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Comparative Analysis of Reported Adverse Events with Nirsevimab and Palivizumab in the FAERS Database

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ABSTRACT

Introduction. Respiratory syncytial virus (RSV) remains a leading cause of hospitalization among infants. Palivizumab has long been used for RSV prophylaxis in high-risk infants, whereas nirsevimab is a newer long-acting monoclonal antibody approved for broader use. Although clinical trials have demonstrated comparable safety profiles, comparative post-marketing safety data remain limited. Authors of this study compared reported adverse events associated with palivizumab and nirsevimab using the FDA Adverse Event Reporting System (FAERS).

Methods. A retrospective cross-sectional pharmacovigilance study was conducted using FAERS reports. Adverse events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes. Comparative analyses were performed using chi-square tests and binary logistic regression, with palivizumab as the reference group. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported.

Results. A total of 2,021 reports met the inclusion criteria, including 1,380 for palivizumab and 641 for nirsevimab. Compared with palivizumab reports, nirsevimab reports had higher odds of including injury, poisoning, and procedural complications (OR, 7.55; 95% CI, 5.57–10.35) and skin and subcutaneous tissue disorders (OR, 2.55; 95% CI, 1.51–4.33). Nirsevimab reports had lower odds of including infections and infestations (OR, 0.51; 95% CI, 0.40–0.65), gastrointestinal disorders (OR, 0.29; 95% CI, 0.15–0.52), investigations (OR, 0.37; 95% CI, 0.18–0.68), and respiratory, thoracic, and mediastinal disorders (OR, 0.64; 95% CI, 0.51–0.80).

Conclusions. Nirsevimab and palivizumab demonstrated distinct post-marketing adverse event reporting patterns. Continued post-marketing surveillance is warranted to further characterize the safety profiles of both agents.

INTRODUCTION

Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory tract infections among infants worldwide.[1] In 2019, an estimated 1.4 million RSV-associated hospital admissions occurred among infants aged 0-6 months, resulting in approximately 13,300 in-hospital deaths globally.[1] In the United States, RSV is highly prevalent among infants, with 53.4% of healthy term infants infected during their first year of life.[2] Although most infections are mild, RSV remains a leading cause of pediatric hospitalization, with a hospitalization rate of 8.5 per 1,000 infants aged 0-7 months during the 2024-2025 RSV season.[3]

Management of RSV infection primarily is supportive and includes respiratory support when needed. Additional therapies include ribavirin, monoclonal antibodies, glucocorticoids, and bronchodilators.[4] Ribavirin, a nucleoside analog that inhibits both DNA and RNA virus replication, is expensive and teratogenic, limiting its use primarily to selected immunocompromised patients. Monoclonal antibodies, including palivizumab and motavizumab, have not demonstrated significant reductions in hospital length of stay.[5,6] Likewise, glucocorticoids and bronchodilators have not been shown to improve the clinical course of hospitalized infants and children[7] or reduce hospitalization rates or duration for respiratory viral infections.[8] Consequently, preventing RSV through vaccination and passive immunization has become a major public health priority.

Palivizumab, the first passive immunization approved by the United States Food and Drug Administration (FDA) for RSV prevention, is a humanized monoclonal antibody that targets the RSV fusion (F) protein, preventing viral entry into respiratory epithelial cells.[9] Although it is not effective for treating active RSV infection, monthly intramuscular administration reduces RSV-related hospitalizations by approximately 56% among high-risk infants.[10] Nirsevimab is a recombinant human monoclonal antibody that binds the prefusion RSV F protein and likewise prevents viral entry into respiratory epithelial cells.[11] Unlike palivizumab, nirsevimab provides season-long protection with a single dose and has been shown to reduce RSV-associated hospitalizations by 78%.[12] Clinical trials have demonstrated comparable safety profiles for palivizumab and nirsevimab.[13]

Despite favorable clinical trial findings, post-marketing surveillance remains essential for detecting rare or serious adverse events that may not be identified during pre-approval studies. To our knowledge, no published study has directly compared post-marketing adverse event reports for nirsevimab and palivizumab. Given the increasing use of nirsevimab and the historical role of palivizumab in RSV prophylaxis, understanding differences in their post-marketing safety profiles is important for informing clinical practice and ensuring patient safety. Although palivizumab was discontinued on December 31, 2025, after more than two decades of clinical use, it remains an important comparator for evaluating the safety of newer long-acting monoclonal antibodies. Therefore, we compared adverse event reports associated with nirsevimab and palivizumab using the FDA Adverse Event Reporting System (FAERS).

METHODS

Participants

The United States FDA FAERS is a publicly available pharmacovigilance database used for post-marketing surveillance of pharmaceuticals and biologic products.[14] It contains voluntary reports of adverse events and medication errors submitted by health care professionals, consumers, and manufacturers. The analysis included reports submitted from July 2023, when nirsevimab received FDA approval, through March 2025, the most recent data available at the time of analysis. Reports were eligible if patients were ≤2 years of age and either nirsevimab or palivizumab was listed as the primary suspect drug. Reports with missing information required to determine eligibility or drug exposure (e.g., drug name or adverse event details) were excluded. Duplicate reports identified by matching case numbers were also excluded.

Instruments

Data extracted from FAERS included patient demographics (age, sex, and country of origin), reporter type (healthcare professional or consumer), drug characteristics (route of administration, dose, dosage form, dosing frequency, cumulative dose before the adverse event, and indication for use), reported adverse events, and patient outcomes (hospitalization, disability, life-threatening event, death, and other medically important conditions).

Adverse events were coded using the MedDRA, an internationally standardized medical terminology for regulatory reporting of medical products.[14] MedDRA classifies adverse

events using a hierarchical structure consisting of System Organ Classes (SOCs), High-Level Group Terms, High-Level Terms (HLTs), Preferred Terms (PTs), and Lowest Level Terms.

Procedures

The study was approved by the University of Kansas Medical Center Institutional Review Board (IRB). FAERS data from the third quarter of 2023 through the first quarter of 2025 were extracted and deduplicated according to FDA recommendations and published methods.[15,16] When multiple reports shared the same CASEID, the report with the most recent FDA_DT (FDA receipt date) was retained. If both the CASEID and FDA_DT were identical, the report with the higher PRIMARYID was retained. This approach ensured inclusion of the most complete and up-to-date version of each adverse event report. Both generic and brand names – palivizumab (Synagis®) and nirsevimab (Beyfortus®) – were used to identify eligible reports.

Following data extraction and deduplication, adverse events were coded using MedDRA Preferred Terms and subsequently grouped into their corresponding SOCs for analysis.

Statistical Analysis

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Data preparation included applying the eligibility criteria, removing duplicate reports, addressing missing or inconsistent data, calculating time to adverse event onset when available, and classifying adverse events according to MedDRA.

Continuous variables (e.g., age) were summarized using means, standard deviations, medians, interquartile ranges, minima, and maxima. Categorical variables (e.g., sex, reported drug, adverse event categories, and patient outcomes) were summarized using frequencies and percentages.

Baseline characteristics were compared between palivizumab and nirsevimab reports using chi-square or Fisher's exact tests for categorical variables and Student's *t*-tests or Mann-Whitney *U* tests for continuous variables, as appropriate.

To compare adverse event reporting across SOCs, separate binary logistic regression models were fitted for each SOC. The dependent variable was the presence or absence of at least one adverse event within the SOC, and the independent variable was drug exposure (nirsevimab versus palivizumab), with palivizumab serving as the reference group. Odds ratios (ORs), 95% confidence intervals (CIs), and p values were reported.

All statistical tests were two-sided, and statistical significance was defined as $p < 0.05$. Because the SOC-specific analyses were exploratory and hypothesis-generating, no adjustment was made for multiple comparisons. Findings were interpreted based on the magnitude and precision of the estimated ORs and their 95% CIs rather than statistical significance alone. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[17]

RESULTS

A total of 1,389 reports involving palivizumab (Synagis) and 670 reports involving nirsevimab (Beyfortus) were identified from the FAERS database. After applying inclusion and exclusion criteria, 38 reports were excluded due to age >2 years. The final analytic sample included 2,021 reports: 1,380 for palivizumab and 641 for nirsevimab.

