率を算出した結果、統合失調症の受療率は1.16%と推定された。これら元に推定した日本の一般住民における入院外の統合失調症有病率は 1.24%(= 1.59% - 0.35%)となった。この数値は生涯有病率を推計した可能性もあり、現時点で治療を必要とする者に限った有病率よりは高く推計された可能性も考えられる。

Ｆ．健康危険情報

該当なし

Ｇ．研究発表

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Ｈ. 知的財産権の出願・登録状況（予定を含む。）

１．特許取得

- 人工画像データ生成装置、予測装置、人工画像データ生成方法、予測方法、及びプログラム（出願中、He Yupeng）

２．実用新案登録

なし

３．その他

なし

資料. 本研究で使用した個人特性と身体的・精神的・社会的併存症状を尋ねるアンケート調査における質問項目一覧

あなたの年齢は?　【＊＊歳】

あなたの性別は？　【男、女】

現在の身長は？　【＊＊＊cm】（小数点以下は四捨五入する）

現在の体重は？　【＊＊＊kg】（小数点以下は四捨五入する）

自分の歯は何本ありますか?　【＊＊本】

治療してかぶせた歯やさし歯は、自分の歯として数えます。

インプラントは、自分の歯として数えません。

現在の結婚状況についてお聞きします。 1 つだけマークして下さい。

【結婚・再婚・内縁、離婚、別居、死別、未婚】

現在、どなたと一緒にお住まいですか?同居しているすべての人にマークして下さい。

【配偶者、子供、両親、その他、独り暮らし】

→　現在の同居人数は何人ですか？　【＊＊＊人】(うち､14 歳未満の子供【＊＊人】)

（あなたは含めません。）

今までに、医師から次の病気があるといわれたり、次の手術を受けましたか?

あてはまるものをすべてマークして下さい。

病気

がん：【胃がん、大腸がん、肺がん、肝がん、乳がん、前立腺がん、その他のがん】

循環器疾患：【心筋梗塞、狭心症、脳卒中(脳出血・脳こうそく・くも膜下出血)

心不全、心房細動、高血圧、その他の心臓の病気】

その他の疾患：【糖尿病、高コレステロール血症（高脂血症・脂質異常症）、痛風

ぜんそく、慢性閉塞性肺疾患(COPD)、慢性気管支炎

慢性腎不全(腎透析を含む)、白内障、緑内障

胃ポリープ、大腸ポリープ、胃かいよう、十二指腸かいよう

慢性肝炎・肝硬変、胆石、尿管結石・腎結石

睡眠時無呼吸症候群(睡眠呼吸障害)、うつ病

腰の骨折、腕か手首の骨折、大腿骨(太ももの骨)の付け根の骨折

（骨折は交通事故・転落・労務上の事故を除く）】
上記以外の病気
内視鏡手術：【胃、大腸、その他の部位】
手術：【心臓(バイパス術）、心臓(弁置換術)
胃、大腸、肺、肝臓、胆のう(胆石)、乳房、子宮
卵巣、前立腺、その他の部位】

あなたは昨年 1 年間に、市町村や職場で提供される健診・検診や、個人的に病院などで受ける 健診・検診(人間ドックなど)を受けましたか?
「受けた」と答えた方は、何を受けたか、あてはまるものすべてにマークして下さい。
【受けた、受けていない】
→ 【定期健康診断·一般住民健診(がん検診を除く）
胃がん検診、肺がん検診、大腸がん検診、子宮がん検診
乳がん検診、前立腺がん検診】

便通はどのくらいの頻度でありますか?
【週に 3 回未満、週に 3~4 回、週に 5~6 回、毎日 1 回、毎日 2 回以上】

普段の大便の状態は?
【下痢便、軟便、普通の便、硬い便、特に硬い便、下痢と便秘を繰り返す】

昨年 1 年間、睡眠は通常どのくらいとっていましたか?
【5 時間以下、6 時間、7 時間、8 時間、9 時間、10 時間以上】

昨年 1 年間、あなたは通常何時頃、寝床につきましたか?
【午後 7 時頃以前、午後 8 時頃、午後 9 時頃、午後 10 時頃、午後 11 時頃、午前 0 時頃
午前 1 時頃、午前 2 時頃、午前 3 時頃、午前 4 時頃、夜勤などがあり不規則】

過去 1 か月間の睡眠の状態についておうかがいします。
寝床についてから 30 分以内に眠れなかったことがありましたか?
【ほとんどない、週に 1 回未満、週に 1~2 回、週に 3~4 回、週に 5~6 回、ほぼ毎日】
夜間または早朝に目が覚めたことがありましたか?
【ほとんどない、週に 1 回未満、週に 1~2 回、週に 3~4 回、週に 5~6 回、ほぼ毎日】
朝起きたときにひどく疲れた感じがありましたか?
【ほとんどない、週に 1 回未満、週に 1~2 回、週に 3~4 回、週に 5~6 回、ほぼ毎日】

あなたは過去 1 か月間において、どのくらいの頻度で、眠るための薬(処方薬や 市販薬)を服用しましたか?

【なし、週に 1 回未満、週に 1~2 回、週に 3~4 回、週に 5~6 回、毎日】

生まれてからこれまでに、合計して少なくとも 100 本以上のたばこを吸っていますか?

【はい、　→　現在もたばこを吸っていますか？

【吸っている、　→　何歳から吸い始めましたか？　【＊＊歳】

→　一日何本吸いますか？　【＊＊本】

やめた】　→　何歳の時たばこをやめましたか？　【＊＊歳】

→　何歳から吸い始めましたか？　【＊＊歳】

→　一日何本吸っていましたか？　【＊＊本】

→　やめた理由はなんですか？

【病気をしたから、病気はしないが健康に悪いから、

その他（経済的理由など)】

いいえ】

現在、お酒を飲みますか？

【飲む、　→　どのくらいの頻度で飲みますか?

【ほとんど飲まない、　→　次の質問へ

月に 1〜3 日、週に 1〜2 日、週に 3〜4 日、週に 5〜6 日、毎日飲む】

→　１日に飲む、もっとも普通の組み合わせを選んでください。

（例）ふだんビールを大ビン 1 本飲んだあとに、日本酒を 2 合飲むなら、

「ビール」のところの「 1 本」と、「日本酒」のところの「 ２合」をぬりつぶし

「焼酎・泡盛」「ウィスキー」「ワイン」のところは「飲まない」をぬりつぶす。

・日本酒　1 合(180ml)

【飲まない、0.5 合未満、0.5〜1 合未満、1 合、2 合、3 合、4 合、5 合以上】

・焼酎・泡盛　原液 1 合(180ml)で

(チューハイ 350ml 缶 1 本を 0. 7 合と換算して下さい)

【飲まない、0.5 合未満、0.5〜1 合未満、1 合、2 合、3 合、4 合、5 合以上】

・ビール(発泡酒)大ビン（633ml)で

（中ビン又は 50 伽缶を 0.8 本、小ピン又は 350ml 缶を 0.6 本と換算して下さい)

【飲まない、0.5 本未満、0.5〜1 本未満、1 本、2 本、3 本、4 本、5 本以上】

・ウィスキー・ブランデー シングル（30ml）で

【飲まない、0.5 杯未満、0.5〜1 杯未満、1 杯、2 杯、3 杯、4 杯、5 杯以上】

・ワイン　グラス（100ml）で

【飲まない、0.5 杯未満、0.5〜1 杯未満、1 杯、2 杯、3 杯、4 杯、5 杯以上】

やめた、　→　何歳のときにお酒をやめましたか？　【＊＊歳】
　　　　　→　やめた理由はなんですか？
　　　　　　　【病気をしたから、病気はしないが健康に悪いから、
　　　　　　　　その他（経済的な理由など）】
飲まない】　→　次の質問へ

昨年 1 年間の「身体の動かし方」についておたずねします。

昨年 1 年間のうち、通常の時期の 1 日の時間の内訳を教えて下さい。
通動、仕事、家事などの時間をすべて含めてお答え下さい。余暇は含めません。

時間の内訳（通勤・仕事・家事などの時間）
座っている時間、立っている時間、歩いている時間、力のいる作業をしている時間
上記項目のそれぞれに対して、以下の時間を選択する。
【なかった、1 時間以上 3 時間未満、3 時間以上 5 時間未満、5 時間以上 7 時間未満、
7 時間以上 9 時間未満、9 時間以上 11 時間未満、11 時間以上】

余暇での「身体の動かし方」についておたずねします。昨年、次のことを行う頻度と 1 回当たりの時間はどのくらいでしたか。頻度と時間のそれぞれにマークして下さい。

余暇での体の動かし方
散歩などでゆっくり歩く、ウォーキングなど早足で歩く、
ゴルフ・ゲートボール・庭いじりなどの 軽・中程度の運動、
テニス・ジョギング・エアロビクス・水泳 などの激しい運動

上記項目に対して、以下の頻度と時間を選択する。
頻度：【月に 1 回未満、月に 1〜3 回、週に 1〜2 回、週に 3〜4 回、ほぼ毎日】
1 回当りの時間：【30 分未満、30〜59 分、1〜2 時間未満、2〜3 時間未満、
3〜4 時間未満、4 時間以上】

あなたの現在の状況について、以下の質問にお答え下さい。
必要な時に、あなたの話を聞いてくれる人がいますか?
【ほとんどいない、たまにいる、ときどきいる、よくいる、いつでもいる】
なにか困ったことがあった時、よいアドバイスをくれる人がいますか?
【ほとんどいない、たまにいる、ときどきいる、よくいる、いつでもいる】
あなたを心配したり、あなたに愛情をかけてくれる人はいますか?

【ほとんどいない、たまにいる、ときどきいる、よくいる、いつでもいる】

日常の家事をしたり、手伝ってくれる人はいますか?

【ほとんどいない、たまにいる、ときどきいる、よくいる、いつでもいる】

あなたに情緒的な支えを与えてくれるような人、(たと えば、あなたの直面する問題について相談できる人、 難しい判断が必要な時に助けてくれる人)はいますか?

【ほとんどいない、たまにいる、ときどきいる、よくいる、いつでもいる】

必要な時にいつでも連絡がとれる、親しくて、信頼・信用できる人はいますか?

【ほとんどいない、たまにいる、ときどきいる、よくいる、いつでもいる】

気軽に個人的な相談ができる親しい友人は何人いますか?

【0 人、1 人、2 人、3 人以上】

気軽に個人的な相談ができる親類は何人いますか?

【0 人、1 人、2 人、3 人以上】

地域組織、自助集団、チャリティー、ボランティアグループや、 宗教団体などの集まりにどれくらいの頻度で参加していますか?

【全く／ほとんど参加しない、時々参加する、週に 1 回未満、週に 1 回以上】

あなたは、生きがいがあると感じていますか?

【非常にある、ある、あまりない、まったくない】

あなたはご自分がどれくらい幸せだと感じていますか?

【大変幸せ、幸せ、どちらとも言えない、幸せでない】

最近 1 週間の体や心の状態について、お聞きします。それぞれ最も当てはまる選択肢 1 つにマークして下さい。

食べたくない。食欲がおちた。

【全く／ほとんどなかった、たまにあった（1〜2 日)、しばしばあった（3〜4 日)、いつもあった（ほぼ毎日)】

ゆううつだ。

【全く／ほとんどなかった、たまにあった（1〜2 日)、しばしばあった（3〜4 日)、いつもあった（ほぼ毎日)】

何をするのも面倒だ。

【全く／ほとんどなかった、たまにあった（1〜2 日)、しばしばあった（3〜4 日)、いつもあった（ほぼ毎日)】

なかなか眠れない。

【全く／ほとんどなかった、たまにあった（1～2 日）、しばしばあった（3～4 日）、
いつもあった（ほぼ毎日）】

生活について満足して過ごせる。

【全く／ほとんどなかった、たまにあった（1～2 日）、しばしばあった（3～4 日）、
いつもあった（ほぼ毎日）】

一人ぼっちでさびしい。

【全く／ほとんどなかった、たまにあった（1～2 日）、しばしばあった（3～4 日）、
いつもあった（ほぼ毎日）】

皆がよそよそしいと思う。

【全く／ほとんどなかった、たまにあった（1～2 日）、しばしばあった（3～4 日）、
いつもあった（ほぼ毎日）】

毎日が楽しい。

【全く／ほとんどなかった、たまにあった（1～2 日）、しばしばあった（3～4 日）、
いつもあった（ほぼ毎日）】

悲しいと感じる。

【全く／ほとんどなかった、たまにあった（1～2 日）、しばしばあった（3～4 日）、
いつもあった（ほぼ毎日）】

皆が自分を嫌っていると感じる。

【全く／ほとんどなかった、たまにあった（1～2 日）、しばしばあった（3～4 日）、
いつもあった（ほぼ毎日）】

仕事が手につかない。

【全く／ほとんどなかった、たまにあった（1～2 日）、しばしばあった（3～4 日）、
いつもあった（ほぼ毎日）】

あなたの気持ち、考えなどについてお伺いします。

過去 1 か月、「人生での大切な事が自分の思うように ならない」と感じましたか?

【全くない、ほとんどない、ときどき、頻繁に、とても頻繁に】

過去 1 か月、「自分の問題を解決する能力に自信がある」 と感じましたか?

【全くない、ほとんどない、ときどき、頻繁に、とても頻繁に】

過去 1 か月、「思うように物事がいっている」と感じましたか?

【全くない、ほとんどない、ときどき、頻繁に、とても頻繁に】

過去 1 か月、「多くの困難が山積みで自分の手に負えない」と感じましたか?

【全くない、ほとんどない、ときどき、頻繁に、とても頻繁に】

あなたの周りの状況について、以下の質問にお答え下さい。

一般的に、人は信用できると思いますか?

【全く思わない、あまり思わない、思う、非常によく思う】

多くの人は隙さえあれば、他の人を利用しようとするものだと 思いますか?

【全く思わない、あまり思わない、思う、非常によく思う】

多くの場合、人は他の人の役に立とうとすると思いますか?

【全く思わない、あまり思わない、思う、非常によく思う】

あなたは、パソコン(コンピュータ)や携帯電話を使って、どのくらいの頻度で、 インターネットやメールのやりとりをしていますか?

【まったくしない、週に 1 日未満、週に 1~2 日、週に 3~4 日、週に 5~6 日、毎日】

→　使用する日の利用時間　1 日約【＊＊時間】

学校教育はどのくらいまで受けられましたか? 1 つだけマークして下さい。

【中学校、高校、短大卒・専門学校・ 4 年制大学中退、大学以上】

現在の従事している職業は何ですか?

【無職、主婦、専門的・技術的職業従事者、管理的職業従事者、
事務従事者、販売従事者、サービス職業従事者、保安職業従事者、
農業漁業作業者、運輸・通信従事者、生産工程・労務作業者、分類不能の職業】

現在従事されているお仕事の雇用形態は何ですか?

【正社員・職員、契約社員・職員、派遣社員・職員、パート・アルバイト、自営・経営者】

現在の世帯年収(税込み)はどのくらいですか?

【0~299 万円、300~599 万円、600~899 万円、
900~1199 万円、1200~1499 万円、1500 万以上】

最近 5 年以内に食習慣が大きく変わりましたか?

【変わらない、1 年以内に変わった、1～2 年前に変わった、3～5 年前に変わった】

→　変わったのはなぜですか？（いくつでもマークしてください）

【病気になったため、検査などで異常があったため、
健康にいいと思ったから、好みが変わった、その他】

ついつい食べ過ぎてしまう方ですか?　【はい、いいえ】

食べる速さはどのくらいですか?

【かなり速い、やや速い、ふつう、やや遅い、かなり遅い】

「朝食」は、どれくらいの頻度で食べますか?
【月に 1 回未満、月に 1~3 回、週に 1~2 回、週に 3~4 回、週に 5~6 回、毎日食べる】

「外食」は、どれくらいの頻度でしますか?(店で買った弁当やおにぎりは、外食に数える)
【月に 1 回未満、月に 1~3 回、週に 1~2 回、週に 3~4 回、週に 5~6 回、毎日する】

「インスタント食品」は、どれくらいの頻度で食べますか?(ラーメン・カップ麺・レトルト食品など)
【月に 1 回未満、月に 1~3 回、週に 1~2 回、週に 3~4 回、週に 5~6 回、毎日食べる】

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REVIEW ARTICLE

NEUROPSYCHOPHARMACOLOGY REPORTS

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Recent findings on subjective well-being and physical, psychiatric, and social comorbidities in individuals with schizophrenia: A literature review

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Abstract

Aim: Care for people with schizophrenia is shifting the locus from long-stay mental hospitals to nonspecialized community-based settings. Knowledge on the care is not a sole property of psychiatric specialists. Community healthcare workers who do not specialize in psychiatry are recommended to learn more about schizophrenia. This review aimed to summarize recent findings on subjective well-being and physical, psychiatric, and social comorbidities in individuals with schizophrenia.

Methods: A literature review was conducted. We retrieved findings from existing systematic reviews and meta-analyses as our preferred method. When data were not available, we referred to other types of studies.

Results: As per our review, individuals with schizophrenia demonstrated poor subjective well-being, happiness, and life satisfaction despite individual differences. Pharmacotherapy caused weight gain and constipation, whereas race and hospitalization might affect weight reduction. Individuals with schizophrenia demonstrated poor oral health, a high prevalence of noncommunicable diseases, and unique eating behaviors. Depression, sleep disorders, smoking, and alcohol and drug consumption were frequently found in the individuals. Research findings regarding problematic internet and smartphone use and stress perception were limited. Low health literacy and neglect of preventable behaviors were frequently seen in individuals with schizophrenia. They tended to be less educated, poor, unemployed, unmarried/unattached, and had poor social cognition, resulting in little social support and a small social network.

Conclusion: Retrieving recent data, we confirmed that individuals with schizophrenia had poor subjective well-being and suffer from various physical, psychiatric, and social comorbidities.

KEYWORDS
comorbidity, epidemiology, literature review, schizophrenia, subjective well-being

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1 | INTRODUCTION

Mental disorders have drawn much attention worldwide in recent years.[1] Schizophrenia is a common mental disorder that affects more than 20 million people worldwide.[2] A systematic review reported a median 12-month and lifetime prevalence of 0.33% and 0.48%.[3] Another systematic review demonstrated a median point, 12-month, and lifetime prevalence as high as 0.39%, 0.40%, and 0.75%, respectively.[4] In Japan, Okui estimated the point prevalence of schizophrenia, including schizotypal and delusional disorders, to be approximately 0.7% by using the national data of the Patient Survey.[5] Japan has more than 300000 psychiatric care beds.[6] It is by far the biggest number among the member countries of the Organization for Economic Co-operation and Development (OECD).[7] About half of psychiatric inpatients suffer from schizophrenia or its allied disorders, and more than 70% of those are admitted for more than a year.[6]

The World Health Organization (WHO) advocates the deinstitutionalization of individuals with schizophrenia, that is, a shift of the locus of care for people with mental disorders from long-stay mental hospitals to nonspecialized community-based health settings to provide comprehensive, integrated, and responsive mental health and social care in the Comprehensive Mental Health Action Plan 2013–2030.[8] In these circumstances, knowledge on the care is not a sole property of psychiatric specialists. Community healthcare workers who do not specialize in psychiatry are recommended to learn more about schizophrenia. Individuals with schizophrenia exhibit various symptoms, including positive (eg delusions, hallucinations) and negative (eg blunted affect, avolition) symptoms, which lead to physical, psychiatric, and social comorbidities.[9,10] This review summarizes relevant recent findings.

2 | METHOD

In this review, we targeted the physical, psychiatric, and social comorbidities along with subjective well-being, happiness, and life satisfaction. Overweight and obesity, oral health, noncommunicable diseases (NCDs), constipation, and eating behaviors were examined as physical comorbidities. Depression and sleep disorders; smoking, alcohol, and drug consumption; problematic internet and smartphone use; and stress perception and allostatic load were adopted as psychiatric comorbidities. Social comorbidities included health literacy and behaviors, socioeconomic status (such as education, employment, income, marital status, and family structure), and social cognitive bias, support, and network. Using these terms, potentially relevant papers were collected. We retrieved the findings from existing systematic reviews and meta-analyses as our preferred method. When they were not available, we referred to existing cohort, case–control, and cross-sectional studies. We searched the literature published up to February 2022 through PubMed. The existing research employed for this review was limited to clinical and epidemiological studies written in English.

TABLE 1 Summary of findings

Subjective well-being, happiness, and life satisfaction
Worsened subjective well-being, happiness, and life satisfaction at a group level but varied by individual.
Overweight and obesity
High prevalence of obesity but varied by race.
Consequence of antipsychotics.
Oral health
Poor oral health: the greater number of missing and decayed teeth.
Noncommunicable diseases
High prevalence of chronic obstructive pulmonary disease, metabolic syndrome, type 2 diabetes, hypertension, and hypertriglyceridemia.
Constipation
Constipation and ileus caused by psychotropic medications, especially clozapine.
Eating behaviors
High dietary energy, sodium, and saturated fat.
Poor diet in fiber, fruit, and unsaturated fatty acids.
Depression and sleep disorders
High prevalence of comorbid major depressive disorder and sleep disturbances.
Smoking, alcohol, and drug consumption
High prevalence of smoking, drinking, and drug consumption.
Problematic internet and smartphone use
Problematic internet and smartphone use reported in South Korea.
Stress perception and allostatic load
Inconsistent evidence on whether to perceive more stress.
Related to greater allostatic load.
Health literacy and behaviors
Low health literacy and poor understanding of preventive behaviors.
Socioeconomic status: education, employment, income, marital status, and family structure
Low employment rate and income.
Less educated and likely to be unmarried/unattached.
Social cognitive bias, support, and network
Low ability to navigate social cues and behaviors.
Deficits in building relationships; lack of social support, community integration, and friends; and small size of social network.

3 | RESULTS

We summarized the results in Table 1.

3.1 | Subjective well-being, happiness, and life satisfaction

A Canadian cross-sectional study by Fervaha et al[11] revealed that young adults with schizophrenia demonstrated worse subjective

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well-being and less happiness and life satisfaction than those without schizophrenia at a group level. Similar findings were confirmed in other studies on adults in Spain[12] and United States.[13] It was concurrently reported that a substantial number of individuals with schizophrenia felt high levels of subjective well-being[11] and happiness.[13] Evidence for improvement of their subjective well-being by pharmacological treatment and psychosocial therapy has been clarified.[14,15] Gutiérrez-Rojas et al[12] also reported that cognitive impairment might modulate the relationship between subjective happiness and functioning.

3.2 | Physical comorbidities

3.2.1 | Overweight and obesity

A meta-analysis reported that almost half of the individuals with schizophrenia were obese.[16] Whether those with schizophrenia were overweight or obese might differ according to the treatment they were receiving. A review by Shah et al[17] indicated that compared to healthy controls, individuals with schizophrenia who were antipsychotic-naive and minimally treated showed lower body mass indices (BMIs) and no difference in waist circumferences. Antipsychotics would make those with schizophrenia overweight and obese. A review by Tarricone et al[18] exhibited that weight and BMIs of antipsychotic-naive patients increased after the beginning of antipsychotic medications. Another systematic review presented those antipsychotic medications, such as haloperidol, olanzapine, quetiapine, and risperidone, except for ziprasidone, were associated with weight gain and BMI increase in individuals with first-episode psychosis.[19] The longer the duration of antipsychotic medication, the higher the weight gain.[19]

Weight gain in individuals with schizophrenia may differ according to race. A meta-analysis reported that Asian people presented lower weight gain than Western counterparts.[19] A systematic review focused on underweight in individuals with schizophrenia and reported a high pooled prevalence of underweight of 17.6% in Japanese inpatients with schizophrenia, nearly 3-fold higher than that in the patients worldwide.[20]

3.2.2 | Oral health

We found two meta-analyses reporting poor oral health in individuals with schizophrenia.[21,22] In both of them, individuals with schizophrenia had higher decayed, missing, and filled teeth (DMFT) index scores. They had the greater number of missing and decayed teeth, but with fewer number of filled teeth, compared to healthy controls.

3.2.3 | Noncommunicable diseases (NCDs)

Individuals with schizophrenia were more likely to suffer from NCDs. A systematic review showed an about 1.5-fold greater likelihood of suffering from comorbid chronic obstructive pulmonary disease in those with schizophrenia compared to the general population.[23] Meta-analyses reported a high prevalence of metabolic syndrome of more than 30% in those with schizophrenia.[16,24] Previous studies reported the prevalence of type 2 diabetes in individuals with schizophrenia, ranging between 8% and 23.3%.[25] Some studies also reported the genetic predisposition for comorbidity of schizophrenia and type 2 diabetes.[26,27] A meta-analysis indicated that about 19% of those with schizophrenia had hyperglycemia.[16] It also showed that 38.7% and 39.3% of individuals with schizophrenia had hypertension and hypertriglyceridemia, respectively.[16]

3.2.4 | Constipation

Constipation often occurs in individuals with schizophrenia. The association between clozapine and constipation and ileus has been well examined. A meta-analysis estimated that nearly one-third of individuals with schizophrenia who were using clozapine experienced constipation.[28] This study also reported that clozapine induced constipation more frequently than other antipsychotics. Another study showed that clozapine doubled the risk of ileus compared with other psychotropic medications.[29] It caused fatal ileus more frequently than other psychotropic medications.

3.2.5 | Eating behaviors

We found two systematic reviews that focused on the eating behaviors of individuals with schizophrenia. One suggested that those with schizophrenia consumed higher dietary energy and sodium compared to healthy controls.[30] Another revealed that, compared to healthy controls, those with schizophrenia were more likely to consume a poor diet in fiber, fruit, and unsaturated fatty acids and a diet rich in saturated fat.[31]

3.3 | Psychiatric comorbidities

3.3.1 | Depression and sleep disorders

Depression is also prevalent in individuals with schizophrenia. A systematic review reported that a pooled estimate of the prevalence of the comorbid major depressive disorder was 32.6% in those with schizophrenia.[32] It is suggested that even individuals with first-episode schizophrenia indicated depressive symptoms more frequently than healthy controls.[33] Existing findings were inconsistent regarding which of the two, patients with early- or chronic-stage schizophrenia, expressed more severe depression.[33] No significant difference in the rates of major depressive disorder was detected between patients with first-episode schizophrenia and schizoaffective disorder.[34]

Sleep disturbances are often observed in individuals with schizophrenia. A systematic review reported that those with remitted

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schizophrenia showed a longer sleep duration, time in bed, and sleep latency than the healthy control.[35] Another study found that insomnia (50%) and nightmare disorder (48%) were the most prevalent sleep problems among individuals with schizophrenia.[36] Sleep disruption predicts the onset and persistence of psychotic experiences such as paranoia and hallucinations.

3.3.2 | Smoking, alcohol, and drug consumption

A multi-institutional study in the United States revealed that smoking, drinking, and drug consumption were more prevalent in those with schizophrenia than in the general population.[37] Smoking was suggested as a risk factor for schizophrenia incidence.[38,39]

3.3.3 | Problematic internet and smartphone use

Problematic internet use, also called internet addiction, is characterized by persistent compulsive use of the internet that interferes with daily life.[40] Lee et al[40] reported that 22% of individuals with schizophrenia spectrum disorders suffered from problematic internet use in South Korea. They were more likely to have high levels of perceived stress and dysfunctional coping strategies.[40] With the popularity of smartphones in recent years, problematic internet use has gradually turned into a form of problematic smartphone use.[41] The South Korean researchers reported that the severity of problematic smartphone use was significantly associated with both high anxiety and low agreeableness.[41] Since the subjects in these studies did not include healthy controls, it is unclear whether internet addiction is comparatively more frequent in those with schizophrenia.

3.3.4 | Stress perception and allostatic load

Stress has been linked to the etiology of schizophrenia because of its significant role in different stages of the illness.[42] Gutiérrez-Rojas et al[12] did, and Nugent et al[42] did not find that individuals with schizophrenia were more likely to perceive stress than healthy controls. Nugent et al focused on allostatic load, that is, the wear and tear of bodily experiences after responding to external stressors. They reported that those with schizophrenia had greater allostatic load compared to healthy controls, and greater allostatic load was found in both individuals with early course and chronic schizophrenia.[42]

3.4 | Social comorbidities

3.4.1 | Health literacy and behaviors

A systematic review highlighted a low health literacy of individuals with schizophrenia.[43] A cross-sectional study reported that those with psychosis, 85% of whom suffered from schizophrenia, demonstrated a lack of understanding of preventive behaviors and poor knowledge of physical illnesses.[44] Compared to the healthy control, they were less likely to undergo regular medical checkups and exercise, and to acknowledge the importance of early cancer detection and controlling NCDs.

3.4.2 | Socioeconomic status: education, employment, income, marital status, and family structure

Systematic reviews have indicated that individuals with schizophrenia tend to be less educated[45] and exhibit a low employment rate[33] than healthy controls. A Chinese study found that a lower income was associated with having schizophrenia at an individual level.[46] Research using Danish population-based data revealed that individuals with schizophrenia were likely to be unmarried/unattached.[47,48] An association between social dysfunction and marital status was found in individuals with schizophrenia in China.[49] A Japanese study reported that approximately 10% of homeless people were diagnosed with schizophrenia or other psychotic disorders.[50]

3.4.3 | Social cognitive bias, support, and network

A meta-analysis indicated that, compared to healthy controls, those with schizophrenia performed worse in social cognition, that is, a low ability to navigate social cues and behaviors inherently dependent on a knowledge base and set of skills.[51] A psychological investigation revealed that social cognitive bias provided information about cognition, symptoms, and functioning related to interpersonal conflict in those with schizophrenia.[52]

It was highlighted that individuals with schizophrenia often had loneliness, deficits in building relationships, and lack of social support, community integration, and friends.[53] A systematic review presented that a smaller social network size was associated with more severe psychiatric symptoms in individuals with schizophrenia.[54] In an Australian nationwide survey, adults with psychotic illness (47% with schizophrenia and 16% with schizoaffective disorder) presented a high frequency of experiencing loneliness (80.1%) and a need for more friends (48.1%).[55]

A study in Taiwan reported a cross-sectional association between a high level of social support, especially support from family, and symptomatic nonremission.[56] A qualitative study in Pakistan suggested the association between social support and the willingness for treatment.[57] With support from family, peers, and friends, they received positive emotional feelings, reduced depression, and gradually accepted regular medication and proper treatment. On the other hand, a systematic review pointed out that evidence for the effectiveness of peer support was insufficient.[58]

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4 | DISCUSSION

Retrieving recent data, mainly from systematic reviews and meta-analyses, we have confirmed that individuals with schizophrenia suffer from poor subjective well-being and various physical, psychiatric, and social comorbidities. Our review helps not only psychiatric specialists but also community healthcare workers who do not specialize in psychiatry learn more about the disorder and its management.

Individuals with schizophrenia had worse subjective well-being and less happiness and life satisfaction than those without at the group level,[11,12] while the substantial heterogeneity among individuals with schizophrenia was appreciable as well.[11,13] This fact contributes to an elimination of the general misconception that all with schizophrenia are helpless. Given that cognition modulated the relationship between subjective happiness and functioning as reported,[12] rehabilitation programs for cognitive impairment might improve recovery outcomes with a focus on subjective happiness in individuals with schizophrenia.[59] Optimizing antipsychotic treatment, as well as psychosocial therapy, would improve subjective well-being for individuals with schizophrenia.[14,15]

For physical comorbidities, we targeted overweight and obesity, oral health, NCDs, constipation, and eating behaviors. Existing reviews indicate pharmacotherapy as a cause of weight gain[17–19] and constipation.[28,29] Race[19,20] and hospitalization[20] can also affect body weight. Individuals with schizophrenia tended to present a low DMFT index score,[21,22] suggesting poor health awareness and few opportunities for dental care, prevention, and treatment. This idea might be supported by a systematic review showing their low health literacy and academic achievement and neglect of preventable behaviors.[43–45] Unique eating behaviors[30,31] and low health literacy and academic achievement[43–45] could have contributed to the high prevalence of NCDs among the population.[16,23–25] Weight gain[16–19] and a high prevalence of smoking and drinking[37] must also be monitored to prevent NCDs. Genetic influences may also account for comorbid diabetes.[26,27]

For psychiatric comorbidities, we examined depression and sleep disorders, smoking, alcohol, and other drug consumption, problematic Internet and smartphone use, and stress perception and allostatic load. Depression and sleep disorders have long been known to be common psychiatric comorbidities. Our review confirms this finding.[32–36] We found a clear indication of high prevalence of smoking, drinking, and drug consumption in the U.S. among individuals with schizophrenia.[37] Problematic internet and smartphone use, an emerging addiction of the 21st century, was so far investigated only in South Korea.[40,41] Such findings should be duplicated in other countries. The existing findings were split regarding stress perception among individuals with schizophrenia.[12,42] More study findings are necessary to clarify this topic.

For social comorbidities, we explored health literacy and behaviors, socioeconomic status, and social cognitive bias, support, and network. As mentioned above, low health literacy and neglect of preventable behaviors were noted in individuals with schizophrenia.[43,44] This could contribute to a high prevalence of NCDs,[16,23–27] which are preventable to some extent. Being less educated,[45] poor,[46] unemployed,[33] and unmarried/unattached[47–49] were found as the features of individuals with schizophrenia. They also tend to perform worse in social cognition.[51] As a result, they would have little social support and a small social network. This finding justifies the necessity of psychosocial treatment such as cognitive behavioral therapy, family interventions, social skills training, and supported employment.[60]

The strength of our review is that we summarized various fields of relevant studies in terms of subjective well-being and physical, psychiatric, and social comorbidities. It is helpful for community healthcare workers who do not specialize in psychiatry. Systematic reviews and meta-analyses were primarily included to ensure the findings are comprehensive and persuasive. We revealed under-researched areas related to well-being and comorbidities in individuals with schizophrenia and also provided indications for promising future research. A limitation of this study is that we did not conduct a systematic review with a meta-analysis. Although we preferred recently published systematic reviews and meta-analyses, our interpretation might have been biased by our subjective choices from the existing literature.

AUTHOR CONTRIBUTIONS

AO conceived the study design; YH, TK, YL, MM, ST, and NI helped complete it. YH, AT, and AO collected and interpreted the references. YH, AT, and AO drafted the manuscript. The other authors revised the manuscript critically for important intellectual content. All authors have approved the final version of the manuscript for publication.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Article

Physical, Psychiatric, and Social Comorbidities of Individuals with Schizophrenia Living in the Community in Japan

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Abstract: The physical, psychiatric, and social comorbidities interfere with the everyday activities of community-dwelling individuals with schizophrenia and increase the risk of their readmission. However, these comorbidities have not been investigated comprehensively in Japan. We conducted a self-reported internet survey in February 2022 to identify individuals aged 20–75 years with and without schizophrenia using a prevalence case-control study. The survey compared physical comorbidities such as being overweight, hypertension, and diabetes; psychiatric comorbidities such as depressive symptoms and sleep disturbances; social comorbidities such as employment status, household income, and social support between participants with and without schizophrenia. A total of 223 participants with schizophrenia and 1776 participants without schizophrenia were identified. Participants with schizophrenia were more likely to be overweight and had a higher prevalence of hypertension, diabetes, and dyslipidemia than participants without schizophrenia. Additionally, depressive symptoms, unemployment, and non-regular employment were more prevalent in participants with schizophrenia than those without schizophrenia. These results highlight the necessity of comprehensive support and interventions addressing physical, psychiatric, and social comorbidities in individuals with schizophrenia in the community. In conclusion, effective interventions for managing comorbidities in individuals with schizophrenia are necessary to enable them to continue to live in the community.

Keywords: community support; comorbidity; depression; epidemiology; schizophrenia

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1. Introduction

Schizophrenia is a common illness with a reported lifetime prevalence of approximately 1% [1]. The World Health Organization's Comprehensive Mental Health Action Plan 2013–2030 advocates for deinstitutionalization of individuals with schizophrenia, shifting the place of care from long-term inpatient psychiatric hospitals to non-specialized community-based health settings and providing comprehensive, integrated, and responsive mental health and social care. In Japan, approximately 150,000 individuals with schizophrenia are hospitalized, representing 60% of admissions for mental and behavioral disorders and 12% of all disease admissions [2]. Since the proposal of "The Vision for Reforming Mental Health Care and Welfare" in 2004, there has been a shift toward community-based care for individuals with schizophrenia [3]. Meanwhile, approximately 15–30% of individuals with schizophrenia are readmitted within 90 days of discharge worldwide [4]. Physical, psychiatric, and social comorbidities have been associated with readmission [5–7]. Investigating the physical, psychiatric, and social comorbidities of individuals with schizophrenia in the community can aid in identifying their needs and improving their care.

Evidence on physical, psychiatric, and social comorbidities associated with schizophrenia is accumulating [1]. For example, physical comorbidities include obesity [8], diabetes [9], hypertension [8], and hyperlipidemia [8]; psychiatric comorbidities include depression [10] and sleep disorder [11]; social comorbidities include low employment rate [12] and functional impairment such as community living and work [13]. In Japan, some comorbidities, such as overweight, hypertension, diabetes, depressive symptoms, quality of life, employment rate, and household income, have been reported [14,15]. However, there are no comprehensive reports on the physical, psychiatric, and social comorbidities of Japan's community-dwelling individuals with schizophrenia [1].

Community-dwelling individuals with schizophrenia face unique challenges related to their physical, psychiatric, and social comorbidities. These comorbidities, such as obesity, depression, and low employment rate [16–18], can make it difficult for individuals with schizophrenia to function in everyday life. In addition, obesity is a risk factor for diabetes, and diabetes is one of the most significant mortality risk factors for individuals with schizophrenia [19]. Depression in individuals with schizophrenia can exacerbate the symptoms of schizophrenia, worsen the quality of life, and increase the risk of suicide [20]. Unemployment in individuals with schizophrenia can reduce the quality of life and place an extended burden on social support and disability services [21–23]. Addressing physical, psychiatric, and social comorbidities in primary care in the community is crucial in improving the health outcomes of individuals with schizophrenia.