Report Characteristics

Among palivizumab reports, 56.3% (n = 753; Table 1) were male. The mean age at the time of the adverse event was 6.88 months. The most frequently reported outcomes were hospitalization (69.8%, n = 713), other serious outcomes (18.1%, n = 185), and death (9.8%, n = 100). The most common indication for palivizumab use was prematurity (29.6%, n = 407).

Among nirsevimab reports, 55.6% (n = 223) were male, and the mean age at the time of the adverse event was 3.21 months. The most frequently reported outcomes were hospitalization (50.1%, n = 216), other serious outcomes (36.8%, n = 156), and death (5.9%, n = 25). The most common indication was respiratory syncytial virus immunization (34.2%, n = 145).

Preferred Terms were categorized into SOCs, and results are summarized in Table 2. Binary logistic regression demonstrated higher reporting odds among nirsevimab reports for injury, poisoning, and procedural complications (OR, 7.55; 95% CI, 5.57-10.36, $p < 0.0001$) and skin and subcutaneous tissue disorders (OR, 2.55; 95% CI, 1.51-4.33, $p < 0.001$).

Table 1. Characteristics of FAERS reports for palivizumab vs. nirsevimab.

Characteristic	Palivizumab	Nirsevimab	*t* or $\chi^2(df)$	*P*-value
Age, months	6.88 ± 5.26	3.21 ± 3.64	t = -16.4	<0.0001
Sex, n (%)			$\chi^2(1) = 0.00$	0.9000
Male	753 (56.3)	223 (55.6)		
Female	584 (43.7)	174 (43.4)		
*Missing**	43	244		
Mean weight (kg)	6.49 ± 2.60	5.25 ± 2.20	t = -8.16	<0.0001
Reporter type, n (%)			$\chi^2(3) = 946.40$	<0.0001
Health professional**	309 (22.4)	60 (12.7)		
Medical doctor	123 (8.9)	364 (76.8)		
Consumer	939 (68.1)	25 (5.3)		
Pharmacist	8 (0.6)	25 (5.3)		
*Missing**	1	167		
Serious outcomes, n (%)			$\chi^2(6) = 88.67$	<0.0001
Hospitalization	713 (69.8)	216 (50.1)		
Other serious outcomes	185 (18.1)	156 (36.8)		
Death	100 (9.8)	25 (5.9)		
Life-threatening events	19 (1.9)	18 (4.3)		
Disability	1 (0.1)	4 (0.9)		
Congenital anomaly	3 (0.3)	1 (0.24)		
Required intervention to prevent permanent damage	0 (0.0)	4 (0.94)		
*Missing**	362	222		
Top indications, n (%)			$\chi^2(111) = 1067.36$	<0.0001
Premature baby	407 (29.6)	1 (0.2)		
Antiviral prophylaxis	291 (21.2)	111 (26.2)		
RSV immunization	12 (1.0)	145 (34.2)		
Immunization	2 (0.2)	99 (23.4)		
Unknown indication	190 (12.8)	12 (2.4)		

*Percentages were calculated using reports with non-missing data for each variable. Missing values are presented as counts and were excluded from percentage calculations and statistical comparisons.
**Health professionals included nurses, physician assistants, and other healthcare workers other than physicians.

In contrast, nirsevimab was associated with lower reporting odds for infections and infestations (OR, 0.51; 95% CI, 0.40-0.65, p <0.0001), gastrointestinal disorders (OR, 0.29; 95% CI, 0.15-0.52, p <0.0001), investigations (OR, 0.37; 95% CI, 0.18-0.68, p = 0.0027), and respiratory, thoracic, and mediastinal disorders (OR, 0.64; 95% CI, 0.51-0.80, p <0.001), indicating relatively higher reporting among palivizumab cases.

To further explore SOC-level differences, we examined the distribution of corresponding HLTs within these categories. Table 3 summarizes the most frequently reported HLTs and highlights specific event types contributing to the observed SOC-level differences.

DISCUSSION

Post-marketing surveillance plays an essential role in evaluating drug safety in real-world clinical settings, particularly following the introduction of newly approved therapies. Early post-marketing periods often are characterized by increased adverse event reporting due to expanded clinical adoption, heightened awareness, and increased reporting vigilance among healthcare professionals. Similar patterns have been documented during the early rollout of nirsevimab in Spain, where implementation was associated with increased reporting as utilization expanded.[18] These findings highlight the importance of continued pharmacovigilance during the early adoption phase of novel immunoprophylactic agents, when reporting patterns may reflect both clinical experience and system-level implementation effects.

Demographic and Clinical Characteristics

In this analysis, palivizumab reports involved a slightly

Table 2. Comparison of adverse events by system organ class between palivizumab and nirsevimab, FAERS 2023–2025.

System Organ Class	Palivizumab	Nirsevimab	Odds Ratio (95% CI)
Blood and lymphatic system disorders	8 (0.6%)	3 (0.5%)	0.81 (0.18–2.80)
Cardiac disorders	31 (2.3%)	8 (1.3%)	0.55 (0.23–1.15)
Congenital, familial and genetic disorders	3 (0.2%)	2 (0.3%)	1.44 (0.19–8.69)
Ear and labyrinth disorders	1 (0.1%)	0 (0%)	N/A
Eye disorders	5 (0.4%)	5 (0.8%)	2.16 (0.60–7.80)
Gastrointestinal disorders	84 (6.1%)	12 (1.9%)	0.29 (0.15-0.52)
General disorders and administration site conditions	251 (18.2%)	124 (19.3%)	1.08 (0.85–1.37)
Hepatobiliary disorders	3 (0.2%)	0 (0%)	N/A
Immune system disorders	6 (0.4%)	3 (0.5%)	1.08 (0.23–4.10)
Infections and infestations	337 (24.4%)	91 (14.2%)	0.51 (0.40-0.65)
Injury, poisoning and procedural complications	62 (4.5%)	168 (26.2%)	7.55 (5.57-10.35)
Investigations	62 (4.5%)	11 (1.7%)	0.37 (0.18-0.68)
Metabolism and nutrition disorders	26 (1.9%)	9 (1.4%)	0.74 (0.32-1.53)
Musculoskeletal and connective tissue disorders	6 (0.4%)	1 (0.2%)	0.36 (0.01-2.1)
Neoplasms benign, malignant and unspecified	2 (0.1%)	2 (0.3%)	2.15 (0.25-18.0)
Nervous system disorders	31 (2.3%)	23 (3.6%)	1.62 (0.93–2.79)
Pregnancy, puerperium and perinatal conditions	1 (0.1%)	1 (0.2%)	2.15 (0.09–54.55)
Psychiatric disorders	12 (1.0%)	2 (0.3%)	0.33 (0.05–1.20)
Renal and urinary disorders	5 (0.36%)	1 (0.2%)	0.43 (0.02–2.67)
Reproductive system and breast disorders	1 (0.1%)	0 (0%)	N/A
Respiratory, thoracic and mediastinal disorders	387 (28.0%)	128 (20.0%)	0.64 (0.51–0.80)
Skin and subcutaneous tissue disorders	27 (2.0%)	31 (4.8%)	2.55 (1.51–4.33)
Social circumstances	1 (0.1%)	2 (0.3%)	4.32 (0.41–92.98)
Surgical and medical procedures	7 (0.5%)	4 (0.62%)	1.23 (0.32–4.09)
Vascular disorders	20 (1.5%)	10 (1.6%)	1.08 (0.48–2.26)

Note: OR, Odds Ratio (palivizumab was the reference); CI, Confidence Interval.

higher proportion of male patients (56.3%), consistent with prior literature, including Chen et al.,[19] which also reported male predominance among RSV prophylaxis recipients. The mean age of reported cases was 6.9 months. In contrast, nirsevimab reports showed a similar male predominance (55.6%) but a younger mean age of 3.21 months, consistent with Spanish pharmacovigilance data reporting a comparable age distribution and male predominance.[18] These similarities suggest consistency in demographic reporting patterns across settings.