To aid in the development of better treatment and support services for individuals with schizophrenia in the community, we conducted an internet survey to compare the prevalence of physical, psychiatric, and social comorbidities between individuals with and without schizophrenia living in the community in Japan.

2. Materials and Methods

2.1. Study Design and Participants

We conducted a prevalence case–control study using an internet research agency's pooled panels (Rakuten Insight, which had approximately 2.3 million panelists in 2022). We collected data from those currently without schizophrenia and those currently with schizophrenia in February 2022.

For those currently without schizophrenia, we sampled 28,000 participants in the Japan Society and New Tobacco Internet Survey (JASTIS) [24] and the Japan COVID-19 and Society Internet Survey (JACSIS) [25–27] conducted by the Rakuten Insight Panel. Responses were obtained from 6656 respondents, who were asked the following questions before the survey. Those who answered no to all four questions were considered not to have schizophrenia: (1) Are you currently suffering from mental illness?; (2) Have you had mental illness in the past?; (3) Have you experienced auditory hallucinations?; (4) Have you ever used stimulants or other illegal drugs, been an alcoholic, or received psychiatric treatment? Finally, we obtained 1776 participants between the ages of 20 and 75 according to the sex and age structure of the Rakuten Insight Panel.

For those currently with schizophrenia, we sampled 5584 individuals aged 20 to 75 years who self-reported schizophrenia in the Rakuten Insight disease panel, a subset of the Rakuten Insight Panel. Responses were obtained from 3256 respondents, who were asked the following questions before the survey. Those who answered yes to all four questions were considered to currently have schizophrenia: (1) Are you currently suffering from schizophrenia only, schizophrenia and migraine, schizophrenia and a sleep disorder, or schizophrenia, migraine, and a sleep disorder?; (2) Have you experienced auditory hallucinations lasting more than one month?; (3) Have you never used stimulants or other illegal drugs and never been an alcoholic?; (4) Have you experienced the first auditory hallucination lasting more than one month at less than 60 years of age? A final response was received from 223 respondents.

2.2. Study Variables

A self-administered questionnaire assessed demographic and health-related backgrounds, physical comorbidities, psychiatric comorbidities, and social comorbidities.

Demographic and health-related backgrounds include age, body mass index (BMI) (underweight: <18.5 kg/m^2, normal: 18.5–24.9 kg/m^2, or overweight: ≥25.0 kg/m^2), smoking status (current, past, or never), reason for quitting smoking (bad for health, illness, or other (e.g., financial reasons)), alcohol drinking (current drinker (≥23.0 g/day of ethanol), current drinker (<23.0 g/day ethanol), ex-drinker, or never drinker), reason for quit drinking (bad for health, illness, or other (e.g., financial reasons)), sports (<1 times per week or ≥1 times per week), tendency to overeat, eating speed (fast, normal, or slow), eating instant foods (<1 times per week, 1–4 times per week, or ≥5 times per week), bowel movement (<3 times per week, 3–7 times per week, or ≥2 times per day), stool (soft, normal, hard, or recurrent diarrhea and constipation), restriction in functional capacity, and bad self-rated health status (SRHS).

- Restriction in functional capacity.
  To evaluate functional capacity restrictions, we used the Scale of Independence in Daily Living for the Disabled Elderly published by the Ministry of Health, Labour and Welfare, Japan [28]. The term "restrictions in functional capacity" refers to a multidimensional concept that involves sensory loss, impaired mobility, vascular disorders, gait impairments, problems with activities of daily living (ADLs), and changes in body systems [29]. Participants self-assessed restrictions by choosing one of the following options: (1) "I have no physical disabilities," (2) "I go out alone, using transportation," (3) "I can only go out alone in my neighborhood," (4) "I go out with help and live mostly out of bed during the day," (5) "I can go out with help, but I go out infrequently, and I spend most of the daytime sleeping on and off in bed," (6) "I can ride in a wheelchair by myself and eat and toilet away from the bed," (7) "I can ride in a wheelchair with assistance.," (8) "I can roll over in bed," and (9) "I cannot roll over in bed." Participants who chose options other than option (1) were regarded as having restrictions in functional capacity. Participants who chose option (1), (2), or (3) were regarded as going out alone.
- Self-rated health status (SRHS).
  SRHS is a self-reported measure of health status that incorporates a person's biological, mental, social, and functional aspects, including individual and cultural beliefs and health behaviors. It is a strong predictor of all-cause mortality in general populations [30]. Participants responded to the question "What do you think of your general health status during the previous month?" by choosing one of the following options: "great," "pretty good," "good," "not so good," and "bad." Participants who answered "not so good" or "bad" were defined as bad SRHS.

Physical comorbidities include overweight, cancer, cardiovascular disease, heart failure, hypertension, diabetes, dyslipidemia, gout, sleep apnea syndrome, and fracture.

Psychiatric comorbidities include depressive symptoms (absent or present), sleep time (<5 h, 6–7 h, 8–9 h, or ≥10 h), hypnagogic disorder (<3 times per week or ≥3 times per week), deep sleep disorder (<3 times per week or ≥3 times per week), middle wakening or early wakening (<3 times per week or ≥3 times per week), perceived stress (absent or present), *ikigai* (absent or present), happiness (absent or present), and internet use time per week (h).

- Depressive symptoms (CES-D).
  We used a modified 11-item Center for Epidemiological Studies Depression (CES-D) Scale in this study [31,32]. The existence of depressive symptoms was defined as a score of 8 or higher.
- Hypnagogic disorder.
  Participants were asked, "In the past month, have you had trouble falling asleep within 30 min of getting to bed?" and answered the question from six options: "almost never,"

"less than once a week," "1–2 times per week," "3–4 times per week," "5–6 times a week," or "almost every day." Participants who answered "3–4 times per week," "5–6 times a week," or "almost every day" were defined as having hypnagogic disorder.

- Deep sleep disorder.
  Participants were asked, "In the past month, have you felt terribly tired when you woke up in the morning?" and answered the question from six options: "almost never," "less than once a week," "1–2 times per week," "3–4 times per week," "5–6 times a week," or "almost every day." Participants who answered "3–4 times per week," "5–6 times a week," or "almost every day" were defined as having deep sleep disorder.
- Perceived stress (PSS-4).
  We assessed perceived stress with a 4-item Perceived Stress Scale (PSS-4) [33]. Scores are on a 16-point scale, with higher total scores indicating more severe perceived stress. Perceived stress was defined as being present when the score was higher than 7, the median of the PSS-4 scores for participants without schizophrenia.
- *Ikigai.*
  The Japanese term "*Ikigai*" is a positive reason for living [34]. Participants were asked, "Do you have any positive reasons to live?" and answered the question from four options: "very much so," "yes," "no," or "not at all." Participants who answered "no" or "not at all" were defined as the absence of *ikigai*.
- Happiness.
  Participants were asked, "How happy do you feel about your life?" and answered the question from four options: "very happy," "happy," "neither happy nor unhappy," and "unhappy." Participants who answered "neither happy nor unhappy" or "unhappy" were defined as the absence of happiness.
- Internet use time.
  Internet use time per week was calculated from the hours of use per day and the frequency of use per week. We defined longtime internet use as more than 14 h, a median of participants without schizophrenia.

Social comorbidities include taking regular medical checkups, educational background (junior/senior high school, university, junior college, or vocational school), occupation (unemployed, homemaker, white-collar workers, or blue-collar workers), type of employment (regular, non-regular, or self-employed/business people), household income (million Japanese yen) (<3, 3–6, 6–9, or $\geq$9), marital status (unmarried, married, divorced, widowed, or others), family structure (living alone, living with parents, living with spouse, living with children, and living with other people), social support, and social capital (cognitive and structural dimensions).

- Non-regular employment.
  A regular employee in Japan is a term used to refer to an employee who does not have a set term of employment, works during scheduled hours, and is employed directly by his or her employer. A non-regular employee in Japan is an employee who does not meet one of the conditions for regular employment. In other words, non-regular employment falls within one or more fixed-term, part-time, or indirect employment.
- Social support.
  Social support was assessed using the ENRICHD Social Support Instrument (ESSI), which is a well-validated and widely used self-report questionnaire designed to assess the availability of social support [35,36]. The ESSI consists of 7 items that assess the perceived availability of social support in different domains, including emotional, instrumental, informational, and appraisal support. The 7 items of ESSI are as follows: (1) "Is there someone available you can count on to listen to you when you need to talk?," (2) "Is there someone available to you to give you good advice about a problem?," (3) "Is there someone available to you who shows you love and affection?," (4) "Is there someone available to help with daily chores?," (5) "Can you count on anyone to provide you with emotional support (for instance, talking over problems or helping you make a difficult decision)?," (6) "Do you have as much contact as you

would like with someone you feel close to and you can trust and confide in?," and (7) "Are you living with your spouse or partner?" For the first six items, participants selected one of the following options: "none (score = 1)," "a little (score = 2)," "some (score = 3)," "most (score = 4)," and "all of the time (score = 5)." For item 7, participants who lived with their spouse or partner received a score of 4 and those who did not received a score of 2. Total scores ranged from 8 to 34, with higher scores indicating higher availability of social support.
In the present study, we defined social support as low when the total score on the ESSI was less than 17, which corresponds to the first quartile of the ESSI scores for participants without schizophrenia.

- Social capital.
Social capital was assessed using the Integrated Questionnaire for the Measurement of Social Capital (SC-IQ) [37], which is a comprehensive and multidimensional self-report questionnaire designed to measure different aspects of social capital, typically described as assets such as social networks, social participation, trust, and reciprocity. In the present study, we focused on cognitive and structural social capital using specific items from the SC-IQ [38]. For cognitive social capital, we used the following three items: (1) "Can most people be trusted?"; (2) "Does one have to be alert or is someone likely to take advantage of you?"; (3) "Are most people willing to help if you need it?" Responses were selected from four categories: "strongly disagree," "disagree," "agree," and "strongly agree." For the three questions, cognitive social capital was defined as high when there were two or more responses of "agree" or "strongly agree" to question (1), "disagree" or "strongly disagree" to question (2), and "agree" or "strongly agree" to question (3). For structural social capital, we used the following item from the SC-IQ: "How often do you participate in community organizations, self-help groups, charities, volunteer groups, or religious gatherings?" The response was selected from four categories: "not at all/very seldom," "sometimes," "less than once a week," and "more than once a week." Structural social capital was defined as high when the response was "more than once a week."

2.3. Statistical Analysis

T-tests were used to compare the averages of continuous variables, and Fisher's exact tests were used to compare the proportions of categorical variables between participants with and without schizophrenia.

A logistic regression analysis was used to calculate sex- and age-adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of participants with schizophrenia compared to participants without schizophrenia for physical comorbidities, psychiatric comorbidities, and social comorbidities. All the analyses were conducted using R4.2.1 software (R Foundation: Vienna, Austria). The level of significance was set at $p < 0.05$ (two-sided).

3. Results

The study presented in Table 1 provides a comparison of demographic and health-related characteristics of participants with and without schizophrenia. Males with schizophrenia were more prevalent (52%) than females with schizophrenia. Overall, males were older than females, but there was no significant difference in age between participants with and without schizophrenia for males. On the other hand, women with schizophrenia were older than women without schizophrenia.

A higher percentage of participants with schizophrenia were overweight (BMI $\geq$ 25) in both sexes (53% for participants with schizophrenia vs. 28% for participants without schizophrenia in men and 39% vs. 9.3% in women, respectively). Smoking was more prevalent among women with schizophrenia. Fewer participants with schizophrenia were drinkers, and more participants with schizophrenia were abstinent drinkers compared to participants without schizophrenia. Eating habits were also compared between the two groups. Overeating was more prevalent among female participants with schizophrenia.

Speed-eating was more prevalent among participants with schizophrenia. Additionally, participants with schizophrenia tended to consume instant foods more frequently. Bowel movements were also compared, and it was found that participants with schizophrenia had more frequent bowel movements and soft stools than participants without schizophrenia.

Table 1. Demographic and health-related backgrounds of participants with schizophrenia and participants without schizophrenia according to sex.

Characteristic	Men			Women		
	Schizophrenic Participants, N = 115	Non-Schizophrenic Participants, N = 801	*p*-Value	Schizophrenic Participants, N = 108	Non-Schizophrenic Participants, N = 975	*p*-Value
Age	48 (9)	48 (13)	0.651	44 (10)	42 (13)	0.014
Body mass index (kg/m^{2})			<0.001			<0.001
≥25	61 (53%)	222 (28%)		42 (39%)	91 (9.3%)	
18.5–24.9	52 (45%)	539 (67%)		56 (52%)	691 (71%)	
<18.5	2 (1.7%)	40 (5.0%)		10 (9.3%)	193 (20%)	
Smoking			0.699			<0.001
Current	32 (28%)	231 (29%)		21 (19%)	73 (7.5%)	
Never	52 (45%)	383 (48%)		76 (70%)	802 (82%)	
Past	31 (27%)	187 (23%)		11 (10%)	100 (10%)	
Reason for quitting smoking of past smoker			0.041			0.231
Bad for health	12 (39%)	113 (60%)		5 (45%)	55 (55%)	
Illness	3 (9.7%)	19 (10%)		2 (18%)	5 (5.0%)	
Other (e.g., financial reasons)	16 (52%)	55 (29%)		4 (36%)	40 (40%)	
Alcohol			<0.001			0.052
Never drinker	53 (46%)	338 (42%)		68 (63%)	599 (61%)	
Ex-drinker	32 (28%)	40 (5.0%)		22 (20%)	123 (13%)	
Current drinker (<23 ethanol g/day)	17 (15%)	190 (24%)		11 (10%)	171 (18%)	
Current drinker (≥23 ethanol g/day)	13 (11%)	233 (29%)		7 (6.5%)	82 (8.4%)	
Reason for quitting drinking of Ex-drinker			0.502			0.008
Bad for health	12 (38%)	20 (50%)		6 (27%)	46 (37%)	
Illness	8 (25%)	6 (15%)		6 (27%)	6 (4.9%)	
Other (e.g., financial reasons)	12 (38%)	14 (35%)		10 (45%)	71 (58%)	
Sports			0.072			0.918
<1 times per week	70 (61%)	413 (52%)		62 (57%)	568 (58%)	
≥1 times per week	45 (39%)	388 (48%)		46 (43%)	407 (42%)	
Tendency to overeat	66 (57%)	406 (51%)	0.195	74 (69%)	569 (58%)	0.049
Eating speed			<0.001			0.005
Fast	82 (71%)	404 (50%)		62 (57%)	399 (41%)	
Normal	19 (17%)	318 (40%)		32 (30%)	419 (43%)	
Slow	14 (12%)	79 (9.9%)		14 (13%)	157 (16%)	
Eating instant foods			0.191			0.206
<1 times per week	57 (50%)	459 (57%)		72 (67%)	672 (69%)	
1–4 times per week	49 (43%)	302 (38%)		30 (28%)	279 (29%)	
≥5 times per week	9 (7.8%)	40 (5.0%)		6 (5.6%)	24 (2.5%)	
Bowel motion			0.190			0.037
<3 times per week	10 (8.7%)	47 (5.9%)		11 (10%)	118 (12%)	
3–7 times per week	79 (69%)	608 (76%)		83 (77%)	798 (82%)	
≥2 times per day	26 (23%)	146 (18%)		14 (13%)	59 (6.1%)	

Table 1. *Cont.*

Characteristic	Men			Women		
	Schizophrenic Participants, N = 115	Non-Schizophrenic Participants, N = 801	*p*-Value	Schizophrenic Participants, N = 108	Non-Schizophrenic Participants, N = 975	*p*-Value
Stool			<0.001			<0.001
Soft	39 (34%)	145 (18%)		25 (23%)	86 (8.8%)	
Normal	59 (51%)	575 (72%)		63 (58%)	726 (74%)	
Hard	12 (10%)	64 (8.0%)		13 (12%)	131 (13%)	
Recurrent diarrhea and constipation	5 (4.3%)	17 (2.1%)		7 (6.5%)	32 (3.3%)	
Restrictions in functional capacity	45 (39%)	59 (7.4%)	<0.001	44 (41%)	45 (4.6%)	<0.001
Self-rated health status			<0.001			<0.001
Bad	51 (44%)	136 (17%)		57 (53%)	142 (15%)	
Not bad	64 (56%)	665 (83%)		51 (47%)	833 (85%)	

Continuous variables were expressed as mean (SD), and categorical variables as number (percentage). *p*-values were calculated with the Welch Two-Sample *t*-test for continuous variables and with Fisher's exact test for categorical variables.

Participants with schizophrenia reported a higher level of functional restriction and bad self-rated health status than participants without schizophrenia. The percentage of those who felt a restriction in functional capacity was small in participants without schizophrenia (7.4% in men and 4.6% in women). In comparison, that percentage was about 40% in participants with schizophrenia (39% in men and 41% in women). A total of 94% of participants with schizophrenia went out daily. Similarly, the proportion of bad self-rated health status was higher among participants with schizophrenia than participants without schizophrenia.

As for physical diseases in participants with schizophrenia, in men, hypertension (18%), diabetes (14%), and dyslipidemia (13%) were common. In women, dyslipidemia (11%), hypertension (7.4%), and diabetes/cancer (6.5%) were common (Table 2).

Table 2. Physical comorbidities of participants with schizophrenia and participants without schizophrenia according to sex.

Characteristic	Men			Women		
	Schizophrenic Participants, N = 115	Non-Schizophrenic Participants, N = 801	*p*-Value	Schizophrenic Participants, N = 108	Non-Schizophrenic Participants, N = 975	*p*-Value
Cancer	2 (1.7%)	30 (3.7%)	0.415	7 (6.5%)	36 (3.7%)	0.187
Cardiovascular disease	3 (2.6%)	13 (1.6%)	0.440	0 (0%)	4 (0.4%)	>0.999
Heart failure	1 (0.9%)	3 (0.4%)	0.416	1 (0.9%)	1 (0.1%)	0.190
Hypertension	21 (18%)	112 (14%)	0.256	8 (7.4%)	32 (3.3%)	0.052
Diabetes	16 (14%)	47 (5.9%)	0.005	7 (6.5%)	9 (0.9%)	<0.001
Dyslipidemia	15 (13%)	51 (6.4%)	0.018	12 (11%)	34 (3.5%)	0.001
Gout	6 (5.2%)	32 (4.0%)	0.462	3 (2.8%)	0 (0%)	<0.001
Sleep apnea syndrome	4 (3.5%)	7 (0.9%)	0.039	1 (0.9%)	2 (0.2%)	0.271
Fracture	3 (2.6%)	6 (0.7%)	0.092	6 (5.6%)	4 (0.4%)	<0.001

Categorical variables as number (percentage). *p*-values were calculated with Fisher's exact test for categorical variables.

Figure 1 shows the results of a sex- and age-adjusted logistic regression model investigating the association between schizophrenia and physical comorbidities. Compared to community dwellers without schizophrenia, community dwellers with schizophrenia more frequently reported a history of fracture (AOR: 7.17, 95% CI = 2.81 to 18.1), sleep apnea syndrome (AOR: 4.04, 95% CI = 1.23 to 11.9), overweight (AOR: 3.85, 95% CI = 2.83 to 5.24), diabetes (AOR: 3.25, 95% CI = 1.90 to 5.44), and dyslipidemia (AOR: 2.60, 95% CI = 1.60 to 4.13).

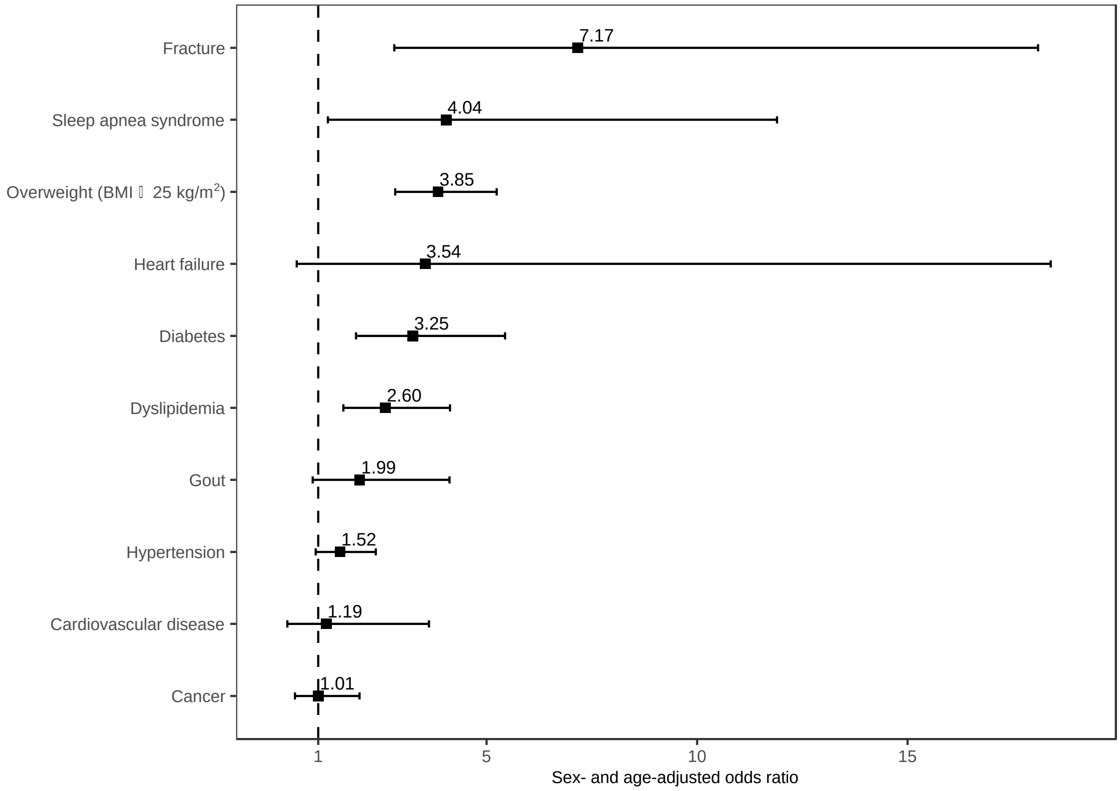

Figure 1. Sex- and age-adjusted odds ratios of participants with schizophrenia compared to participants without schizophrenia in terms of physical comorbidities. Abbreviations: BMI, body mass index. The reference group for overweight is normal BMI (18.5–24.9 kg/m^2).

Table 3 shows the psychiatric comorbidities of participants with and without schizophrenia. Participants with schizophrenia had more severe depressive symptoms (CES-D $\geq$ 8) and were more predominant among participants with schizophrenia compared to participants without schizophrenia (63% for participants with schizophrenia vs. 23% for participants without schizophrenia in men; 77% vs. 29% in women).

Table 3. Psychiatric comorbidities of participants with schizophrenia and participants without schizophrenia according to sex.

Characteristic	**Men**			**Women**		
	Schizophrenic Participants, N = 115	**Non-Schizophrenic Participants, N = 801**	***p*-Value**	**Schizophrenic Participants, N = 108**	**Non-Schizophrenic Participants, N = 975**	***p*-Value**
Depressive symptoms (CES-D $\geq$ 8)			<0.001			<0.001
Absent	42 (37%)	618 (77%)		25 (23%)	691 (71%)	
Present	73 (63%)	183 (23%)		83 (77%)	284 (29%)	
Sleep time			<0.001			<0.001
<5 h	10 (8.7%)	87 (11%)		15 (14%)	113 (12%)	

Table 3. *Cont.*

Characteristic	Men			Women		
	Schizophrenic Participants, N = 115	Non-Schizophrenic Participants, N = 801	*p*-Value	Schizophrenic Participants, N = 108	Non-Schizophrenic Participants, N = 975	*p*-Value
6–7 h	59 (51%)	594 (74%)		50 (46%)	704 (72%)	
8–9 h	33 (29%)	111 (14%)		33 (31%)	150 (15%)	
≥10 h	13 (11%)	9 (1.1%)		10 (9.3%)	8 (0.8%)	
Hypnagogic disorder			<0.001			<0.001
<3 times per week	75 (65%)	688 (86%)		66 (61%)	787 (81%)	
≥3 times per week	40 (35%)	113 (14%)		42 (39%)	188 (19%)	
Deep sleep disorder			<0.001			0.005
<3 times per week	52 (45%)	532 (66%)		60 (56%)	675 (69%)	
≥3 times per week	63 (55%)	269 (34%)		48 (44%)	300 (31%)	
Middle wakening, or early wakening			<0.001			<0.001
<3 times per week	78 (68%)	703 (88%)		62 (57%)	802 (82%)	
≥3 times per week	37 (32%)	98 (12%)		46 (43%)	173 (18%)	
Perceived stress (PSS-4)	9.6 (3.2)	7.1 (2.8)	<0.001	9.9 (3.0)	7.3 (2.8)	<0.001
Ikigai			<0.001			<0.001
Present	49 (43%)	500 (62%)		48 (44%)	628 (64%)	
Absent	66 (57%)	301 (38%)		60 (56%)	347 (36%)	
Happiness			<0.001			<0.001
Present	42 (37%)	494 (62%)		56 (52%)	697 (71%)	
Absent	73 (63%)	307 (38%)		52 (48%)	278 (29%)	
Internet use time per week (h)	26 (24)	21 (21)	0.035	20 (22)	17 (19)	0.147

Continuous variables were expressed as mean (SD), and categorical variables as number (percentage). *p*-values were calculated with the Welch Two-Sample *t*-test for continuous variables and with Fisher's exact test for categorical variables. Abbreviations: CES-D, a modified 11-item Center for Epidemiological Studies Depression Scale; PSS-4, a 4-item Perceived Stress Scale.

In terms of sleep patterns, participants with schizophrenia reported sleeping longer. They were more likely to report sleep disturbances, including hypnagogic disorder, deep sleep disorder, and middle or early awakenings, compared to participants without schizophrenia.

Perceived stress (PSS-4 scores) was higher in participants with schizophrenia than in participants without schizophrenia. More participants with schizophrenia had an absence of *ikigai* (a positive reason for living) and absence of happiness than participants without schizophrenia. Internet use was significantly longer in participants with schizophrenia compared to participants without schizophrenia in men, while no significant differences were found in women.

Figure 2 shows the results of a sex- and age-adjusted logistic regression model investigating the association between psychiatric comorbidities and schizophrenia. Depressive symptoms (CES-D ≥ 8) were associated with more strongly than other psychiatric comorbidities (AOR: 7.54, 95% CI = 5.52 to 10.4). Compared to community dwellers without schizophrenia, community dwellers with schizophrenia more frequently reported long-hour sleep (≥10 h) (AOR: 3.95, 95% CI = 2.89 to 5.39), stressful (PSS-4 > 7) (AOR: 3.60, 95% CI = 2.61 to 5.07), middle wakening or early wakening (AOR: 3.57, 95% CI = 2.62 to 4.84), hypnagogic disorder (AOR: 2.98, 95% CI = 2.20 to 4.02), absence of happiness (AOR: 2.58, 95% CI = 1.94 to 3.43), absence of *ikigai* (AOR: 2.26, 95% CI = 1.70 to 3.00), deep sleep disorder (AOR: 2.07, 95% CI = 1.55 to 2.75), and longtime internet use (>14 h per week) (AOR: 1.50, 95% CI = 1.13 to 1.98).

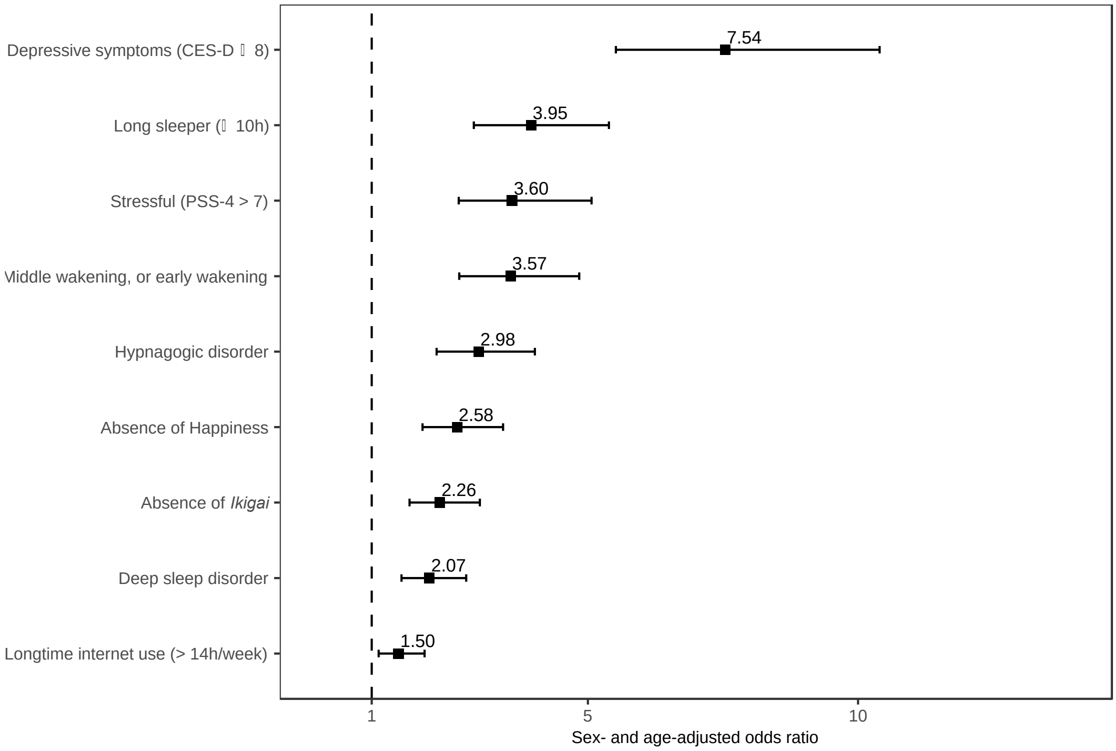

Figure 2. Sex- and age-adjusted odds ratios of participants with schizophrenia compared to participants without schizophrenia in terms of psychiatric comorbidities. Abbreviations: CES-D, a modified 11-item Center for Epidemiological Studies Depression Scale; PSS-4, a 4-item Perceived Stress Scale.

Table 4 shows the social comorbidities of participants with and without schizophrenia. Regarding health literacy and behaviors, participants with schizophrenia did not have regular health examinations compared to participants without schizophrenia. In terms of socioeconomic status, compared to participants without schizophrenia, participants with schizophrenia were less educated (junior/senior high school), unemployed (50% vs. 15% in men; 33% vs. 6.8% in women), non-regular employment (56% vs. 15% in men; 79% vs. 42% in women), low household income (<3 million Japanese yen) (53% vs. 18% in men; 44% vs. 22% in women), unmarried (especially among men), and living with parents. Regarding social support and social capital, the differences in ESSI scores with and without schizophrenia were small. Participants with schizophrenia had a lower cognitive social capital compared to participants without schizophrenia.

Table 4. Social comorbidities of participants with schizophrenia and participants without schizophrenia according to sex.

Characteristic	**Men**			**Women**		
	Schizophrenic Participants, N = 115	**Non-Schizophrenic Participants, N = 801**	***p*-Value**	**Schizophrenic Participants, N = 108**	**Non-Schizophrenic Participants, N = 975**	***p*-Value**
Taking regular medical checkups	52 (45%)	536 (67%)	<0.001	43 (40%)	527 (54%)	0.006
Educational background			<0.001			0.003
Junior/senior high school	51 (44%)	220 (27%)		43 (40%)	251 (26%)	
University, junior college, vocational school	64 (56%)	581 (73%)		65 (60%)	724 (74%)	

Table 4. *Cont.*

Characteristic	Men			Women		
	Schizophrenic Participants, N = 115	**Non-Schizophrenic Participants, N = 801**	***p*-Value**	**Schizophrenic Participants, N = 108**	**Non-Schizophrenic Participants, N = 975**	***p*-Value**
Occupation			<0.001			<0.001
Unemployed	58 (50%)	119 (15%)		36 (33%)	66 (6.8%)	
Homemaker	3 (2.6%)	5 (0.6%)		29 (27%)	257 (26%)	
White-collar workers	21 (18%)	453 (57%)		25 (23%)	482 (49%)	
Blue-collar workers	33 (29%)	224 (28%)		18 (17%)	170 (17%)	
Type of employment			<0.001			<0.001
Regular	14 (26%)	489 (72%)		5 (12%)	343 (53%)	
Non-regular	30 (56%)	103 (15%)		34 (79%)	274 (42%)	
Self-employed/business people	10 (19%)	85 (13%)		4 (9.3%)	35 (5.4%)	
Household income (million Japanese yen)			<0.001			<0.001
<3	61 (53%)	148 (18%)		47 (44%)	211 (22%)	
3–6	40 (35%)	280 (35%)		40 (37%)	375 (38%)	
6–9	12 (10%)	197 (25%)		16 (15%)	231 (24%)	
≥9	2 (1.7%)	176 (22%)		5 (4.6%)	158 (16%)	
Marital status			<0.001			0.004
Unmarried	88 (77%)	286 (36%)		48 (44%)	371 (38%)	
Married	21 (18%)	463 (58%)		41 (38%)	519 (53%)	
Divorced	6 (5.2%)	37 (4.6%)		14 (13%)	67 (6.9%)	
Widowed	0 (0%)	2 (0.2%)		2 (1.9%)	10 (1.0%)	
Others	0 (0%)	13 (1.6%)		3 (2.8%)	8 (0.8%)	
Family structure						
Living alone	22 (19%)	177 (22%)	0.546	11 (10%)	191 (20%)	0.018
Living with parents	73 (63%)	194 (24%)	<0.001	50 (46%)	229 (23%)	<0.001
Living with spouse	21 (18%)	456 (57%)	<0.001	41 (38%)	512 (53%)	0.004
Living with children	15 (13%)	257 (32%)	<0.001	32 (30%)	348 (36%)	0.243
Living with other people	27 (23%)	50 (6.2%)	<0.001	17 (16%)	91 (9.3%)	0.042
Social support (ESSI)	21 (7)	22 (8)	0.262	22 (7)	23 (7)	0.007
Social capital			0.046			0.014
Less cognitive social capital	70 (61%)	404 (50%)		58 (54%)	400 (41%)	
Less structural social capital	99 (86%)	678 (85%)		90 (83%)	858 (88%)	

Continuous variables were expressed as mean (SD), and categorical variables as number (percentage). *p*-values were calculated with the Welch Two-Sample *t*-test for continuous variables and with Fisher's exact test for categorical variables. Abbreviations: ESSI, the ENRICHD Social Support Instrument.

Figure 3 shows the results of a sex- and age-adjusted logistic regression model investigating the association between schizophrenia and social comorbidities. Unemployment (AOR: 6.25, 95% CI = 4.56 to 8.55) and non-regular employment (AOR: 6.24, 95% CI = 3.94 to 10.0) were significantly more strongly associated with schizophrenia than other social comorbidities. For other social comorbidities, compared to community dwellers without schizophrenia, community dwellers with schizophrenia more frequently reported living with parents (AOR: 4.55, 95% CI = 3.37 to 6.16), low household income (<3 million Japanese yen) (AOR: 3.76, 95% CI = 2.82 to 5.02), unmarried (AOR: 3.53, 95% CI = 2.58 to 4.84), not taking regular medical checkups (AOR: 2.20, 95% CI = 1.65 to 2.94), less cognitive social capital (AOR: 2.08, 95% CI = 1.57 to 2.78), low education background (Junior/senior high school) (AOR: 1.99, 95% CI = 1.49 to 2.65), and less social support (ESSI < 17) (AOR: 1.48, 95% CI = 1.09 to 2.00).

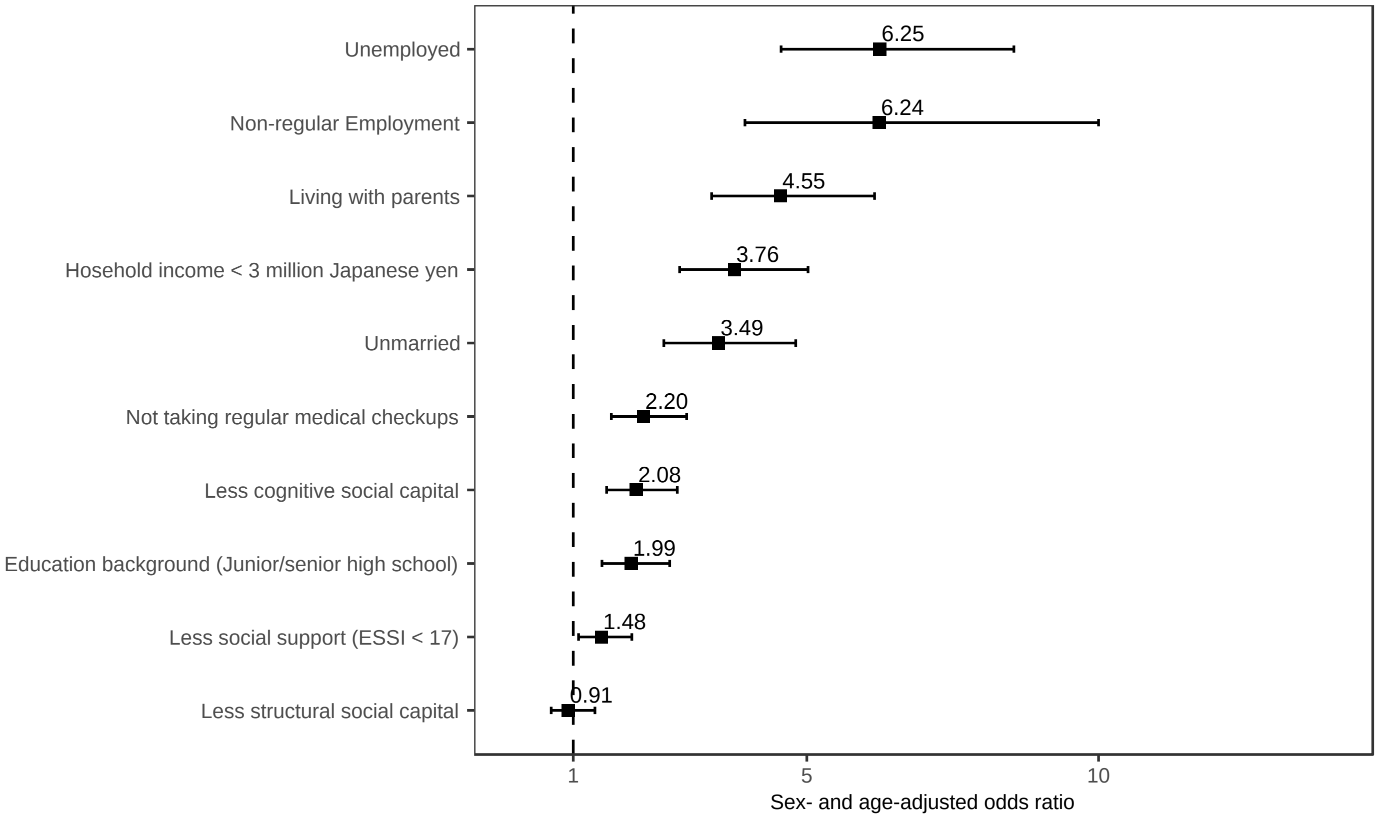

Figure 3. Sex- and age-adjusted odds ratios of participants with schizophrenia compared to participants without schizophrenia in terms of social comorbidities. Abbreviations: ESSI, the ENRICHD Social Support Instrument.