Differences in reported serious outcomes were observed between the two drugs. Hospitalization and death were more frequently reported in palivizumab cases, whereas life-threatening events and other serious outcomes were proportionally more common in nirsevimab reports. However, these differences should be interpreted cautiously. Palivizumab is primarily used in high-risk infants, including those born prematurely or with underlying cardiopulmonary disease, whereas nirsevimab is administered to a broader infant population, including otherwise healthy infants. Therefore, differences in baseline clinical risk, indication, and reporting sources likely contribute to observed outcome differences rather than true differences in safety profiles.

System Organ Class Findings

At the SOC level, palivizumab reports most frequently involved respiratory, thoracic, and mediastinal disorders (28.0%), infections and infestations (24.4%), and general disorders and administration site conditions (18.2%). These findings are consistent with known clinical trial data, which report fever, respiratory infections, and injection-site reactions as common adverse events.[20] Rare hypersensitivity reactions were infrequently reported, consistent with previous studies.[20]

For nirsevimab, the most frequently reported SOCs included injury, poisoning, and procedural complications (26.2%), respiratory disorders (20.0%), and general disor-

Table 3. Most frequently reported high-level terms within significant system organ classes.

System Organ Class/ High-Level Term	Palivizumab	Nirsevimab
Skin and subcutaneous tissue disorders		
Rashes, eruptions, and exanthems NEC	0.4% (n = 6)	1.7% (n = 11)
Urticarias	0.0% (n = 0)	0.9% (n = 6)
Infections and infestations		
Respiratory syncytial viral infections	5.4% (n = 74)	12.0% (n = 77)
Upper respiratory tract infections	3.7% (n = 51)	0.2% (n = 1)
Lower respiratory tract and lung infections	3.1% (n = 43)	0.5% (n = 3)
Influenza viral infections	2.5% (n = 35)	0.2% (n = 1)
Coronavirus infections	2.5% (n = 35)	0.3% (n = 2)
Gastrointestinal disorders		
Nausea and vomiting symptoms	0.4% (n = 6)	0.3% (n = 2)
Diarrhea (excluding infective)	0.4% (n = 6)	0.0% (n = 0)
Gastrointestinal signs and symptoms NEC	0.2% (n = 3)	0.0% (n = 0)
Investigations		
Blood gas and acid-base analyses	0.4% (n = 6)	0.2% (n = 1)
Physical examination procedures and organ system status	0.3% (n = 4)	0.0% (n = 0)
Respiratory, thoracic, and mediastinal disorders		
Bronchial conditions NEC	7.0% (n = 96)	11.2% (n = 72)
Coughing and associated symptoms	7.8% (n = 108)	2.2% (n = 14)
Breathing abnormalities	5.0% (n = 69)	2.7% (n = 17)
Injury, poisoning, and procedural complications		
Product administration errors and issues	1.6% (n = 22)	18.0% (n = 115)
Product storage errors and issues in the product use system	0.0% (n = 0)	3.3% (n = 21)
Medication/product use errors and issues NEC	0.1% (n = 2)	1.6% (n = 10)

Note: NEC, Not elsewhere classified.

ders and administration site conditions (19.3%). The injury, poisoning, and procedural complications category was largely driven by administration errors, product storage issues, and medication use errors. These findings likely reflect real-world implementation challenges associated with early adoption of a newly introduced product rather than pharmacologic toxicity. Similar patterns were observed during early national rollout in Spain.[18]

Respiratory-related events included both therapeutic and non-therapeutic responses and were broadly consistent with clinical trial findings, including injection-site reactions and rash, which were reported as uncommon adverse events.[21] A subset of nirsevimab reports included RSV infection (12.0%), which may represent breakthrough infections; however, FAERS data cannot confirm infection status, causality, or prophylactic effectiveness due to the absence of denominators and detailed clinical information.[22]

Comparative Adverse Event Patterns

Comparative analysis demonstrated differences across several SOCs, including infections and infestations, respiratory disorders, gastrointestinal disorders, investigations, skin disorders, and injury, poisoning, and procedural complications.

Infections and infestations were more frequently reported in palivizumab cases (24.4%) compared with nirsevimab (14.2%). However, RSV infection specifically was more frequently reported in nirsevimab cases (12.0% vs 5.4%). This discrepancy may reflect several factors, including misclassification (e.g., prophylaxis indication recorded as an adverse event), breakthrough infection reporting, or differences in coding practices. FAERS does not allow determination of true infection rates or comparative effectiveness. Additionally, higher infection-related reporting in the palivizumab group may reflect its use in higher-risk infants with prematurity or cardiopulmonary disease, who are inherently more susceptible to infection. These baseline differences limit direct comparison and support a descriptive, hypoth-

esis-generating interpretation.

A marked difference was observed in injury, poisoning, and procedural complications, which were substantially higher in nirsevimab reports (26.2% vs 4.5%). This category was predominantly driven by administration and handling errors. These findings are likely to reflect implementation challenges associated with a newly introduced product. In contrast, palivizumab has been in clinical use for over two decades with well-established administration protocols. Increased reporting among healthcare professionals for nirsevimab also may reflect heightened vigilance related to a newly approved therapy. Overall, these findings likely represent system-level implementation issues rather than intrinsic drug toxicity and may decrease as clinical familiarity increases.

Respiratory, thoracic, and mediastinal disorders were more frequently reported with palivizumab (28.0% vs 20.0%), largely driven by cough and respiratory symptoms. Bronchial conditions not elsewhere classified were more frequently reported with nirsevimab. However, FAERS data do not permit determination of whether these differences reflect true clinical variation, differences in patient populations, or reporting behavior.

Gastrointestinal disorders and investigations also were more frequently reported in palivizumab cases. Although statistically significant, these differences were based on relatively small event counts and should be interpreted cautiously. They may reflect differences in baseline clinical complexity rather than drug-related effects.

Skin and subcutaneous tissue disorders were more frequently reported with nirsevimab, primarily driven by rash and urticaria. This may suggest differences in hypersensitivity reporting patterns between agents; however, low absolute event counts limit definitive interpretation.

Limitations

This study has several limitations inherent to FAERS. As a passive surveillance system, FAERS is subject to underreporting, reporting bias, and variability in data completeness. Reporter type differed between groups, with palivizumab reports more frequently submitted by consumers and nirsevimab reports more frequently submitted by healthcare professionals. This imbalance may influence observed reporting patterns, as healthcare professionals are more likely to report administration or handling errors, whereas consumers may be more likely to report symptoms.

In addition, differences in age, indication, and baseline clinical risk limit direct comparability between groups. Observed differences in serious outcomes likely reflect underlying patient characteristics and reporting behavior rather than true differences in safety profiles. Finally, increased reporting following nirsevimab approval may reflect heightened awareness and reporting intensity rather than true differences in adverse event frequency.

CONCLUSIONS

Nirsevimab and palivizumab demonstrated distinct post-marketing adverse event reporting patterns in FAERS. Higher reporting of procedural and administration-related events with nirsevimab likely reflects early implementation challenges, whereas higher reporting of infectious and respiratory events with palivizumab likely reflects differences in underlying patient populations. Continued pharmacovigilance is warranted to further characterize the real-world safety profiles of these agents.

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Keywords: *respiratory syncytial virus; palivizumab; nirsevimab; pharmacovigilance; drug-related side effects and adverse reactions*

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Associations of Physical Activity and Sleep with Depression, Anxiety, and Loneliness Among U.S. Adults: A Population-Based Cross-Sectional Study

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ABSTRACT

Introduction. Physical activity, strength training, and sleep are important determinants of mental health. The authors of this study examined the associations of these lifestyle behaviors with emotional health outcomes among U.S. adults.

Methods. Authors conducted a cross-sectional analysis of data from the 2024 Health Information National Trends Survey® 7, a nationally representative survey of U.S. adults aged ≥18 years (N = 7278). Outcomes included depression (PHQ-2), anxiety (GAD-2), overall loneliness (PROMIS Social Isolation Short Form), social loneliness, and emotional loneliness. Predictors included moderate-intensity physical activity (≥150 min/week), strength training (≥2 days/week), and weekday and weekend sleep duration. Survey-weighted logistic and multinomial logistic regression analyses were performed, adjusting for sociodemographic and health-related covariates.

Results. Most respondents screened negative for depression (79.4%) and anxiety (78.4%), and 61.6% reported low loneliness. Most respondents did not meet the recommended levels of moderate-intensity physical activity (56.6%) or strength training (55.4%). In adjusted analyses, meeting strength-training guidelines was associated with lower odds of depression (adjusted odds ratio [aOR], 0.71; 95% confidence interval [CI], 0.53-0.95) and loneliness (aOR, 0.65; 95% CI, 0.43-0.98). Moderate-intensity physical activity was not independently associated with emotional health outcomes. Obtaining the recommended 7-9 hours of weekend sleep was associated with lower odds of depression, anxiety, and loneliness, whereas obtaining the recommended weekday sleep duration was associated with lower social and emotional loneliness.

Conclusions. Strength training and adequate sleep were independently associated with better emotional health among U.S. adults. These findings support muscle-strengthening activities and healthy sleep habits as potential targets for mental health promotion.

INTRODUCTION

Depression, anxiety, and loneliness are prevalent mental health concerns among U.S. adults and are associated with impaired functioning, reduced quality of life, and increased health care utilization.[1,2] Identifying modifiable lifestyle behaviors that promote psychological well-being is therefore a public health priority.

Physical activity and sleep are well-established behavioral determinants of mental health.[1-3] Regular moderate-intensity aerobic activity is associated with a lower risk of depression and anxiety through biological, psychological, and social mechanisms, including enhanced neuroplasticity, reduced inflammation, improved self-efficacy, and greater social engagement.[1,2,4-13] Resistance training may provide additional mental health benefits, with evidence linking muscle-strengthening activities to reduced depressive symptoms, improved self-efficacy, and greater participation in social and functional activities.[5,14-20]

Sleep also plays an important role in emotional regulation and psychological functioning. Both insufficient and excessive sleep are associated with poorer mental health, whereas recommended sleep duration is associated with a lower risk of depression and anxiety.[3,21-31] In addition, inadequate sleep may impair social functioning, contributing to social withdrawal and increased loneliness.[26-29]

These lifestyle behaviors are interconnected. Physical activity can improve sleep quality, whereas adequate sleep may facilitate sustained engagement in physical activity.[32-39] Their associations with mental health also may vary across demographic and socioeconomic groups because factors such as age, race/ethnicity, education, income, and body mass index influence both health behaviors and emotional well-being.[40-41] Although substantial evidence supports the independent associations of physical activity and sleep with mental health, fewer population-based studies have examined the relative contributions of moderate-intensity physical activity, strength training, and sleep while simultaneously accounting for demographic and socioeconomic characteristics. Therefore, we examined the associations of moderate-intensity physical activity, strength training, and sleep duration with depression, anxiety, and loneliness among U.S. adults after adjusting for demographic, socioeconomic, and health-related factors.

METHODS

Study Design and Data Source

This cross-sectional study used publicly available data from the 2024 Health Information National Trends Survey® 7 (HINTS 7).[42] The analysis included adults aged ≥18 years who completed measures of depression, anxiety, and loneliness. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[43] and Preferred Reporting Items for Complex Sample Survey Analysis (PRICSSA)[44] guidelines. Institutional Review Board approval was not required because the data were publicly available and de-identified. The NIH Office of IRB Operations designated HINTS 7 as "Not Human Subjects Research" (February 8, 2024; IRB ID: IRB002042).[45] Additional details regarding the survey methodology have been published elsewhere.[46,47]

Target Population and Sample Design

HINTS 7 is a nationally representative mail- and web-based survey of U.S. civilian, noninstitutionalized adults aged ≥18 years conducted between March 25 and September 16, 2024. A two-stage stratified sampling design was used, in which residential addresses were sampled first, followed by the selection of one adult per household. Sampling strata were expanded to incorporate rural-urban classification. The final sample included 7,278 respondents (response rate, 27.3%), representing an estimated 262,266,460 U.S. adults after weighting.[48] Table 1 presents the unweighted sample characteristics.

Outcome Variables

We examined three mental health outcomes. Participants reported how they have felt over the past two weeks. These outcomes were selected *a priori* because previous research has demonstrated associations with physical activity, strength training, and sleep.[5,20,21]

Symptoms of depression. Depression symptoms were measured using the 2-item Patient Health Questionnaire (PHQ-2),[49] which assesses the frequency of (1) little interest or pleasure in doing things and (2) feeling down, depressed, or hopeless during the previous two weeks. Responses were recorded on a 4-point Likert scale (1 = *Nearly every day to* 4 = *Not at all*). Item scores were summed (range, 2-8), with lower scores indicating greater depressive symptoms. Scores of 2-5 were categorized *a priori* as screening positive for depression, whereas scores of 6-8 were categorized as screening negative

Table 1. Demographic information (N = 7278).

Characteristics	Measure[a]
Sex	
Male	4017 (55.2)
Female	2646 (36.4)
Don't know *(a response option in the survey)*	44 (0.6)
Missing	571 (7.8)
Age, years	
Mean (SD), y	49.0 (18.0)
Median	48.3
Minimum	18
Maximum	102
Age group	
18-34	1080 (14.8)
35-49	1355 (18.6)
50-64	1728 (23.7)
65-74	1466 (20.1)
≥75	1036 (14.2)
Missing	613 (8.4)
Educational level	
Up to high school	1564 (21.5)
Post high school/some college	1941 (26.7)
College graduate	1863 (25.6)
Postgraduate	1327 (18.2)
Missing	583 (8.0)
Household income	
< $20,000	1123 (15.4)
$20,000 to < $35,000	802 (11.0)
$35,000 to < $50,000	782 (10.7)
$50,000 to < $75,000	1030 (14.2)
≥75,000 to <$100,000	785 (10.8)
≥100,000	1857 (25.5)
Missing	899 (12.4)
Race/Ethnicity	
Non-Hispanic White	3548 (48.7)
Non-Hispanic Black or African American	968 (13.3)
Hispanic	1323 (18.2)
Non-Hispanic Asian	342 (4.7)
Non-Hispanic Other	257 (3.5)
Missing	840 (11.5)
Place of residence	
Rural	1008 (13.8)
Urban	6270 (86.2)

Note: [a]Data are presented as the No. (%) of respondents unless otherwise indicated.

for depression.

Symptoms of anxiety. Anxiety symptoms were measured using the 2-item Generalized Anxiety Disorder scale (GAD-2),[49] which assesses the frequency of (1) feeling nervous, anxious, or on edge and (2) not being able to stop or control worrying during the past 2 weeks. Responses were recorded on the same 4-point Likert scale. Item scores were summed (range, 2-8), with lower scores indicating greater anxiety symptoms. Scores of 2-5 were categorized *a priori* as screening positive for anxiety, whereas scores of 6-8 were categorized as screening negative for anxiety.

Loneliness. Loneliness was measured using the 4-item PROMIS Social Isolation Short Form as reported in HINTS 7 database,[42] which assesses the frequency of feeling (1) left out, (2) isolated from others, (3) that people barely know me, and (4) that people are around me but not with me. Responses were recorded on a 5-point Likert scale (1 = *never* to 5 = *always*). Item scores were summed (range, 4-20) and categorized *a priori* as low (4-8), moderate (9-14), or high (15-20) loneliness. To examine specific dimensions of loneliness, the measure was further divided into social and emotional loneliness.