4. Discussion

This study revealed the physical, psychiatric, and social comorbidities of individuals with schizophrenia living in the community in Japan, which were seldom reported comprehensively.

The mean age of participants with schizophrenia in this study was 48 years for males and 44 years for females, which is consistent with the mean age of 42.7 years reported in The Japan National Health and Wellness Survey [15]. However, it should be noted that this estimated age of participants with schizophrenia may be younger than the mean age of individuals with schizophrenia in Japan. This is due to the fact that participants in this study were recruited via the internet, which could lead to a higher representation of younger adults with high internet usage [39]. Additionally, this recruitment method may not include hospitalized patients, many of whom are elderly.

Participants with schizophrenia had a higher percentage (53% of men and 39% of women) with a BMI of 25 or higher than participants without schizophrenia. The prevalence of BMI $\geq$ 25.0 kg/m^2 among Japanese outpatients with schizophrenia has been reported to be 48.9% [14]. Individuals with schizophrenia have a shorter life expectancy due to death from cardiovascular causes [40,41]. Previous studies have also shown that outpatients have a higher rate of obesity than inpatients [14], highlighting the need for measures to control obesity in individuals with schizophrenia living in the community.

Approximately 10% of participants with schizophrenia in this study defecated less than three times per week, a prevalence lower than that reported in outpatients in Finland (31.3%) [42] and inpatients in Japan (36.6%) [43]. One potential explanation for this discrepancy may be that participants with schizophrenia had more than two bowel movements per day and a higher percentage of soft stools than those without schizophrenia, some of whom may be constipated. Antipsychotic medications are known to cause constipation, and it has been reported that over 50% of individuals with schizophrenia taking antipsychotic drugs experience constipation [44]. Many participants in this study likely took laxatives, such as osmotic laxatives such as magnesium hydroxide, which can soften stools. However, the anticholinergic effect of antipsychotics may reduce peristalsis in the bowel, leading to constipation with limited stool volume and a feeling of incomplete defecation.

Participants with schizophrenia have been found to engage in overeating and faster eating patterns compared to those without schizophrenia. Overeating may be due to increased appetite caused by the side-effects of antipsychotic medications [45]. In systematic reviews, the prevalence of binge eating among individuals with schizophrenia taking antipsychotic medications ranges from 4.4% to 45%, with the majority of participants being of Western origin [46]. As far as we know, no studies have compared the prevalence of eating fast in individuals with schizophrenia with that of the general population. Eating fast has been reported to be associated with obesity [47]. In clinical practice, it is crucial to instruct individuals with schizophrenia on appropriate food intake in terms of both quantity and speed to prevent obesity.

A comparison of smoking rates between male participants with schizophrenia and those without schizophrenia revealed no significant differences. However, female participants with schizophrenia were found to have smoking rates that were approximately 2.5 times higher than those without schizophrenia. Similarly, a meta-analysis of smoking rates among Japanese individuals with schizophrenia showed that compared to the general population, male individuals with schizophrenia had an odds ratio 1.53 times higher for smoking rates (52.9% for individuals with schizophrenia and 40.1% for the general population) and female individuals with schizophrenia had an odds ratio 2.40 times higher for smoking rates among females (24.4% for individuals with schizophrenia and 11.8% for the general population) [48]. This disparity in smoking rates may be attributed to the fact that the smoking rate in the Japanese population has been decreasing over time among men, but the decline is less pronounced among women [49].

The primary physical diseases among participants with schizophrenia were hypertension, diabetes mellitus, and dyslipidemia, all of which are associated with obesity. The prevalence of these diseases was relatively low compared to a previous study conducted in Japan [14], which may be attributed to the younger age of the participants in this study. However, the prevalence of diabetes mellitus and dyslipidemia was significantly higher than that of participants without schizophrenia. These diseases, as well as obesity, require caution when examining individuals with schizophrenia.

Although the absolute prevalence of fracture and sleep apnea was low, both conditions had high sex- and age-adjusted odds ratios for the prevalence of schizophrenia. Fracture is associated with antipsychotic medications, analgesics, and physical diseases such as hypertension in individuals with schizophrenia [50,51]. It has been reported that bone mineral density is decreased in Japanese outpatients with schizophrenia [52], highlighting the need for osteoporosis prevention. A meta-analysis reported a comorbidity of obstructive sleep apnea as high as 15.4% in schizophrenia [53]. In a Japanese survey, 19% of hospitalized individuals with schizophrenia had sleep apnea [54]. Because the medical history was self-reported, there may be undiagnosed obstructive sleep apnea. Potentially, the prevalence of obstructive sleep apnea could be even higher. Early detection and intervention for obstructive sleep apnea are needed to protect against sleep disturbance and cardiovascular disease [55].

Cardiovascular disease and heart failure, associated with schizophrenia in previous studies of Westerners [56,57], were not associated with schizophrenia in the present study.

This may be partly because these diseases typically have an elderly onset and the sample size of participants with schizophrenia in the study was small. The present study also found no association between gout and schizophrenia, which is consistent with a systematic review and meta-analysis that found no difference in uric acid levels between individuals with and without schizophrenia [58]. Cancer was not associated with schizophrenia in this study, although the prevalence of cancer was higher in female participants with schizophrenia than in female participants without schizophrenia. This result is consistent with previous findings that schizophrenia is associated with a higher risk of breast cancer [59], although the incidence of cancer in individuals with schizophrenia has been reported to vary in comparison to the general population [60].

Depressive symptoms were present in more than two-thirds of participants with schizophrenia, making it the greatest risk factor for psychiatric comorbidities in schizophrenia (AOR: 7.54). This prevalence is higher than that reported in Japan's National Health and Wellness Survey, where 47.8% of individuals with schizophrenia had depressive symptoms (85/178) [15]. The lifetime prevalence of depression in individuals with schizophrenia ranges from 16 to 69%, depending on factors such as the definition of depression, patient setting, and period of observation [10]. This is higher than that in the general population, which is consistent with our findings [17]. Depression in schizophrenia has been reported to be associated with factors that interfere with living in the community, such as schizophrenia relapse, early rehospitalization, impairment of social and occupational functioning, and family and community burden [10,61]. Additionally, depression in individuals with schizophrenia is strongly associated with an increased risk of suicide [62]. Therefore, addressing depressive symptoms is a crucial intervention for individuals with schizophrenia.

Participants with schizophrenia reported longer sleep duration and more sleep disturbances than those without schizophrenia. A systematic review reported that those with remitted schizophrenia showed a longer sleep duration, time in bed, and sleep latency than the healthy control did [63], which is consistent with our results. Individuals with schizophrenia complain of sleep disturbances not only in the acute phase but also in the remission phase [64]. In a Japanese study, the prevalence of individuals with schizophrenia with any sleep disturbances was 49.4% (88/178) [15]. In Chinese outpatients, the prevalence of at least one type of insomnia was 28.9% (180/623), while those with difficulty initiating sleep, difficulty maintaining sleep, and early morning wakening were 20.5%, 19.6%, and 17.7%, respectively [65]. The participants with schizophrenia in this study, most presumed outpatients, showed sleep disturbances at a higher rate compared to the previous research in China. Further studies are needed in different populations. Sleep disturbances tend to precede the onset of schizophrenia, and management of sleep disturbances can prevent acute exacerbation of psychiatric symptoms [63].

Perceived stress was stronger in participants with schizophrenia than in those without schizophrenia, which is consistent with previous evidence in Western populations [66,67]. A common finding is an association between stress and pathophysiology in all stages of schizophrenia [66]. Appropriate coping with stress is associated with improved quality of life in individuals with schizophrenia [68].

Participants with schizophrenia had less *ikigai* and happiness than participants without schizophrenia, which is consistent with less well-being, happiness, and life satisfaction in individuals with schizophrenia among Westerners [67,69]. However, the difference between young adult individuals with schizophrenia and the general population in subjective well-being scores is small [69]. In an interview survey conducted with mentally disabled persons living in a community in Japan, some of them realized *ikigai* through dialogue with interviewees [70]. *Ikigai* or happiness may vary depending on the patient background or may be difficult to realize in individuals with schizophrenia.

Individuals with schizophrenia were reported to spend more time using the internet compared to those without schizophrenia, especially in men. In South Korea, 22% of individuals with schizophrenia were reported to suffer from problematic internet use, which was associated with higher levels of perceived stress and lower coping skills [71].

Participants with schizophrenia did not receive regular medical checkups as compared to participants without schizophrenia. This result is consistent with reports that Korean people with psychosis demonstrated lower knowledge of physical illnesses and did not receive regular medical checkups [72]. Therefore, individuals with schizophrenia must be educated and encouraged to undergo medical checkups.

A higher percentage of participants with schizophrenia were unemployed or had non-regular employment, had lower household incomes, were less likely to be married, and lived with their parents than participants without schizophrenia. Despite evidence indicating that individuals diagnosed with schizophrenia are more likely to be unemployed [22] or have lower income [73] than the general population, there is a paucity of research investigating whether they are more likely to be unmarried or residing with their parents. However, our finding is consistent with a previous Japanese study, which also found a high prevalence of unmarried, unemployed, and low household income among individuals with schizophrenia [15]. Additionally, the number of claims for mental and behavioral disorders per population was lower in the Japanese Medical Data Center (JMDC) database, consisting of corporate health insurance claims, compared to the National Database (NDB), consisting of all claims data constructed by the Japanese government [74]. This aligns with the high percentage of non-regular employment among participants with schizophrenia in the present study.

Sociodemographic features specific to individuals with schizophrenia are interrelated. A survey on family support for individuals with mental disorders in Japan found that 85% of respondents were parents [75], indicating that many individuals with schizophrenia are unmarried and live under parental support. Furthermore, the patients reported that they were unemployed or had non-regular employment, and their household income was low. In addition to the patient's work arrangement, family members are expected to work fewer hours to support the patient's daily needs, resulting in lower household income. With the parents' aging, further measures are needed to ensure that individuals with schizophrenia can continue to live in the community because the parents are concerned about livelihood support (74.8%) and financial aspects (60.1%) after the parents' death [75]. From a medical and social perspective, there is a need for educational programs that can help individuals with schizophrenia support themself while also managing their mental health or programs that can help parents better understand the condition and how to support their children with schizophrenia.

Social support tended to be lower among participants with schizophrenia than those without schizophrenia. Cognitive social capital was significantly lower in participants with schizophrenia than in participants without schizophrenia, while structural social capital did not differ between participants with and without schizophrenia. It has been reported in Westerners that schizophrenia was associated with low social support [76] and low cognitive social capital at the ecological level [77], which is consistent with the results of this study. Community development from the perspective of social support and social capital is required to improve community residents' mental health.

The present study has several strengths and limitations. First, online surveys may be susceptible to sampling bias and response bias, compared to population-based surveys. However, we did not use a stratified sampling technique to obtain as many responses as possible from respondents with schizophrenia. Second, the diagnosis of schizophrenia in this study was based on self-reports, which may limit the accuracy of the diagnosis. To address this limitation, we asked preliminary questions based on the DSM-5 diagnostic criteria [78] to exclude psychiatric disorders other than schizophrenia, such as depression, delusional disorder, and alcoholism, and to increase the specificity of the self-reported schizophrenia status. However, the sensitivity of the self-report survey may be low due to the lack of insight that often accompanies schizophrenia [79], potentially leading to an underestimation of the prevalence of the condition. In future studies, we plan to consider alternative approaches for assessing schizophrenia, such as clinical interviews or medical records, to improve the validity of our results. Third, the potential for underestimation of the prevalence of physical conditions among individuals with schizophrenia is due to the self-reported nature of the data, which can be influenced by cognitive deficits and low health literacy. Fourth, some of the participants with schizophrenia might not be living in the community, because we did not collect data about whether they lived there. This misclassification may cause the prevalence of comorbidities in schizophrenia to be biased, while the estimate of 94% with schizophrenia being out daily would support that most of the participants with schizophrenia live in the community. In addition, due to low health literacy, their comorbidities may be underreported. A more focused sample of community-dwelling individuals with confirmed psychiatric and medical diagnoses would be needed in future research. Fifth, the study design did not adequately include self-reflective components critical to understanding the daily experiences and perceptions of individuals with schizophrenia. Future research should consider self-reflective components because self-reflection could influence the perception of comorbidities. Sixth, the study has not collected sufficient data on other confounding variables, such as medication and menopause, that may have influenced the outcomes. Hence, in future research, it is imperative to collect data on potential confounding variables associated with the identified risk factors for schizophrenia. This would allow for a more comprehensive understanding of the underlying factors and their association with schizophrenia. Finally, this study was cross-sectional, and causal relationships must be carefully evaluated.

5. Conclusions

This study provides an overall description of comorbidities in individuals with schizophrenia living in the community in Japan using an internet survey. Physical comorbidities included overweight, hypertension, dyslipidemia, and diabetes. As for psychiatric comorbidities, depressive symptoms and sleep disorders were common. Social comorbidities included low education, unemployment/non-regular employment, low income, and living with parents. These findings suggest that a comprehensive approach is necessary to manage the physical, psychiatric, and social comorbidities in individuals with schizophrenia to continue to live in the community. The interventions should include lifestyle modifications, psychological therapies, vocational rehabilitation programs, job coaching, and supported employment programs. Such interventions can help individuals with schizophrenia to manage their comorbidities, improve their overall health outcomes and quality of life, and reduce the risk of readmission to hospitals. Healthcare providers, policymakers, and other stakeholders should work together to develop and implement interventions that address these comorbidities and improve the health outcomes and overall quality of life of individuals with schizophrenia living in the community.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Bioethics Review Committee of Fujita medical university, Japan (no. HM21-408).

Informed Consent Statement: Informed consent was obtained via the internet from all subjects involved in the study.

Data Availability Statement: Raw data supporting reported results of this study are human research participant data and are not publicly available but could be made available upon justified requests and after appropriate procedures, including approval from the institutional ethics review committee.

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Original Paper

Classifying Schizophrenia Cases by Artificial Neural Network Using Japanese Web-Based Survey Data: Case-Control Study

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Abstract

Background: In Japan, challenges were reported in accurately estimating the prevalence of schizophrenia among the general population. Retrieving previous studies, we investigated that patients with schizophrenia were more likely to experience poor subjective well-being and various physical, psychiatric, and social comorbidities. These factors might have great potential for precisely classifying schizophrenia cases in order to estimate the prevalence. Machine learning has shown a positive impact on many fields, including epidemiology, due to its high-precision modeling capability. It has been applied in research on mental disorders. However, few studies have applied machine learning technology to the precise classification of schizophrenia cases by variables of demographic and health-related backgrounds, especially using large-scale web-based surveys.

Objective: The aim of the study is to construct an artificial neural network (ANN) model that can accurately classify schizophrenia cases from large-scale Japanese web-based survey data and to verify the generalizability of the model.

Methods: Data were obtained from a large Japanese internet research pooled panel (Rakuten Insight, Inc) in 2021. A total of 223 individuals, aged 20-75 years, having schizophrenia, and 1776 healthy controls were included. Answers to the questions in a web-based survey were formatted as 1 response variable (self-report diagnosed with schizophrenia) and multiple feature variables (demographic, health-related backgrounds, physical comorbidities, psychiatric comorbidities, and social comorbidities). An ANN was applied to construct a model for classifying schizophrenia cases. Logistic regression (LR) was used as a reference. The performances of the models and algorithms were then compared.

Results: The model trained by the ANN performed better than LR in terms of area under the receiver operating characteristic curve (0.86 vs 0.78), accuracy (0.93 vs 0.91), and specificity (0.96 vs 0.94), while the model trained by LR showed better sensitivity (0.63 vs 0.56). Comparing the performances of the ANN and LR, the ANN was better in terms of area under the receiver operating characteristic curve (bootstrapping: 0.847 vs 0.773 and cross-validation: 0.81 vs 0.72), while LR performed better in terms of accuracy (0.894 vs 0.856). Sleep medication use, age, household income, and employment type were the top 4 variables in terms of importance.

Conclusions: This study constructed an ANN model to classify schizophrenia cases using web-based survey data. Our model showed a high internal validity. The findings are expected to provide evidence for estimating the prevalence of schizophrenia in the Japanese population and informing future epidemiological studies.

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KEYWORDS

artificial neural network; schizophrenia; prevalence; Japan; web-based survey; mental health; psychosis; machine learning; epidemiology

Introduction

Schizophrenia is a common mental illness that disrupts a person's thinking processes, perceptions, emotional responsiveness, and social interactions [1]. Estimates of international prevalence range from 0.33% to 0.75% [2,3]. The lifetime prevalence and median 12-month prevalence of schizophrenia were reported to be 0.33% and 0.48%, respectively [4]. In Japan, the point prevalence of schizophrenia, including schizotypal and delusional disorders, is approximately 0.7% according to national data from a patient survey [5]. While the real prevalence was considered quite different owing to the obstacles when operating the investigation. Patients with mild cases might not seek medical attention, and some cases are diagnosed as schizophrenia just for prescriptions to pass the medical insurance review.

We envisioned whether the prevalence of schizophrenia in individuals could be predicted by several factors and estimated the prevalence in the general population. By retrieving data from previous systematic reviews and meta-analyses, we confirmed that individuals with schizophrenia experience poor subjective well-being and various physical, psychiatric, and social comorbidities. For instance, studies conducted in Canada and the United States [6,7] have reported that young adults with schizophrenia tend to experience poorer subjective well-being and lower life satisfaction. Additionally, individuals with schizophrenia are prone to higher risk of noncommunicable diseases and experience poor oral health [8-10]. Patients with schizophrenia frequently exhibit symptoms of depression and experience sleep disorders [11,12]. Furthermore, individuals with schizophrenia typically have lower employment rates [11] and exhibit challenges in social cognition [13]. These factors are strongly associated with the incidence and existence of schizophrenia [14].