Social loneliness. Social loneliness was assessed using the first two items ("left out" and "isolated from others"), with summed scores ranging from 2 to 10. Scores of 2-4, 5-7, and 8-10 were categorized *a priori* as low, moderate, and high social loneliness, respectively.

Emotional loneliness. Emotional loneliness was assessed using the last two items ("people barely know me" and "people are around me but not with me"), with summed scores ranging from 2 to 10. Scores of 2-4, 5-7, and 8-10 were categorized *a priori* as low, moderate, and high emotional loneliness, respectively.

Predictors

Three modifiable lifestyle behaviors were selected *a priori* based on their clinical relevance and prior evidence linking them to mental health outcomes.[50,51]

Moderate-intensity physical activity. Moderate-intensity physical activity was estimated from participants' self-reported weekly frequency and duration of moderate-intensity activity. Total minutes per week were calculated and categorized as <150 or ≥150 minutes/week, consistent with the *Physical Activity Guidelines for Americans.*[52,53]

Strength training. Strength training was assessed as the number of days per week participants engaged in leisure-time muscle-strengthening activities and categorized as <2 or ≥2 days/week, consistent with national guidelines.[52,53]

Sleep. Sleep duration was assessed using participants'

self-reported average weekday and weekend sleep during the past 30 days, as collected in HINTS 7.[54] Because HINTS 7 includes measures of sleep duration but not sleep quality, analyses were limited to sleep duration. Sleep duration was categorized as <7 hours (insufficient sleep), 7-9 hours (recommended sleep), and >9 hours (long sleep), consistent with categories commonly used in sleep research.[55]

Covariates

Covariates were selected *a priori* to reduce confounding based on previous literature.[56,57] Included covariates were age (18-34, 35-49, 50-64, 65-74, and ≥75 years), sex (male, female), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Asian, and non-Hispanic Other [including American Indian or Alaska Native, Native Hawaiian, Guamanian or Chamorro, Samoan, and other Pacific Islander groups]), education (≤high school, some college/post-high school, college graduate, postgraduate), household income (<$20,000, $20,000-$34,999, $35,000-$49,999, $50,000-$74,999, $75,000-$99,999, and ≥$100,000), residence (urban, rural), and body mass index (BMI; <18.5, 18.5-24.9, 25.0-29.9, and ≥30.0 kg/m2). Rural-urban classification was based on the 2013 USDA Rural-Urban Continuum Codes (RUCC), with codes 1-3 classified as urban and codes 4-9 as rural.[54]

Missing Data

Missing data were assumed to be missing at random (MAR) and were handled using maximum likelihood estimation.[58,59] Under the MAR assumption, the probability of missingness may depend on observed characteristics but not on unobserved values. Although the MAR assumption cannot be empirically distinguished from a missing not at random (MNAR) mechanism using the observed data alone, it is widely accepted for handling incomplete survey data and helps reduce bias while improving the stability of parameter estimates and standard errors.[60]

Statistical Analysis

Analyses followed a three-stage survey-weighted approach. First, descriptive analyses summarized participant characteristics using weighted frequencies and percentages for categorical variables and weighted means for continuous variables. Second, bivariate associations between mental health outcomes and covariates (age, sex, education, race/ethnicity, residence, and BMI) were assessed using Rao-Scott adjusted chi-square tests with Bonferroni or false discovery rate correction for multiple comparisons.

Third, survey-weighted multivariable logistic regression models estimated the independent associations of lifestyle behaviors with depression and anxiety after adjustment for potential confounders. To reduce small-sample bias and address potential separation resulting from outcome imbalance, a multivariable extension of Firth's bias-reduced logistic regression was applied when appropriate (with PROC LOGISTIC).[56] Models incorporated sampling weights, stratification, and clustering, and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were reported.

Because social and emotional loneliness were categorized into three levels (low, moderate, and high), survey-weighted multinomial logistic regression with a generalized logit link was used rather than proportional odds models, thereby avoiding the proportional odds assumption. A two-sided p <0.05 was considered statistically significant. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) with PROC SURVEYLOGISTIC and a generalized *logit* link. Analyses were conducted in May 2026.

RESULTS

Demographic Information

Tables 1 and 2 summarize respondent characteristics and health outcomes. As shown in Table 1 (N = 7278), the mean age was 49.0 years (SD, 18.0); 55.2% of respondents were male, 48.7% were non-Hispanic White, 48.2% had some college education or less, 51.3% reported an annual household income <$75,000, and 86.2% resided in urban areas.

As shown in Table 2, the mean BMI was 28.8 kg/m² (SD, 6.9), and 35.8% of respondents had obesity. Most respondents screened negative for depression (79.4%) and anxiety (78.4%). Regarding loneliness, 6.8% reported high overall loneliness, 24.7% reported high social loneliness, and 6.7% reported high emotional loneliness. Most respondents did not meet the recommended levels of physical activity, with 56.6% reporting <150 minutes/week of moderate-intensity physical activity and 55.4% reporting strength training on <2 days/week. In contrast, most respondents met the recommended sleep duration on both weekdays (57.4%) and weekends (63.2%).

Table 2. Proportion of participants' emotional health outcomes and lifestyle activities, HINTS 2024 (N = 7278).

Variables	N (%)
Depression	
Screened negative	5779 (79.4)
Screen positive	1499 (20.6)
Anxiety	
Screened negative	5708 (78.4)
Screen positive	1570 (21.6)
Loneliness	
Low	4483 (61.6)
Moderate	1866 (25.6)
High	492 (6.8)
Missing	437 (6.0)
Social loneliness	
Low	3141 (43.2)
Moderate	1924 (26.4)
High	1799 (24.7)
Missing	414 (5.7)
Emotional loneliness	
Low	4661 (64.0)
Moderate	1699 (23.3)
High	487 (6.7)
Missing	431 (5.9)
Minutes per week of moderate-intensity exercise	
<150 minutes/week	4119 (56.6)
≥150 minutes/week	2643 (36.3)
Missing	516 (7.1)
Strength training	
<2 days/week	4035 (55.4)
≥2 days/week	2795 (38.4)
Missing	448 (6.2)
Weekday sleep	
<7 hours of sleep per night (insufficient sleep)	2279 (31.3)
7-9 hours of sleep per night (recommended sleep)	4176 (57.4)
>9 hours of sleep per night (long sleep)	309 (4.2)
Missing	514 (7.1)
Weekend sleep	
<7 hours of sleep per night (insufficient sleep)	1501 (20.6)
7-9 hours of sleep per night (recommended sleep)	4597 (63.2)
>9 hours of sleep per night (long sleep)	678 (9.3)
Missing	502 (6.9)
Body mass index	*n* = 6806
Mean (SD), kg/m^2	28.8 (6.9)
<18.5 kg/m^2 (Underweight)	136 (2.0)
18.5-24.9 kg/m^2 (Healthy weight)	2019 (29.7)
25.0-29.9 kg/m^2 (Overweight)	2215 (32.5)
≥30.0 kg/m^2 (Obese)	2436 (35.8)
30.0-34.9 kg/m^2 (Obesity Class I)	1348 (55.3)
35.0-39.9 kg/m^2 (Obesity Class II)	612 (25.1)
≥40.0 kg/m^2 (Severe obesity)	476 (19.5)

Note: HINTS, Health Information National Trends Survey.

Results of Bivariate Analysis

Physical activity. Table 3a presents the distribution of physical activity behaviors across respondent characteristics. Among respondents who did not meet the recommended moderate-intensity physical activity guideline (<150 minutes/week), the proportion was higher among men (38.8%; $\chi^2[2] = 70.63$, $p < 0.0001$), adults aged 50-64 years (15.8%; $\chi^2[4] = 11.42$, $p = 0.0223$), non-Hispanic White individuals (32.0%; $\chi^2[4] = 55.78$, $p < 0.0001$), respondents with some college or post-high school education (18.2%; $\chi^2[3] = 82.51$, $p < 0.0001$), those with annual household incomes ≥$100,000 (15.7%; $\chi^2[5] = 111.24$, $p < 0.0001$), and urban residents (52.1%; $\chi^2[1] = 4.04$, $p = 0.0445$).

Similarly, among respondents who did not meet the muscle-strengthening activity recommendation (<2 days/week), the proportion was higher among men (36.9%; $\chi^2[2] = 30.88$, $p < 0.0001$), adults aged 50-64 years (15.9%; $\chi^2[4] = 42.43$, $p < 0.0001$), non-Hispanic White individuals (33.1%; $\chi^2[4] = 11.08$, $p = 0.0257$), respondents with some college or post-high school education (18.3%; $\chi^2[3] = 80.87$, $p < 0.0001$), those with annual household incomes ≥$100,000 (15.6%; $\chi^2[5] = 51.69$, $p < 0.0001$), and urban residents (50.2%; $\chi^2[1] = 10.13$, $p = 0.0115$).

Mental health outcomes. Table 3b summarizes the distribution of depression, anxiety, and loneliness outcomes across respondent characteristics.

Depression. Among respondents screening negative for depression, the proportion was higher among men (49.2%; $\chi^2[2] = 15.95$, $p = 0.0003$), non-Hispanic White individuals (47.8%; $\chi^2[4] = 69.56$, $p < 0.0001$), college graduates (24.1%; $\chi^2[3] = 140.88$, $p < 0.0001$), adults aged 50-64 years (21.7%; $\chi^2[4] = 84.28$, $p < 0.0001$), and respondents with annual household incomes ≥$100,000 (27.0%; $\chi^2[5] = 315.79$, $p < 0.0001$).

Anxiety. Among respondents screening negative for anxiety, the proportion was higher among men (48.0%; $\chi^2[2] = 33.97$, $p < 0.0001$), non-Hispanic White individuals (46.7%; $\chi^2[4] = 46.79$, $p < 0.0001$), respondents with some college or postsecondary education (23.7%; $\chi^2[3] = 70.07$, $p < 0.0001$),

Table 3a. Distribution of participants' physical activities, HINTS 2024 (N = 7278).[a]

Measure	Minutes per week of moderate-intensity physical activity[b]				Strength training			
	<150 minutes/week	≥150 minutes/week	Rao-Scott $\chi^2(df)$	*P*-value	<2 days/week	≥2 days/week	Rao-Scott $\chi^2(df)$	*P*-value*
Sex			70.62 (2)	<0.0001			30.88 (2)	<0.0001
Male	2541 (38.8)	1377 (21.0)			2444 (36.9)	1513 (22.9)		
Female	1418 (21.6)	1180 (18.0)			1447 (21.9)	1171 (17.7)		
Don't know *(a response option)*	28 (0.4)	12 (0.2)			20 (0.3)	24 (0.4)		
Total	3987 (60.8)	2569 (39.2)			3911 (59.1)	2708 (40.9)		
Age category			11.42 (4)	0.0223			42.43 (4)	<0.0001
18-34	637 (9.8)	431 (6.6)			562 (8.5)	511 (7.8)		
35-49	838 (12.8)	505 (7.7)			755 (11.5)	593 (9.0)		
50-64	1033 (15.8)	662 (10.1)			1045 (15.9)	663 (10.1)		
65-74	825 (12.6)	605 (9.3)			884 (13.4)	561 (8.5)		
≥75	631 (9.7)	359 (5.5)			649 (9.9)	360 (5.5)		
Total	3964 (60.7)	2562 (39.3)			3895 (59.2)	2688 (40.8)		
Race/Ethnicity[c]			55.76 (4)	<0.0001			11.08 (4)	0.0257
Non-Hispanic White	2022 (32.0)	1476 (23.4)			2106 (33.1)	1405 (22.1)		
Non-Hispanic Black	665 (10.5)	272 (4.3)			593 (9.3)	360 (5.7)		
Hispanic	778 (12.3)	514 (8.1)			737 (11.6)	572 (9.0)		
Non-Hispanic Asian	219 (3.5)	122 (1.9)			193 (3.0)	148 (2.3)		
Non-Hispanic Other	150 (2.4)	102 (1.6)			144 (2.3)	113 (1.8)		
Total	3834 (60.7)	2486 (39.3)			3773 (59.2)	2598 (40.8)		
Educational level			82.51 (3)	<0.0001			80.87 (3)	<0.0001
Up to high school	1022 (15.6)	470 (7.2)			1004 (15.2)	523 (7.9)		
Post high school/some college	1192 (18.2)	705 (10.8)			1209 (18.3)	709 (10.7)		
College graduate	1075 (16.4)	768 (11.7)			1008 (15.3)	834 (12.6)		
Postgraduate	689 (10.5)	622 (9.5)			689 (10.4)	631 (9.6)		
Total	3978 (60.8)	2565 (39.2)			3910 (59.2)	2697 (40.8)		
Household income			111.24 (5)	<0.0001			51.69 (5)	<0.0001
< $20,000	757 (12.1)	319 (5.1)			687 (10.9)	399 (6.3)		
$20,000 to < $35,000	534 (8.5)	241 (3.9)			516 (8.2)	277 (4.4)		
$35,000 to < $50,000	484 (7.7)	291 (4.7)			486 (7.7)	289 (4.6)		
$50,000 to < $75,000	603 (9.6)	414 (6.6)			609 (9.7)	416 (6.6)		
≥75,000 to <$100,000	443 (7.1)	330 (5.3)			452 (7.2)	326 (5.2)		
≥$100,000	981 (15.7)	858 (13.7)			981 (15.6)	867 (13.8)		
Total	3802 (60.8)	2453 (39.2)			3731 (59.2)	2574 (40.8)		
Place of residence			4.04 (1)	0.0445			10.13 (1)	0.0015
Rural	598 (8.8)	338 (5.0)			606 (8.9)	344 (5.0)		
Urban	3521 (52.1)	2305 (34.1)			3429 (50.2)	2451 (35.9)		
Total	4119 (60.9)	2643 (39.1)			4035 (59.1)	2795 (40.9)		

[a]Data are presented as the No. (%) of respondent. [b]Frequencies and proportions were derived from the weighted survey analysis, with unweighted frequencies reported in the table. Chi-square statistics and corresponding p-values were calculated using the Rao–Scott first-order adjusted chi-square test. [c]Non-Hispanic Other included American Indian or Alaska Native, Native Hawaiian, Guamanian or Chamorro, Samoan, and Other Pacific Islander. *The association between the variables were tested using Rao-Scott chi-square based on the weighted survey results.

Table 3b. Distribution of participants' mental health outcomes, HINTS 2024 (N = 7278).[a]