Machine learning techniques have recently drawn increasing attention in psychiatric studies. Birnbaum et al [15] built machine learning diagnostic and relapse classifiers for schizophrenia based on internet search activity (timing, frequency, and content), which achieved the area under the curve value of 0.74 and 0.71, respectively. Natural language processing has been applied to detect schizophrenia signs from social media content with extremely high accuracy [16]. Lejeune et al [17] concluded in their review that studies using social media to diagnose mental disorders were promising, while limitations included lack of clinical diagnostic data, small sample size, and heterogeneity in study quality. Previous studies have reported the effectiveness of detecting various types of mental disorders [18,19]. In other epidemiological fields, machine learning techniques also manifested promise, especially excelling at dealing with large-scale data [20,21]. We recently researched developing estimation methods for schizophrenia among the Japanese population [22]. Data were collected using a large-scale web-based survey. Individuals who participated in this survey were asked to answer questions about demographics, health-related backgrounds, physical comorbidities, psychiatric comorbidities, and social comorbidities. Compared with classical epidemiological surveys, web-based surveys make it easy to reach a large sample size and amount of data. Few studies have referred to the precise prediction of schizophrenia using large-scale web-based surveys.

If schizophrenia cases could be classified by variables of demographic and health-related backgrounds, it would be possible to estimate schizophrenia cases among general population, who are not seeking psychiatric care (namely, whose psychiatric syndromes are unknown). Therefore, we aimed to construct a machine learning model that can accurately classify the schizophrenia case and verify its generalizability.

Methods

Study Design: Participants and Survey Items

A prevalence case-control study was conducted using an internet research agency's pooled panel (Rakuten Insight, Inc, incorporated approximately 2.3 million panelists by 2022) [23]. Participants' ages were restricted from 20 to 75 years. Individuals who participated in this study answered a web-based survey.

Among participants who currently have schizophrenia, 5584 individuals who self-reported schizophrenia were sampled in the Rakuten Insight disease panel [24]. A total of 3256 respondents answered the following four questions before the survey: (1) are you currently experiencing schizophrenia only; schizophrenia and migraine; schizophrenia and a sleep disorder; or schizophrenia, migraine, and a sleep disorder? (2) Have you experienced auditory hallucinations lasting more than 1 month? (3) Have you never used stimulants or other illegal drugs and have never been an alcoholic? (4) Have you experienced your first auditory hallucination lasting more than 1 month at less than 60 years of age? Those who answered "yes" to all 4 questions were considered to have schizophrenia. Therefore, 223 participants who currently had schizophrenia were included in the survey.

For participants who do not currently have schizophrenia, all 28,000 participants in the Japan COVID-19 and Society Internet Survey (which was also conducted using the Rakuten Insight Panel) [25] were sampled. A total of 6656 respondents answered the following four questions before the survey: (1) are you currently experiencing mental illness? (2) Have you experienced a mental illness in the past? (3) Have you experienced auditory hallucinations? (4) Have you ever used stimulants or other illegal drugs, been alcoholic, or received psychiatric treatment? Those who answered "no" to all 4 questions were considered to not have schizophrenia. Therefore, 1776 participants who did not currently have schizophrenia were included in the survey.

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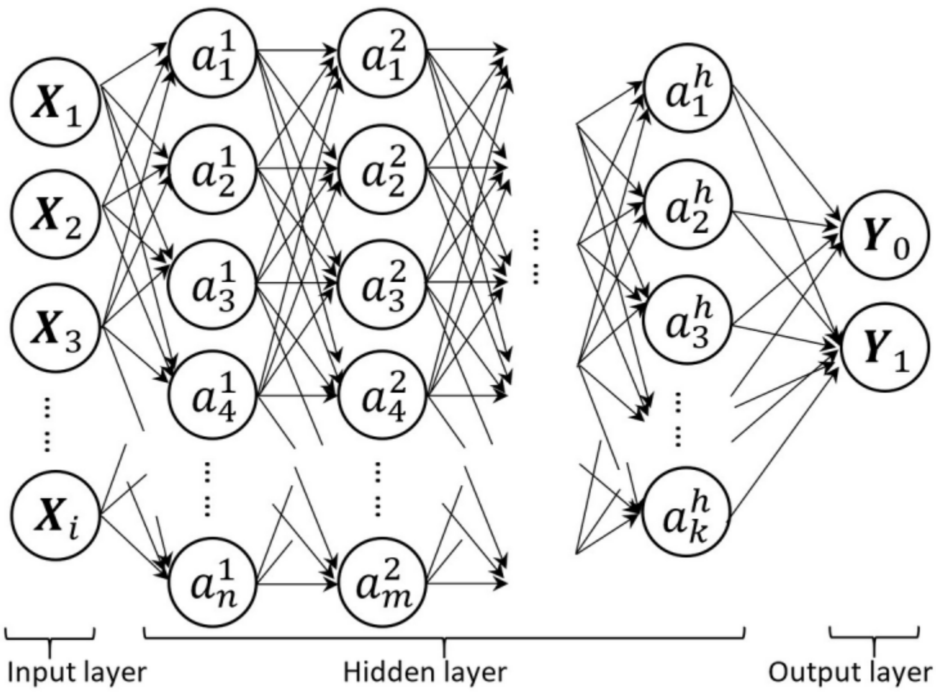
In the survey, 223 participants with schizophrenia and 1776 healthy controls answered a self-administered questionnaire. The question items were designed to assess (1) demographic and health-related backgrounds and physical comorbidities, (2) psychiatric comorbidities, and (3) social comorbidities. Answers to the question items were formatted to 1 response variable (diagnosed with schizophrenia, "yes" or "no") and 75 feature variables (demographic, health-related backgrounds, physical comorbidities, psychiatric comorbidities, and social comorbidities). Details of the study participants and variable definitions have been published elsewhere [26] and are described in Multimedia Appendix 1.

Artificial Neural Network

An artificial neural network (ANN) is a computing system that imitates the signals transmitted between neurons in biological brains [27]. Neurons in an ANN are divided into layers: 1 input layer, several hidden layers, and 1 output layer, where the number of neurons and hidden layers is not fixed. "Signals" transmitting is accomplished by weights and activation functions. As long as the initialized weights are updated by the self-learning process, the ANN can generate a "perfect" model. On behalf of the complex structure, an ANN can capture nonlinear associations and reveal potential interactions between variables. In our study, we structured an ANN with 5 hidden layers (neurons of each layer: 128-64-32-16-8), HeNormal weight initializer [28], ReLU activation function in the hidden layers, and sigmoid activation in the output layer [29]. These settings partially referred to previous studies [20,30] (Figure 1).

Figure 1. Structure of the artificial neural network. *X* refers to each of the feature variables. *a* refers to neurons in hidden layers. *Y* refers to response variables during training process and prediction results during test process.



Logistic Regression

Logistic regression (LR) estimates the probability of an event (outcome variable) taking place (success) based on a given data set of independent variables. In the LR equation, the outcome variable is transformed into log odds, the natural logarithm of the probability of success divided by the probability of failure. The independent variables are linearly structured by distributing coefficients to them. These coefficients are commonly estimated via maximum likelihood estimation to optimize the best fit of the log odds. The model is fixed once the optimal coefficients are found [31]. As a typical method that is widely used in epidemiological research, LR is introduced in this study to compare its performance with the novel ANN method.

Data Processing

The data were randomly split into a training data set and a test data set at an 80:20 ratio. Before applying the 2 selected algorithms (ANN and LR), the training data set was balanced based on the synthetic minority oversampling technique [32]. Models were trained using ANN and LR on the training data set separately, and the test data set was used to evaluate the 2 models (ANN and LR model). The area under the receiver operating characteristic curve (AUC) was applied to interpret the results because the outcome was binary. The 95% CI for the AUC was generated from 10,000 bootstraps of the training data set (Figure 2).

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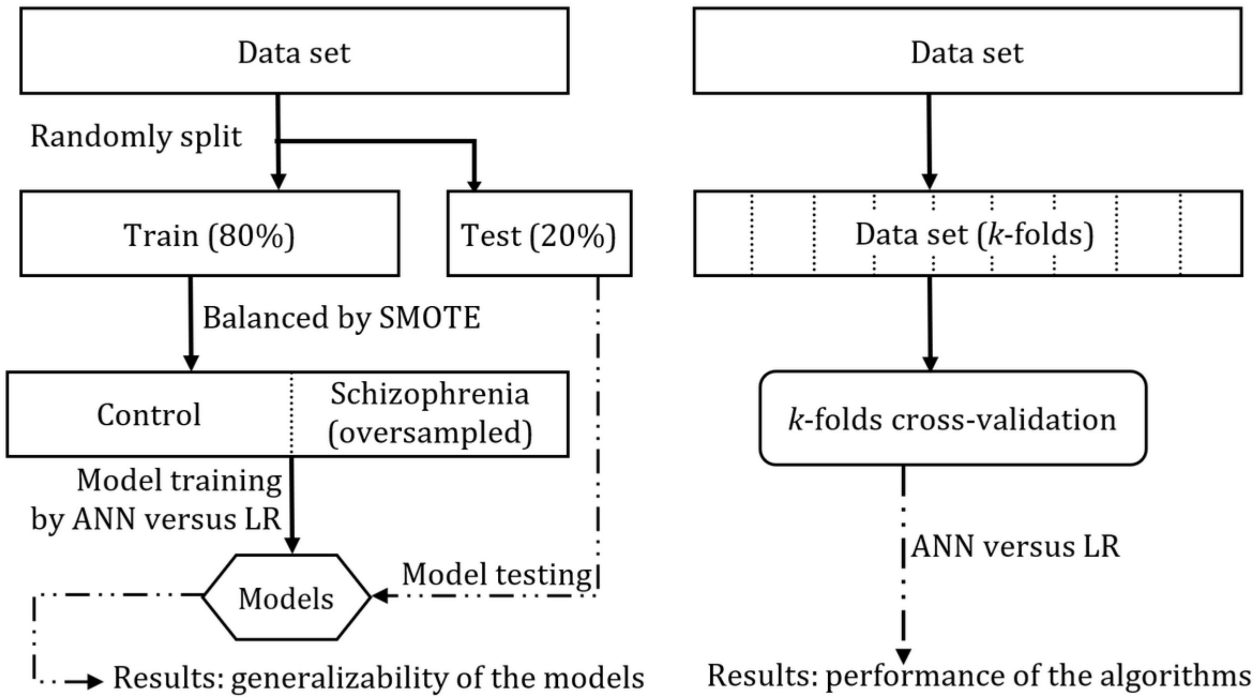
Figure 2. Flowchart of data processing, model training, and evaluation. ANN: artificial neural network; LR: logistic regression; SMOTE: synthetic minority oversampling technique.



Evaluation

The following thresholds were used to evaluate the performance in terms of AUC score: 0.5=no discrimination, 0.5-0.7=poor discrimination, 0.7-0.8=acceptable discrimination, 0.8-0.9=excellent discrimination, and >0.9=outstanding discrimination [33]. Two strategies were designed to evaluate the performance of the models and algorithms. To compare the generalizability of the trained LR and ANN models, their AUCs on the test data sets were compared. To compare the performance of LR and ANN algorithms, the AUCs were compared based on a 10-fold cross-validation. The differences in the AUCs were tested using the Delong method [34].

Model Interpretation (Variable Importance)

To interpret the ANN model, we introduced a shuffle test for each variable to evaluate variable importance. Among all the *N* variables in the test data set, the *n*th variable is shuffled at random; this resampled test data set is applied to the ANN model, and the AUC obtained from the resampled test data set is compared with the AUC obtained from the original test data set. The difference between the 2 AUCs explains the importance of the variable. A higher difference indicates that the *n*th variable has relatively higher importance.

Statistical Analyses

Statistical analyses were performed using Python (version 3.7; Python Software Foundation). The computational environment used was the Jupyter Notebook (Project Jupyter). Means and SDs are presented for continuous variables. Categorical variables are presented as proportions. Differences in means for continuous variables and categorical variables were tested using analysis of variance and chi-square test, respectively.

Ethical Considerations

This study was approved by the Bioethics Review Committee of Fujita Health University (HM21-408). All procedures performed in this study were in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Ministry of Health, Labour and Welfare, Government of Japan, and the 1964 Helsinki Declaration and its later amendments.

Results

Table 1 shows the characteristics of the normal and schizophrenia groups. Compared with the control group, participants with schizophrenia were more likely to be men. They had a significantly higher proportion of obesity, lower education levels, and lower household income. Participants with schizophrenia were more likely to have poor self-rated health status, depressive symptoms, perceived stress, and lower availability of social support. More details of these characteristics are provided in Table S1 in Multimedia Appendix 1.

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Table 1. Characteristics of schizophrenia cases and healthy controls.

	Schizophrenia case (N=223)	Healthy control (N=1776)	*P* value[a]
Age (years), mean (SD)	46 (9.3)	44 (13.5)	.08
Gender, n (%)			
Women	108 (48)	975 (55)	.07
BMI (≥25 kg/m^2), n (%)	103 (46)	313 (18)	<.001
Education, n (%)			
Junior or senior high school or lower	94 (42)	471 (27)	<.001
Household income, n (%)			
<3 million Japanese yen[b]	108 (48)	359 (20)	<.001
Self-rated health status, n (%)			
Bad	108 (48)	386 (19)	<.001
Physical disease, n (%)			
≥1 disease	135 (61)	610 (31)	<.001
Depressive symptoms, n (%)			
CES-D[c] ≥8	156 (70)	467 (26)	<.001
Perceived stress (PSS-4[d]), median (IQR)	10 (8-12)	7 (6-8)	<.001[e]
Social support (ESSI[f]), median (IQR)	21 (15-28)	23 (17-28)	.007[e]

[a]Based on analysis of variance and chi-square test for continuous and categorical variables, respectively, except specified notes.

[b]Around US $20,000.

[c]CES-D: Center for Epidemiological Studies Depression.

[d]PSS-4: 4-item Perceived Stress Scale.

[e]*P* values by the Kruskal-Wallis test.

[f]ESSI: ENRICHD Social Support Instrument.

Figure 3 illustrates the internal validity of the models trained using the ANN and LR. The model trained by ANN performed better than LR in terms of AUC (0.86 vs 0.78), accuracy (0.93 vs 0.91), and specificity (0.96 vs 0.94), whereas the model trained by LR performed better in terms of sensitivity (0.63 vs 0.56). Table 2 shows the algorithm performance comparing between ANN and LR by using bootstrapping and cross-validation. ANN performed better in terms of AUC (bootstrapping: 0.847 vs 0.773 and cross-validation: 0.81 vs 0.72), whereas LR performed better in terms of accuracy (0.894 vs 0.856).

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Figure 3. Confusion matrixes of artificial neural network and logistic regression models. AUC: area under the receiver operating characteristic curve.

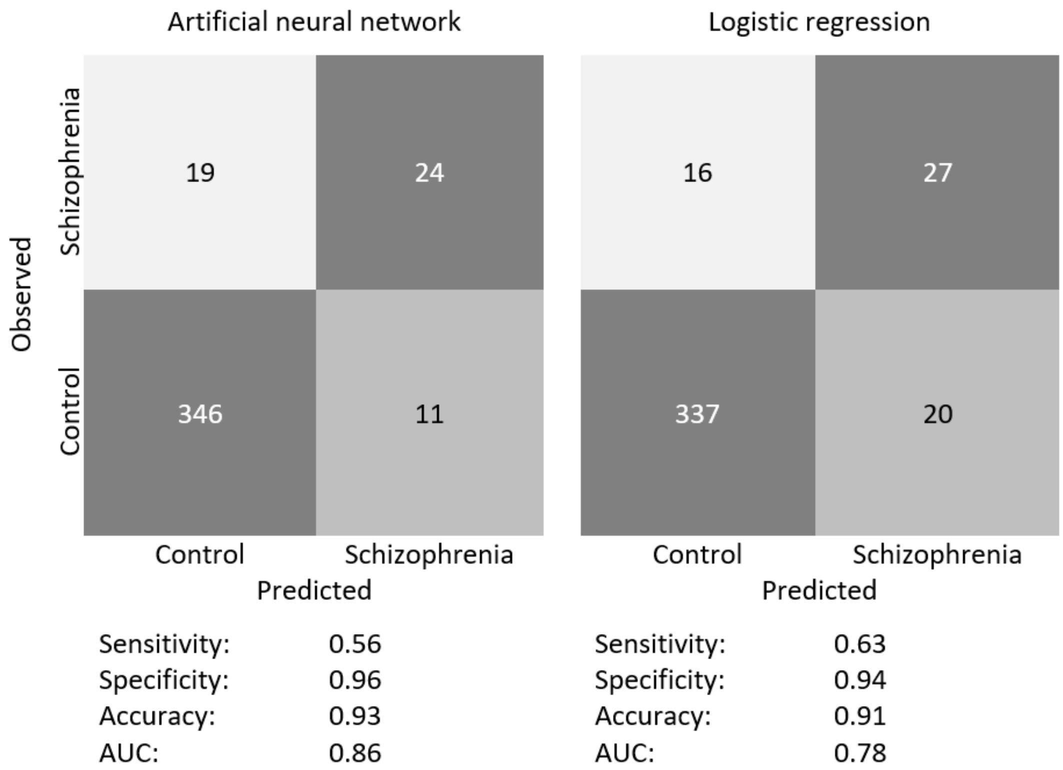

Table 2. Comparison between artificial neural network and logistic regression by bootstrapping and cross-validation.

	Artificial neural network, mean (SD)	Logistic regression, mean (SD)	*P* value
Results from 10,000 bootstrapping			
Accuracy	0.856 (0.18)	0.894 (0.01)	<.001
AUC[a]	0.847 (0.11)	0.773 (0.02)	<.001
Results from 10-fold cross-validation			
Accuracy	0.92 (0.04)	0.82 (0.28)	.27
AUC	0.81 (0.28)	0.72 (0.26)	.49

[a]AUC: area under the receiver operating characteristic curve.

Figure 4 shows the feature importance ranking estimated from the ANN model (only the top 15 items are displayed). The frequency of sleep medication use ranked first, illustrating the most important factor associated with schizophrenia. Age took second place. Household income and type of employment ranked third as they showed similar values. Bedtime, BMI, number of cigarettes smoked per day, and educational background followed, with a marked decrease in importance. Hours of sleep, perceived stress, positive reason for living (aka, *ikigai*, a Japanese term), restriction in functional capacity, type of occupation, number of teeth, and bowel frequency ranked 9th to 15th; however, their importance was not as high as those in the above places.

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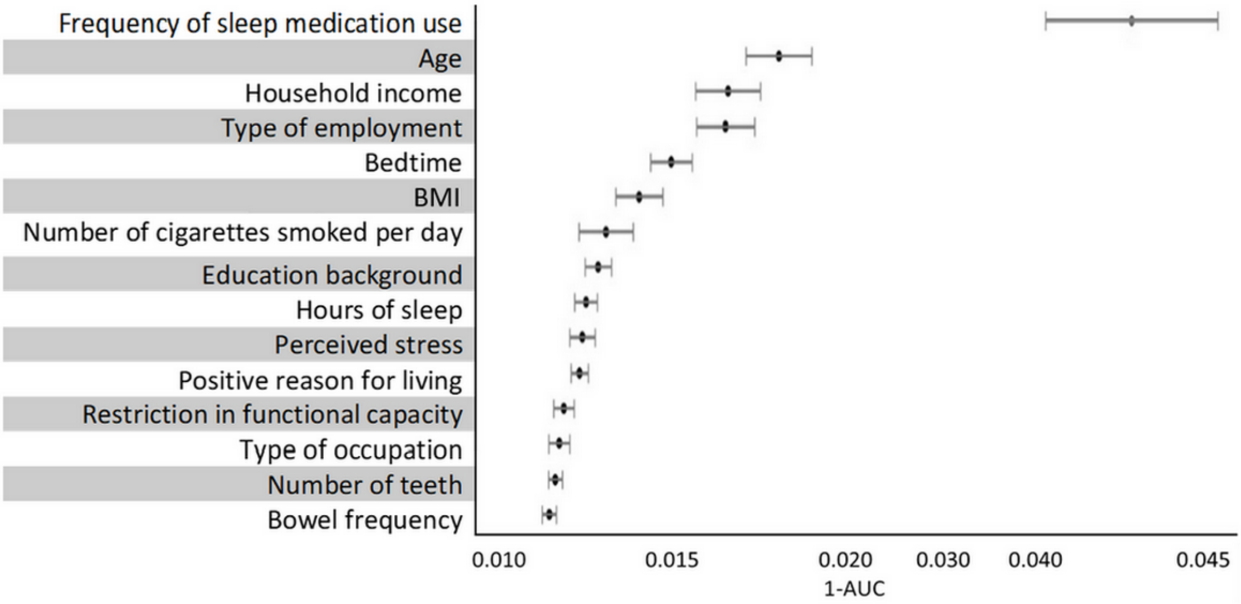
Figure 4. Feature importance (top 15) from artificial neural network model. AUC: area under the receiver operating characteristic curve.



Discussion

Principal Findings

In this study, we developed an ANN model for classifying schizophrenia cases with high internal validity, which achieved an excellent AUC of 0.86. This ANN model also achieved a specificity of 0.96, which implies that it has a good ability to designate an individual without schizophrenia as negative, and a sensitivity of 0.56, which represents the model's limitation in designating an individual with schizophrenia as positive. Our study demonstrated that the ANN has the potential for applying to estimate the prevalence of schizophrenia in large-scale epidemiological studies.

To our knowledge, this is the first study that uses a machine learning technique (ie, ANN) to classify schizophrenia cases from web-based survey data in the Japanese population. A novel machine learning approach has been reported for the detection of schizophrenia from social media content, which achieved an accuracy of 96% [16]. In addition, machine learning techniques might provide an opportunity to improve diagnostic certainty [35] and explain mental disorders in complex states [36]. On the other hand, ANN algorithms have proven their advantages in disease prediction using large-scale survey data. For predicting type 2 diabetes, models developed by ANN have achieved an AUC of 0.86, which is the highest compared to other algorithms such as random forest and support vector machine [21]. Another study reported that models developed by ANN for predicting hypertension achieved an AUC of 0.78; however, there was no significant advantage compared with the classic method [20].

In comparison of the algorithm performance, ANN performed better than LR. Several reasons might be considered: (1) ANN is more competent for approximate relations that do not follow the linearized assumption owing to its structure [37]. In generalized linear models (eg, LR), the relation between the response variable and the feature variables is applied to a linear equation; therefore, linear models face difficulty in analyzing nonlinear combinations. As the number of feature variables in a linear model increases, multicollinearity [38] and overfitting may occur easily [39]. (2) The ANN is more effective for analyzing interactions among more than 2 variables. In linear models, interaction terms (usually products between 2 variables) are added. However, interaction features are often selected based on rules of thumb. Additionally, multicollinearity should be cautiously considered as the number of interaction terms increases [38]. While in an ANN, the variable relationships are assumed to be extremely high-dimensional and complex [40]. After inputting all the variables, each hidden neuron takes, as input, all nodes from the previous layer and creates a high-order interaction between these nodes [41]. Nevertheless, the complex structure of an ANN prevents the model from being easily visualized and understood.

In terms of the AUC value, ANN outperformed LR both in algorithm and model comparisons. However, in this study, the ANN model exhibited better specificity but lower sensitivity compared to LR as the cutoff threshold was set to the default 0.5. The model's performance metrics indicate a trade-off between sensitivity and specificity. This trade-off could impact the model's ability to correctly classify schizophrenia cases and noncases, which has clinical implications. Further experiments are necessary, involving the adjustment of the cutoff threshold [42] to determine a suitable balance point in practical scenarios.

This study suggested the possibility of classifying schizophrenia cases among general population. We expected to estimate schizophrenia cases among those who are not seeking psychiatric care, typically, whose psychiatric syndromes are unknown. Hence, no clinical assessment or diagnostic criteria were involved in the feature variables. As we ranked the feature importance, sleep problems were the most important factor associated with schizophrenia in terms of sleep medication use, bedtime, and sleep duration. The importance of factors such as age, socioeconomic background, BMI, physical activity, smoking, depression, and oral health followed. These factors

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have also been reported to be strongly associated with schizophrenia [8,43-50]. The advantage of our study was that we ranked those previously reported factors according to their "priority" for classifying schizophrenia, which may provide potential evidence for screening and early detection of schizophrenia when using massive data.

In this study, no variable selection technique was preselected because we hope to mine as much potentially useful information as possible when training the models. Previous studies have reported that fully input variables might lead to unstable estimates in linear models such as LR [51]. Some methodologists have suggested that statistical significance–based variable selection techniques are mechanical and, as such, have limitations [51,52]. We conducted an additional experiment for the sake of "fairness"; the LR model was trained using only the top 15 most important features reported by the ANN model. The results obtained from this partial-featured LR model did not improve compared with the all-feature LR model (sensitivity: 0.69, specificity: 0.87, accuracy: 0.91, and AUC: 0.78). The machine learning approach might be used for feature selection to compensate for the limitations of classical epidemiology studies.

Limitations

This study has several limitations. First, participants with mental disorders other than schizophrenia were not included. Hence, our model is not suitable for distinguishing schizophrenia from other types of mental disorders. Second, although the data in this study were obtained from a large Japanese internet research pooled panel, we should cautiously explain the representativeness for the entire Japanese population. This could introduce sampling bias, potentially excluding individuals who are less likely to participate in web-based surveys, such as those with limited internet access or severe mental health conditions. In addition, the self-reported diagnoses of schizophrenia might not be as reliable as clinically confirmed diagnoses, as individuals might misinterpret symptoms or misunderstand their condition. There might also be issues related to stigma or disclosure bias, where individuals might be hesitant to disclose mental health diagnoses. Third, the important variables determined by our model cannot be arbitrarily used as a criterion for identifying schizophrenia. For example, sleep medication use is often observed in patients with depression, although our model determined that it was most associated with schizophrenia. In future studies, we plan to include samples with various types of mental disorders and construct a model that can classify multiple mental disorders. Additionally, Clinical assessments and diagnostic criteria used by health care professionals were not included in the analysis. In future studies, we can introduce essential information to enhance the model construction. Fourth, all variables (feature variables and response variables) were self-reported at the same time. The answers were possibly biased because the participants might have been reluctant to answer some sensitive questions truthfully. The existence of schizophrenia might be different from the actual situation because the history of schizophrenia was reported by the participants themselves. Patients who did not use the internet and those who had difficulty completing the web-based survey due to their illness were not included in this study. These issues may have affected the accuracy and generalizability of the model. Fifth, the findings of this study were derived from a cross-sectional design; therefore, it is difficult to explain any causal or temporal associations. Sixth, because of the "black-box" design of the ANN model, it is difficult to interpret how variables and variable interactions contribute to the classification of schizophrenia. Further research is necessary to focus on model visualization and interpretation. Finally, the ideal model should be dynamic (ie, can be updated to adopt the latest data structure) [53]; hence, we need to input more large-scale data to improve the current model and to assess the model performance by external validation.

Conclusions

In this study, an ANN model was constructed to classify schizophrenia cases using web-based survey data. The model achieved a high internal validity. ANN performed better compared to the classical statistic method. These findings are expected to provide evidence for estimating the prevalence of schizophrenia in the Japanese population and informing future epidemiological studies.

Acknowledgments

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Data Availability

The data sets analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

YH made the conceptualization, conducted the data curation, methodology, data analysis, and interpretation, and wrote the original paper. MM made the conceptualization, conducted the investigation and data curation, and revised the paper. YL, NI, and TT revised the paper. TK and ST made the conceptualization and revised the paper. AO made the conceptualization, supervised the investigation, conducted the methodology and data curation, wrote part of the paper, and revised the paper. All authors reviewed the final paper.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Data source and variable definition.
[DOCX File , 47 KB-Multimedia Appendix 1]

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Abbreviations

ANN: artificial neural network
AUC: area under the receiver operating characteristic curve
LR: logistic regression

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External Validation of a Machine Learning Model for Schizophrenia Classification

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Abstract: Background and Objective: Excellent generalizability is the precondition for the widespread practical implementation of machine learning models. In our previous study, we developed the schizophrenia classification model (SZ classifier) to identify potential schizophrenia patients in the Japanese population. The SZ classifier has exhibited impressive performance during internal validation. However, ensuring the robustness and generalizability of the SZ classifier requires external validation across independent sample sets. In this study, we aimed to present an external validation of the SZ classifier using outpatient data. **Methods:** The SZ classifier was trained by using online survey data, which incorporate demographic, health-related, and social comorbidity features. External validation was conducted using an outpatient sample set which is independent from the sample set during the model development phase. The model performance was assessed based on the sensitivity and misclassification rates for schizophrenia, bipolar disorder, and major depression patients. **Results:** The SZ classifier demonstrated a sensitivity of 0.75 when applied to schizophrenia patients. The misclassification rates were 59% and 55% for bipolar disorder and major depression patients, respectively. **Conclusions:** The SZ classifier currently encounters challenges in accurately determining the presence or absence of schizophrenia at the individual level. Prior to widespread practical implementation, enhancements are necessary to bolster the accuracy and diminish the misclassification rates. Despite the current limitations of the model, such as poor specificity for certain psychiatric disorders, there is potential for improvement if including multiple types of psychiatric disorders during model development.

Keywords: external validation; schizophrenia; bipolar; depression; machine learning; classification; neural network

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1. Introduction

Models trained using machine learning approaches have been applied in various fields of medical research [1,2]. They utilize multiple features to detect or estimate an individual's existence or likelihood of a medical condition [3]. During the training process, it is essential to evaluate the model's performance in terms of discriminating individuals who have the outcome from those who do not or to accurately estimate the individual's risk. This can be tested through internal validation, such as bootstrapping, using the same dataset that was used in the training process. However, before deploying these pretrained models in real-world scenarios, the generalizability should be thoroughly confirmed through external validation. This involves testing the pretrained model using one or more independent sample sets. A model that deserves promotion and can be encapsulated as a tool for commercial use should exhibit excellent generalizability.

From 2021 to 2023, we conducted a research program focused on developing a prevalence estimation method for out-of-hospital schizophrenia and schizophrenia-related disorders in the general population. The program used large-scale epidemiological study data collected from an online survey. It involved information on demographic details, health-related backgrounds, physical and psychiatric comorbidities, and social comorbidities [4]. Based on that information, we developed a machine-learning model for classifying the presence or absence of schizophrenia (SZ classifier), in order to identify potential patients and estimate the prevalence of schizophrenia within the general population. The research design of the program is the first of its kind in Japan.

We envision that if there is a tool that can accurately detect the presence or absence of schizophrenia, it could contribute to the accurate estimation of the prevalence. However, the exact prevalence among the general population is poorly reported. Charlson et al. estimated the global age-standardized point prevalence of schizophrenia in 2016 to be 0.28%, but the actual prevalence could be higher, considering population growth and aging [5]. In Japan, an age–period–cohort analysis reported that the point prevalence was approximately 0.7% [6]. Challenges in the accurate estimation are considered, as (1) some patients may not know that they have the disease. Those who are sick may not always visit the doctor in time; (2) patients with mild disease may not seek medical attention; and (3) some diagnosed cases are for prescriptions to pass a medical insurance review. Hence, the estimated prevalence based solely on medical institution data may not represent the actual incidence in the population. Detecting these "potential" patients in the general population will be the key to estimating the prevalence.

The SZ classifier has provided a promising solution. In the internal validation, it achieved an area under the receiver operating characteristic curve (AUC) score of 0.86 [7]. This indicates that our SZ classifier successfully captures the differences between patients and healthy controls in demographic details, health-related backgrounds, physical and psychiatric comorbidities, and social comorbidities. For example, compared to healthy controls, individuals with schizophrenia demonstrate poor subjective well-being, happiness, and life satisfaction [8,9]. They are also more likely to have chronic diseases, such as poor oral health, noncommunicable diseases, and sleep disorders [8,9]. They also tend to have a lower socioeconomic status [8,9].

The SZ classifier was developed using artificial neural networks. Typically, machine learning validation reports rely on internal validation, employing a subset of the training sample set to assess the model performance. However, this approach carries the risk of inflating the model performance due to overfitting [10]. To accurately evaluate model generalizability, external validation is essential, utilizing an independent sample set [11]. Ideally, the sample set should comprise real-world data, which may provide evidence for medical application [12]. Therefore, in the current study, we aimed to present the external validation results of the SZ classifier. To further assess the external validation, we sampled 150 patients from those who visited the Psychiatric Department of Fujita Health University Hospital. The majority of these patients are from Central Japan, where the hospital is located. We anticipate that the SZ classifier can serve as a tool for detecting "potential" patients within the regional community, thereby allowing for estimating the incidence rate, and the subsequent promotion for broader population-level applications.

2. Materials and Methods

2.1. Development of the Schizophrenia Classification Model (SZ Classifier)

The SZ classifier was developed in our previous study [7] using a sample set collected from an internet research agency's pooled panel (Rakuten Insight, Inc., Tokyo, Japan) [13]. It comprised 223 schizophrenia patients and 1776 healthy controls. Each sample's data comprised the presence of schizophrenia, serving as the response variable, along with 76 features. These features included demographic details, health-related backgrounds, physical and psychiatric comorbidities, and social comorbidities. Details of the inclusion criteria have been published elsewhere [9], and the feature definitions are described in

Supplementary Materials. The SZ classifier was constructed based on an artificial neural network, considering the significance of capturing nonlinear relationships and higher-order interactions. Specifically, it was structured with five hidden layers, with 128, 64, 32, 16, and 8 neurons in each layer, respectively. The details of the SZ classifier development have been published elsewhere [7] and described in Supplementary Materials. The model performance was examined using the AUC score.

In the internal validation results, 20% of the whole samples were left out as the test set to assess the model performance. The SZ classifier achieved an AUC of 0.86, accuracy of 0.93, sensitivity of 0.56, and specificity of 0.96 [7]. Also, the results of 10-fold cross-validation exhibited that models trained by artificial neural networks could achieve an AUC of around 0.81 [7].

2.2. Samples for External Validation

We targeted patients who visited the Psychiatric Department of Fujita Health University Hospital between January 2022 and May 2023. The patients aged between 20 and 75 years and were diagnosed with schizophrenia, major depressive disorder (MDD), bipolar disorder (BD), or obsessive–compulsive disorder (OCD) were selected. The authors, KS and TK, explained the study's purpose and methods to the patients. Patients voluntarily decided whether to participate in our study. All the participants provided written informed consent to participate in this study. We confirmed that they had not participated in our research team's online survey (the aforementioned SZ classifier study).

Participants were asked to complete a survey identical to that used in our previous SZ classifier study. The answers were collected face to face. When necessary, trained assistants helped them complete the survey. These assistants provided only technical help and did not influence the answers. Notably, all participant diagnoses in this study were provided by experienced psychiatrists who had access to comprehensive treatment records, ensuring the sample quality for external validation. In total, we collected 150 samples from 61 schizophrenia patients, 56 MDD patients, 32 BD patients, and 1 OCD patient. Using these samples, we assessed the external validity of the SZ classifier. The primary reason for selecting MDD, BD, and OCD as the control group is that these disorders are theoretically easier to distinguish from schizophrenia, despite often presenting with overlapping clinical features that require careful differential diagnosis. The study design is also considered to possibly simulate the complexities encountered in actual clinical scenarios.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Bioethics Review Committee of Fujita Health University (HM21-408).

2.3. Statistical Analysis

Statistical analyses in the current study were performed using Python (version 3.7; Python Software Foundation). The computational code editor used was the Jupyter Notebook 7 (Project Jupyter).

3. Results

Of the 61 schizophrenia patients, 46 were accurately classified, and the sensitivity of the model reached 75%. Among the 89 non-schizophrenia patients, 50 were incorrectly classified as having schizophrenia (Table 1). Of the 56 MDD patients, 31 (55%) were incorrectly classified as having schizophrenia, and of the 32 BD patients, 19 (59%) were incorrectly classified as having schizophrenia (Table 2).

Table 1. Confusion matrix of external validation for the SZ classifier: results of all cases.

		Observed Cases	
		Schizophrenia	**Major Depressive Disorder, Bipolar, and Obsessive-Compulsive Disorder**
Predicted cases	Schizophrenia	46	50
	Major depressive disorder, bipolar, and obsessive-compulsive disorder	15	39
	Total	61	89
	Sensitivity	0.75	–
	Specificity	–	0.44

Table 2. Confusion matrix of external validation for the SZ classifier: results of the non-schizophrenia cases.

		Observed Cases		
		Major Depressive Disorder	**Bipolar**	**Obsessive-Compulsive Disorder**
Predicted cases	Schizophrenia	31	19	0
	Non-schizophrenia	25	13	1
Total		56	32	1
Misclassification rate		0.55	0.59	0

4. Discussion

This study conducted an external validation of our predeveloped SZ classifier using outpatient data. The SZ classifier achieved a sensitivity of 0.75 (46 out of 61 patients) when applied to individuals diagnosed with schizophrenia. However, when applied to patients diagnosed with BD or MDD, the misclassification rates were 59% (19 out of 32) and 55% (31 out of 56), respectively.

The sensitivity achieved in the external validation exceeded that of the internal test (0.56) [7]. This disparity may stem from the fact that the external validation sample set relies on diagnoses by clinicians and regular medical visits, which are deemed more reliable than self-reported diagnoses obtained through online surveys. Hohmann emphasized that the dependency of the output is reliant on the accuracy of the big data and the sample size [14]. The model performance is limited by poor data quality and insufficient confounding variables [14]. Moreover, the sample set used for developing the SZ classifier was imbalanced. We adopted a well-defined algorithm—Synthetic Minority Over-sampling Technique (SMOTE)—to solve this problem [15]. Nevertheless, SMOTE does not always work perfectly when solving such a problem. Hence, it is reasonable to speculate that if the data used for developing the model were of higher quality, the performance of the SZ classifier would likely improve.