Measure	Depression[b]				Anxiety[b]			
	Screened negative	Screened positive	Rao-Scott $\chi^2(df)$	*P*-value	Screened negative	Screened positive	Rao-Scott $\chi^2(df)$	*P*-value
Sex			15.95 (2)	0.0003			33.97 (2)	<0.0001
Male	3297 (49.2)	720 (10.7)			3218 (48.0)	799 (11.9)		
Female	2263 (33.7)	383 (5.7)			2267 (33.8)	379 (5.7)		
Don't know *(a response option)*	33 (0.5)	11 (0.2)			36 (0.5)	8 (0.1)		
Total	5593 (83.4)	1114 (16.6)			5521 (82.3)	1186 (17.7)		
Age category			84.28 (4)	<0.0001			219.41 (4)	<0.0001
18-34	817 (12.3)	263 (4.0)			745 (11.2)	335 (5.0)		
35-49	1106 (16.6)	249 (3.7)			1069 (16.0)	286 (4.3)		
50-64	1446 (21.7)	282 (4.2)			1453 (21.8)	275 (4.1)		
65-74	1288 (19.3)	178 (2.7)			1311 (19.7)	155 (2.3)		
≥75	907 (13.6)	129 (1.9)			910 (13.7)	126 (1.9)		
Total	5564 (83.5)	1101 (16.5)			5488 (82.3)	1177 (17.7)		
Race/Ethnicity[c]			69.56 (4)	<0.0001			46.79 (4)	<0.0001
Non-Hispanic White	3076 (47.8)	472 (7.3)			3007 (46.7)	541 (8.4)		
Non-Hispanic Black	787 (12.2)	181 (2.8)			803 (12.5)	165 (2.6)		
Hispanic	1037 (16.1)	286 (4.4)			1014 (15.8)	309 (4.8)		
Non-Hispanic Asian	298 (4.6)	44 (0.7)			290 (4.5)	52 (0.8)		
Non-Hispanic Other	195 (3.0)	62 (1.0)			205 (3.2)	52 (0.8)		
Total	5393 (83.8)	1045 (16.2)			5319 (82.6)	1119 (17.4)		
Educational level			140.88 (3)	<0.0001			76.07 (3)	<0.0001
Up to high school	1181 (17.6)	383 (5.7)			1193 (17.8)	371 (5.5)		
Post high school/some college	1588 (23.7)	353 (5.3)			1587 (23.7)	354 (5.3)		
College graduate	1616 (24.1)	247 (3.7)			1564 (23.4)	299 (4.5)		
Postgraduate	1204 (18.0)	123 (1.8)			1172 (17.5)	155 (2.3)		
Total	5589 (83.5)	1106 (16.5)			5516 (82.4)	1179 (17.6)		
Household income			315.79 (5)	<0.0001			221.32 (5)	<0.0001
< $20,000	775 (12.2)	348 (5.5)			776 (12.2)	347 (5.4)		
$20,000 to < $35,000	632 (9.9)	170 (2.7)			633 (9.9)	169 (2.7)		
$35,000 to < $50,000	639 (10.0)	143 (2.2)			638 (10.0)	144 (2.3)		
$50,000 to < $75,000	856 (13.4)	174 (2.7)			856 (13.4)	174 (2.7)		
≥75,000 to <$100,000	699 (11.0)	86 (1.4)			680 (10.7)	105 (1.7)		
≥$100,000	1721 (27.0)	136 (2.1)			1666 (26.1)	191 (3.0)		
Total	5322 (83.4)	1057 (16.6)			5249 (82.3)	1130 (17.7)		
Place of residence			0.01 (1)	0.9072			0.04 (1)	0.8330
Rural	799 (11.0)	209 (2.9)			788 (10.8)	220 (3.0)		
Urban	4980 (68.4)	1290 (17.7)			4920 (67.6)	1350 (18.6)		
Total	5779 (79.4)	1499 (20.6)			5708 (78.4)	1570 (21.6)		

Continued on next page.

Table 3b. ***Continued.***

	Overall Loneliness[b]				
Measure	**Low**	**Moderate**	**High**	**Rao-Scott χ^2(*df*)**	***P*-value***
Sex				25.61 (4)	<0.0001
Male	2512 (38.0)	1147 (17.3)	302 (4.6)		
Female	1797 (27.2)	652 (9.9)	163 (2.5)		
Don't know *(a response option)*	27 (0.4)	10 (0.2)	7 (0.1)		
Total	4336 (65.5)	1809 (27.3)	472 (7.1)		
Age category				279.49 (8)	<0.0001
18-34	533 (8.1)	393 (6.0)	150 (2.3)		
35-49	797 (12.1)	432 (6.6)	119 (1.8)		
50-64	1136 (17.3)	461 (7.0)	107 (1.6)		
65-74	1062 (16.1)	313 (4.8)	63 (1.0)		
≥75	777 (11.8)	206 (3.1)	31 (0.5)		
Total	4305 (65.4)	1805 (27.4)	470 (7.1)		
Race/Ethnicity[c]				60.30 (8)	<0.0001
Non-Hispanic White	2289 (36.0)	1010 (15.9)	221 (3.5)		
Non-Hispanic Black	656 (10.3)	226 (3.6)	72 (1.1)		
Hispanic	854 (13.4)	338 (5.3)	107 (1.7)		
Non-Hispanic Asian	237 (3.7)	82 (1.3)	20 (0.3)		
Non-Hispanic Other	123 (1.9)	95 (1.5)	38 (0.6)		
Total	4159 (65.3)	1751 (27.5)	458 (7.2)		
Educational level				61.45 (6)	<0.0001
Up to high school	1011 (15.3)	361 (5.5)	154 (2.3)		
Post high school/some college	1228 (18.6)	537 (8.1)	153 (2.3)		
College graduate	1180 (17.9)	564 (8.5)	101 (1.5)		
Postgraduate	912 (13.8)	348 (5.3)	58 (0.9)		
Total	4331 (65.6)	1810 (27.4)	466 (7.1)		
Household income				149.86 (10)	<0.0001
< $20,000	616 (9.8)	330 (5.2)	152 (2.4)		
$20,000 to < $35,000	490 (7.8)	240 (3.8)	56 (0.9)		
$35,000 to < $50,000	486 (7.7)	226 (3.6)	67 (1.1)		
$50,000 to < $75,000	669 (10.6)	280 (4.4)	75 (1.2)		
≥75,000 to <$100,000	525 (8.3)	211 (3.3)	40 (0.6)		
≥$100,000	1317 (20.9)	467 (7.4)	61 (1.0)		
Total	4103 (65.0)	1754 (27.8)	451 (7.2)		
Place of residence				5.24 (2)	0.0728
Rural	607 (8.9)	265 (3.9)	85 (1.2)		
Urban	3876 (56.7)	1601 (23.4)	407 (6.0)		
Total	4483 (65.5)	1866 (27.3)	492 (7.2)		

[a]Data are presented as the No. (%) of respondent. [b]The frequencies and proportions were derived from the weighted survey analysis, with unweighted frequencies reported in the table. Chi-square statistics and corresponding p-values were calculated using the Rao–Scott first-order adjusted chi-square test. [c]Non-Hispanic Other included American Indian or Alaska Native, Native Hawaiian, Guamanian or Chamorro, Samoan, and Other Pacific Islander. *The association between the variables were tested using Rao-Scott chi-square based on the weighted survey results.

adults aged 50-64 years (21.8%; $\chi^2[4] = 219.41$, p <0.0001), and those with annual household incomes ≥$100,000 (26.1%; $\chi^2[5] = 221.32$, p <0.0001).

Loneliness. Among respondents reporting high loneliness, the proportion was higher among men (4.6%; $\chi^2[4] = 25.61$, p <0.0001), non-Hispanic White individuals (3.5%; $\chi^2[8] = 60.30$, p <0.0001), respondents with some college or postsecondary education (2.5%; $\chi^2[6] = 61.45$, p <0.0001), adults aged 18-34 years (2.3%; $\chi^2[8] = 279.49$, p <0.0001), and respondents with annual household incomes <$20,000 (20.9%; $\chi^2[10] = 149.86$, p <0.0001).

Results of Multivariable Analysis

Table 4a presents survey-weighted multivariable logistic regression results comparing respondents who screened positive versus negative for depression and anxiety. Tables 4b and 4c present survey-weighted multinomial regression results examining associations with overall, social, and emotional loneliness.

Depression. Meeting moderate-intensity physical activity guidelines (≥150 minutes/week) was not associated with screening positive for depression in unadjusted or adjusted analyses. In contrast, meeting strength-training guidelines (≥2 days/week) was associated with lower odds of screening positive for depression in both unadjusted (OR, 0.69; 95% CI, 0.54-0.88) and adjusted analyses (aOR, 0.71; 95% CI, 0.53-0.95). Weekday sleep duration was not associated with depression; however, obtaining 7-9 hours of weekend sleep was associated with lower odds of screening positive for depression in unadjusted (OR, 0.49; 95% CI, 0.34-0.70) and adjusted analyses (aOR, 0.57; 95% CI, 0.39-0.84; Table 4a).