The SZ classifier demonstrated a misclassification rate of >50% when applied to MDD and BD patients. This could be attributed to the similarities between schizophrenia, MDD, and BD. The top five features, ranked according to their importance, of the SZ classifier were the frequency of sleep medication use, age, household income, type of employment, and bedtime [7]. Table S1 lists the characteristics of the external validation sample set based on these five features. The distributions between schizophrenia and MDD, as well as between schizophrenia and BD, were similar (see Supplementary Materials, Table S1). Clinically, MDD, BD, and OCD often present with symptoms similar to those of schizophrenia; thus, a careful differential diagnosis is required. Since our SZ classifier was not built using samples of MDD, BD, and OCD, the poor specificity observed in the external validation results was anticipated.

Although the SZ classifier achieved a respectable sensitivity of 0.75, the misclassification rate exceeding 50% indicates that the model still requires significant improvements before it can be widely promoted across various communities or populations. We found no prior studies discussing external validation for machine learning models in schizophrenia classification. However, some relevant research based on machine learning techniques could be referenced and utilized. For instance, Bae used content from social media and compared four machine learning methods using natural language processing techniques for classifying schizophrenia [16]. The Random Forest model obtained the best AUC of 0.97, while Bae's study did not involve artificial neural networks. Bracher-Smith trained schizophrenia classification models using genetic and demographic factors from the UK Biobank, where the neural network model achieved an AUC of only 0.67 [17], which is lower than the 0.86 AUC from our study (internal validation). Shanarova designed a machine learning-based diagnostic for schizophrenia using event-related potential data, achieving a sensitivity and specificity of 91% and 90.8%, respectively [18]. Overall, the prospects for machine learning in schizophrenia research are promising, primarily because it can analyze speech, behavior, image, and people's creativity [19]. It has been shown that various machine learning-based models can assist specialists in predicting and diagnosing schizophrenia using medical history, genetic data, and even epigenetic information [19].

The primary advantage of using machine learning to construct a classification model is its ability to extract valuable information from extensive datasets, particularly those related to feature engineering, without explicit instructions [20]. For example, machine learning techniques have great potential for quantitatively distinguishing the differences among similar feature expressions. We have previously reported that schizophrenia patients have an increased likelihood of developing diabetes, cardiovascular disease, worsening of metabolic syndrome, depression, and sleep disorders [8]. Similar findings were reported for MDD [21]. Additionally, schizophrenia patients are observed to exhibit elevated rates of smoking, drinking, and drug consumption [8], and a similar pattern is also observed in MDD and BD patients [21,22]. Schizophrenia patients typically exhibit lower health literacy [8], while older BD patients experience a faster decline in health perception [23]. However, previous studies have rarely addressed the distinctions among these similar feature expressions for those diseases. Given that our survey questionnaire delved into the aforementioned issues (namely, the information was collected quantitatively), we have reason to believe that introducing samples of MDD, BD, and OCD during the model development could improve the SZ classifier's performance.

This study had several limitations. First, the sample set used for the external validation was collected only from Central Japan and may not be representative of the broader population. Additionally, the sample size was limited. Future studies should include more patients from diverse regions, as well as healthy controls, to enhance the reliability. Second, biases may arise from the online study design. Some individuals may not use the internet frequently, and patients with severe illnesses may struggle to complete the questionnaire owing to difficulties in concentration. However, in light of the changes in people's habits following the Coronavirus pandemic in recent years, online methods such as apps have become increasingly applicable for conducting epidemiological research [24]. Third, relying on nonpsychiatric symptoms to detect the presence of mental disorders may seem arbitrary, despite yielding favorable results. Therefore, the findings of such studies should be interpreted and promoted with caution.

5. Conclusions

The SZ classifier currently faces challenges in accurately determining the presence or absence of schizophrenia at the individual level. The performance of the SZ classifier would likely improve if the data used during model development were of higher quality. Prior to widespread practical implementation, enhancements are necessary to bolster the accuracy and diminish misclassification rates. Considering the results of external validation and the inherent characteristics of machine learning techniques, there exists significant potential to improve the performance of the SZ classifier if samples of multiple diseases are included during the model development phase.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jcm13102970/s1. References [25–36] are cited in the supplementary materials.

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Brief Communications

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Can feature structure improve model's precision? A novel prediction method using artificial image and image identification

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Abstract

Objectives: This study aimed to develop an approach to enhance the model precision by artificial images.

Materials and Methods: Given an epidemiological study designed to predict *1* response using *f* features with *M* samples, each feature was converted into a pixel with certain value. Permutated these pixels into *F* orders, resulting in *F* distinct artificial image sample sets. Based on the experience of image recognition techniques, appropriate training images results in higher precision model. In the preliminary experiment, a binary response was predicted by 76 features, the sample set included 223 patients and 1776 healthy controls.

Results: We randomly selected 10 000 artificial sample sets to train the model. Models' performance (area under the receiver operating characteristic curve values) depicted a bell-shaped distribution.

Conclusion: The model construction strategy developed in the research has potential to capture feature order related information and enhance model predictability.

Lay Summary

We aimed to demonstrate a novel method to investigate the effect of feature structure on model predictability with epidemiological data. The concept was inspired from image identification. Pixels in digital images are used as features when training the identification model. The quality of a given digital image will be damaged when pixels' position and their values changed arbitrarily, which obstructs the model training and model's precision. We assume the structure-related relationship exists in epidemiological data. Given a certain dataset, features are transformed to pixel values for generating artificial images. To explore the effect of feature structure, orders of pixels are randomly permutated and the model is trained using pixel-permutated artificial image sample sets. In the preliminary experiment, one binary response was designed to be predicted by 76 features. We randomly selected 10 000 artificial image sample sets to train the model. Models' performance (area under the receiver operating characteristic curve values) depicted a bell-shaped distribution. Namely, the performance of each model's predictability was studied and the feature structure information had a strong impact on model performance. Our novel model construction strategy has potential to capture feature order related information and enhance model predictability.

Key words: artificial image; image identification; prediction model; machine learning; neural network.

Introduction

Linear models are considered as cornerstone in epidemiological studies. They are widely used for estimating associations between factors and disease,[1] and for predicting the incidence or existence of disease.[2] These models encompass a range of techniques within generalized linear regression, such as linear regression, logistic regression, and Cox regression. Previous studies reported the limitations in linear models such as explaining nonlinear association, complexed interactions, etc. Nonlinear models were adopted to solve those problems.[3,4] For example, nonlinear models represented by artificial neural networks have been introduced into epidemiological research.[5,6]

To enhance the model accuracy, previous research implemented the following solutions: (1) Increasing the number of features and expanding the sample size. (2) Optimizing the parameters in an attempt to achieve maximum accuracy.[7] (3) Comparing various machine learning methods to identify the one that yields the highest performance. For instance, employing nonlinear models (eg, neural networks, support vector machines, etc.) to address the weaknesses in linear equations caused by multicollinearity among features,[4,8] unsophisticated variable selection,[9] and to extract more complex information.

Inspired from image recognition techniques, good feature structure is the key point for model training. Taking handwritten digit recognition as an example (Figures S1 and S2 in Appendix 1), the digital picture is composed of pixels (Figure S1-a), where the pixel values range from 0 to 255 (Figure S1-b),

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corresponding to the color change from black to white (Figure S1-a). Each pixel is used as a feature for image recognition model training (Figure S1-b). If the order of the pixels is changed arbitrarily (Figure S1-c), handwritten digits cannot be correctly recognized.

This research investigated the effect of feature structure on model predictability with epidemiological data, which was less explored in this field. To introduce the feature structure, we generated artificial images with each pixel representing a feature. To explore the effect of feature structure, we randomly permutated the order of pixels and used pixel-permutated image sample sets to train the model. The model used in this study is neural networks which is an artificial intelligence-based computer analysis, designed to extract "certain information" from digitalized images. The performance of each model predictability was studied and the result showed the feature structure information had a strong impact on model performance.

On the other hand, previous studies on neural networks have demonstrated the exceptional accuracy achieved through image identification based on deep-learning techniques, often surpassing 98%.[10,11] Therefore, the method discussed in this research has potential to develop a novel method for achieving higher precision predictions using artificial images and image identification technology.

Methods

Generating the artificial image

The process of generating artificial images involved 2 key aspects: variable pixelization and pixel sequencing.

Variable pixelization

In a grayscale image, pixels are represented conventionally by an 8-bit integer giving a range of possible values from 0 to 255. This is how an image stored in computer. While data collected from an epidemiology study is not conventionally arranged. Hence, to apply image recognition techniques, variables must be rearranged between 0 and 255, as the way of pixel is represented.

For each feature in a given epidemiological study, we applied the rescale function $\mathbb{P}$ to normalize the feature's value within the range of 0 to 255. This transformation ensured that each feature could be accurately represented in the artificial images.

$$\mathbb{P}(X_n) = \left\lfloor \left(\frac{X_n - \min(X_n)}{\max(X_n) - \min(X_n)} \right) \times 255 + 0.5 \right\rfloor, \quad n = 1, \ \ldots, \ f$$

where X_n represents the value of feature n of a certain sample, $\min(X_n)$ corresponds to the minimum of X_n within the sample set, and $\max(X_n)$ corresponds the maximum of X_n within the sample set. f is the number of features. For instance, in an epidemiological study that included 5 samples; one of the features was their age: 20, 30, 40, 50, and 60 years. The age values were rescaled to 0, 64, 128, 191, and 255 gray-level. This pixelization process was crucial for ensuring that the artificial images accurately represented the underlying features.

Pixel sequencing

Given a certain epidemiology study with f features transformed to f pixels, there exist $f!$ possible pixel orders. To simplify our study design, we opted to organize pixels into a square array, without considering rotation (90°, 180°, or 270°) or flips (vertical, horizontal, or diagonal) of images. Consequently, the possibility of images being given f features is F, where F is equal to 1/8 $f!$. Figure 1 shows an example of an artificial image of a certain sample with a certain pixel order.

Dataset expansion

To study the effect of feature structure on model predictability, we generated artificial images for each sample by using variable pixelization and randomly permutated the order of pixels to create distinct sample sets.

The original dataset, denoted as S_{original}, was obtained from an epidemiological study encompassing M samples and f features with a certain feature order. As previously described, f features can generate F different orders. Hence, the S_{original} dataset was expanded to F types of distinct datasets, represented by S_1, $S_2\ldots$, S_F (Figure 2). These expanded datasets, referred to as "*candidate* datasets".

Data processing

Each of the F *candidate* datasets underwent an identical data processing procedure. Initially, we randomly divided each *candidate* dataset into training, validation, and test sets in a 70:10:20 ratio. To ensure balanced training, we applied the Synthetic Minority Oversampling Technique to the training set.[12] The model was trained using an image identification technique on the training and validation sets. Specifically, the model training process took place within the training set,

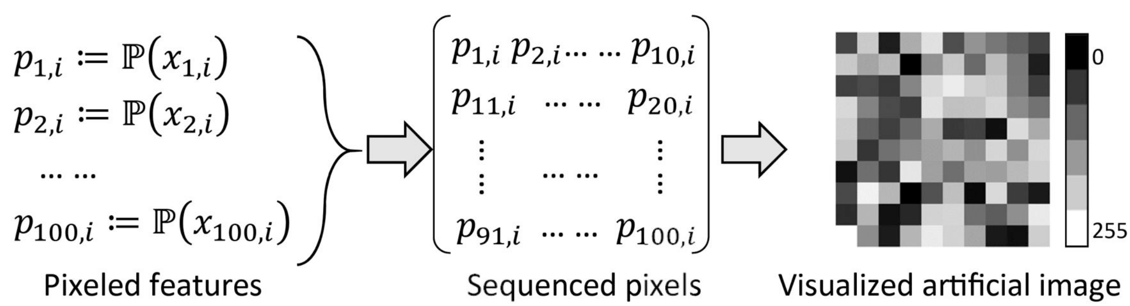

Figure 1. Given the feature information of a certain sample i, generating an artificial image by sequencing pixels in a square array—assuming the number of features is 100. $p_{n,i}$, $n = 1, \ \ldots, \ 100$ represents the pixel value of feature n for sample i calculated by function $\mathbb{P}$.

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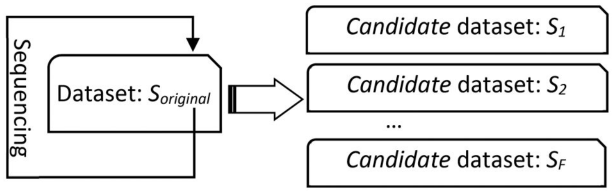

Figure 2. Dataset expansion. $S_{original}$: the original sample set with *M* samples and *f* features in a certain order. S_n, *n* = *1,2, . . ., F*: generated samples sets with distinct feature order.

with continuous validation to assess learning effectiveness. The training concluded once the loss function's value, evaluated on the validation set, ceased to increase, which indicated optimal model development. The model was then applied to the test set to assess its performance, and the results were recorded (Figure S2 in Appendix 1).

The model that achieved the highest performance was deemed the optimal prediction model. Consequently, this *candidate* dataset containing artificial images generated from a certain feature order, was considered the optimal dataset for model construction. These artificial images effectively captured the intricate relationship between the features and the response.

Preliminary experiment

In this section, we describe the process of model construction with the method introduced in previous sections. A preliminary experiment was carried out to explore the effectiveness of the method.

The model, namely the schizophrenia classifier was trained by using a sample set from online survey data collected by an internet research agency's pooled panel (Rakuten Insight, Inc., incorporated ∼2.3 million panelists by 2022).[13] The sample set comprised 223 patients with schizophrenia and 1776 healthy controls aged 20-75 years. For each sample, the following information was extracted from the survey: the existence of schizophrenia which corresponds to the response and 76 features, including demographic, health-related backgrounds, physical comorbidities, psychiatric comorbidities, and social comorbidities. The details of the study participants and variable definitions have been published elsewhere (Appendix 1).[14]

The models were trained using artificial neural network. We conducted another study using this machine learning technique based on the same dataset; therefore, we applied the same model structure to the current experiment.[15] The model was structured with 5 hidden layers (neurons per each layer: 128-64-32-16-8), HeNormal weight initializer, ReLU activation function in the hidden layers, sigmoid activation in the output layer, a learning rate of 0.01, and early stopping when 5 consecutive updates were <0.001.[15] Model performance was assessed using the area under the receiver operating characteristic curve (AUC).[15] The following AUC thresholds were used to categorize model discrimination quality: 0.5 = no discrimination; 0.5-0.7 = poor discrimination; 0.7-0.8 = acceptable discrimination; 0.8-0.9 = excellent discrimination; and >0.9 = outstanding discrimination. Given the extensive permutations of feature orders (namely, 1/8 × 76!), we experimented with 10 000 randomly selected *candidate* datasets to explore the impact of different feature orders on model performance. Statistical analyses were performed using Python 3.8 (Python Software Foundation, http://www.python.org), with the Jupyter Notebook (Jupyter, http://www.jupyter.org/) serving as the computational environment.

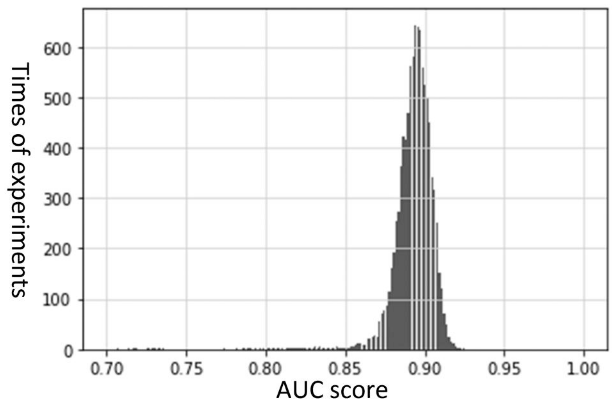

Figure 3. The distribution of AUC scores from the 10 000 experiments. Abbreviation: AUC, the area under the receiver operating characteristic curve.

Results

Based on our preliminary experiment, Figure 3 illustrates the distribution of AUC scores across 10 000 experiments. The majority of models yielded an AUC score of approximately 0.88, indicating excellent discrimination. However, some models achieved AUC scores between 0.5 and 0.7, and even fewer attained scores exceeding 0.93, demonstrating outstanding discrimination (Figure 3).

Discussion

This study introduces the novel concept of an artificial image, representing a departure from traditional epidemiological research methods. The novelty of this approach lies in its transformation of features into pixels to reconstruct images in reverse, enabling the application of techniques from diverse fields to classical epidemiological research.

In our preliminary experiment, we observed that the accuracy of the trained models varied depending on the positions of the features within the artificial image. Models exhibiting high accuracy correspond to a small number of datasets. This finding indirectly supports our hypothesis regarding the existence of optimal artificial images.

The core of our method revolves around increasing the number of dimensions. By doing so, our approach becomes a powerful tool for exploring and explaining complex non-linear information. We hypothesize that the linear equation structure commonly used in generalized linear models may lead to the loss of essential information among features.[16,17] Moreover, linear equations often describe the relationship between the feature and the response as a monotonic increase or decrease which may oversimplify the intricate nature of the data. The construction of artificial images may provide a new perspective for model interpretation. For instance, we can potentially explain feature importance and feature interactions through their spatial locations within the artificial image: Features situated centrally may be considered more "important" than those on the periphery, and adjacent features may indicate closer interactions (Figure S3 in Appendix 1).

Despite the strengths of our innovative method, several challenges must be addressed for full implementation. First, the method demands significant computational power, which could potentially be mitigated with advancements in quantum computing. Second, in the preliminary experiment, the dataset lacked an adequate number of features. Therefore, it is

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insufficient to rely on more mature image-recognition technologies such as convolutional neural networks for model training. We anticipate the introduction of at least 400 features in future experiments. Third, the relationship between features and response cannot be overlooked. Even the most advanced methods may struggle to construct a high-precision prediction model when faced with either no relation or a weak relation between the features and the response. Fourth, there is another limitation during the procedure of data splitting. In this work, data was randomly split to training, validation, and test set at the 70:10:20 ratio. This might cause bias in the results, especially when the response following a skewed distribution. These are important considerations for the continued development and application of our approach.

Conclusion

In this study, we introduced a novel concept and provided evidence of its potential for developing a novel predictive method using artificial images and image identification. The model construction strategy has potential to capture feature order related information and enhance model predictability.

Acknowledgments

The concept of the study has been submitted to Japan Patent Office for applying a patent.

Author contributions

Conceptualization and design: Y.H.; Data acquisition: A.O., M.M.; Data analysis and interpretation: Y.H.; Drafting of the manuscript: Y.H.; Theoretical support: Q.S.; Revising of the manuscript: Y.H., Q.S., M.M., A.O.

Supplementary material

Supplementary material is available at *JAMIA Open* online.

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Conflicts of interest

The authors have no competing interests to declare.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Masaaki Matsunaga, Yuanying Li, Yupeng He, Taro Kishi, Shinichi Tanihara, Nakao Iwata, Takahiro Tabuchi, Atsuhiko Ota	Physical, psychiatric, and social comorbidities of individuals with schizophrenia living in the community in Japan	International Journal of Environmental Research and Public Health	20	4336	2023
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Yupeng He, Masaaki Matsunaga, Yuanying Li, Taro Kishi, Shinichi Tanihara, Nakao Iwata, Takahiro Tabuchi, Atsuhiko Ota	Classifying Schizophrenia Cases by Artificial Neural Network Using Japanese Web-Based Survey Data: Case-Control Study.	JMIR Formative Research	7	e50193	2023
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