In adjusted analyses, overweight BMI category (aOR, 0.71; 95% CI, 0.51-0.99), non-Hispanic Asian race/ethnicity (aOR, 0.37; 95% CI, 0.17-0.80), and higher household income (≥$100,000; aOR, 0.23; 95% CI, 0.14-0.38) were associated with lower odds of screening positive for depression. Conversely, adults aged 18-34 years had higher odds of screening positive for depression (aOR, 3.33; 95% CI, 2.00-5.57; Table 4a).

Anxiety. Moderate-intensity physical activity and strength-training guidelines were not associated with screening positive for anxiety in unadjusted or adjusted analyses. Similarly, weekday sleep duration was not associated with anxiety. However, obtaining 7-9 hours of weekend sleep was associated with lower odds of screening positive for anxiety in unadjusted (OR, 0.54; 95% CI, 0.38-0.77) and adjusted analyses (aOR, 0.51; 95% CI, 0.35-0.75; Table 4a).

In adjusted analyses, non-Hispanic Black race/ethnicity (aOR, 0.59; 95% CI, 0.41-0.86) and household income ≥$100,000 (aOR, 0.25; 95% CI, 0.16-0.40) were associated with lower odds of screening positive for anxiety. Adults aged 18-34 years had higher odds of screening positive for anxiety (aOR, 5.73; 95% CI, 3.18-10.34; Table 4a).

Overall loneliness. Meeting moderate-intensity physical activity guidelines was not associated with high loneliness in unadjusted or adjusted analyses. In contrast, meeting strength-training guidelines was associated with lower odds of reporting high loneliness in unadjusted (OR, 0.60; 95% CI, 0.42-0.85) and adjusted analyses (aOR, 0.65; 95% CI, 0.43-0.98). Obtaining 7-9 hours of sleep on weekdays and weekends also was associated with lower odds of reporting high loneliness in adjusted analyses (weekday: aOR, 0.57; 95% CI, 0.37-0.88; weekend: aOR, 0.44; 95% CI, 0.27-0.70; Table 4b).

In multinomial models, non-Hispanic Black race/ethnicity (aOR, 0.46; 95% CI, 0.28-0.77) and household income ≥$100,000 (aOR, 0.34; 95% CI, 0.17-0.66) were associated with lower odds of high loneliness. Adults aged 18-34 years had higher odds of high loneliness (aOR, 26.28; 95% CI, 11.81-58.49; Table 4b).

Social loneliness. Meeting moderate-intensity physical activity and strength-training guidelines was not associated with high social loneliness. However, obtaining 7-9 hours of weekday sleep was associated with lower odds of high social loneliness in unadjusted (OR, 0.64; 95% CI, 0.49-0.82) and adjusted analyses (aOR, 0.58; 95% CI, 0.44-0.76). Weekend sleep duration was not associated with social loneliness (Table 4c).

In adjusted multinomial models, female sex (aOR, 0.77; 95% CI, 0.59-0.99), high school education or less (aOR, 0.59; 95% CI, 0.36-0.98), non-Hispanic Black race/ethnicity (aOR, 0.43; 95% CI, 0.30-0.61), and household income ≥$100,000 (aOR, 0.32; 95% CI, 0.21-0.48) were associated with lower odds of high social loneliness. Adults aged 18-34 years had higher odds of high social loneliness (aOR, 4.47; 95% CI, 2.78-7.16; Table 4c).

Emotional loneliness. Meeting moderate-intensity physical activity guidelines (≥150 minutes/week) was not associated with high emotional loneliness in either unadjusted or adjusted analyses. Meeting strength-training guidelines (≥2 days/week) was associated with lower odds of reporting high

Table 4a. Factors associated with mental health outcomes, HINTS 2024.

Variable	Depression[a] Screened positive vs Screened negative		Anxiety[b] Screened positive vs Screened negative	
	aOR (95% Confidence Limits)	Standard Error	aOR (95% Confidence Limits)	Standard Error
Intercept		0.16		0.17
Minutes per week of moderate-intensity exercise				
≥150 minutes/week vs <150 minutes/week	0.83 (0.61, 1.13)	0.08	1.00 (0.74, 1.36)	0.08
Strength training				
≥2 days/week vs <2 days/week	**0.71 (0.53, 0.95)**	**0.07**	0.91 (0.69, 1.21)	0.07
Weekday sleep				
7-9 hours of sleep per night vs <7 hours of sleep per night	0.72 (0.52, 1.00)	0.12	0.73 (0.53, 1.01)	0.12
>9 hours of sleep per night vs <7 hours of sleep per night	1.67 (0.85, 3.29)	0.23	1.36 (0.66, 2.84)	0.23
Weekend sleep				
7-9 hours of sleep per night vs <7 hours of sleep per night	**0.57 (0.39, 0.84)**	**0.10**	**0.51 (0.35, 0.75)**	**0.10**
>9 hours of sleep per night vs <7 hours of sleep per night	0.64 (0.38, 1.08)	0.15	0.62 (0.37, 1.05)	0.15
Body Mass Index				
Underweight vs Obese	1.85 (0.73, 4.67)	0.34	1.46 (0.57, 3.75)	0.10
Healthy weight vs Obese	0.84 (0.58, 1.22)	0.15	0.78 (0.55, 1.11)	0.15
Overweight vs Obese	**0.71 (0.51, 0.99)**	**0.14**	0.90 (0.66, 1.22)	
Age, y				
18-34 vs ≥75	**3.33 (2.00, 5.57)**	**0.15**	**5.73 (3.18, 10.34)**	**0.15**
35-49 vs ≥75	**2.45 (1.50, 4.02)**	**0.11**	**3.06 (1.83, 5.10)**	**0.11**
50-64 vs ≥75	**2.37 (1.46, 3.85)**	**0.12**	**2.29 (1.35, 3.88)**	**0.12**
65-74 vs ≥75	**1.09 (0.65, 1.84)**	**0.18**	1.01 (0.54, 1.87)	0.18
Sex				
Female vs Male	1.09 (0.79, 1.49)	0.08	0.77 (0.57, 1.05)	0.08
Educational level				
Up to high school vs postgraduate	1.34 (0.82, 2.18)	0.13	1.12 (0.68, 1.84)	0.13
Post high school/some college vs postgraduate	1.16 (0.80, 1.68)	0.11	0.87 (0.56, 1.35)	0.11
College graduate vs postgraduate	1.26 (0.82, 1.93)	0.12	1.04 (0.68, 1.60)	0.12
Race and ethnicity				
Non-Hispanic Black vs Non-Hispanic White	0.81 (0.58, 1.13)	0.17	**0.59 (0.41, 0.86)**	**0.17**
Hispanic vs Non-Hispanic White	1.09 (0.81, 1.46)	0.13	0.96 (0.71, 1.32)	0.13
Non-Hispanic Asian vs Non-Hispanic White	**0.37 (0.17, 0.80)**	**0.34**	0.63 (0.28, 1.41)	0.34
Non-Hispanic Other vs Non-Hispanic White	1.55 (0.81, 3.00)	0.28	0.84 (0.45, 1.58)	0.28
Annual income, $				
20,000 to <35,000 vs <20,000	0.75 (0.49, 1.16)	0.17	0.77 (0.50, 1.18)	0.17
35,000 to <50,000 vs <20,000	**0.53 (0.35, 0.80)**	**0.15**	**0.42 (0.27, 0.65)**	**0.15**
50,000 to <75,000 vs <20,000	**0.55 (0.36, 0.83)**	**0.13**	**0.45 (0.30, 0.66)**	**0.13**
≥75,000 to 100,000 vs <20,000	**0.37 (0.23, 0.58)**	**0.16**	**0.47 (0.30, 0.75)**	**0.16**
>100,001 vs <20,000	**0.23 (0.14, 0.38)**	**0.15**	**0.25 (0.16, 0.40)**	**0.15**
Place of residence				
Urban vs Rural	0.91 (0.64, 1.29)	0.11	0.86 (0.57, 1.29)	0.11

Note: HINTS, Health Information National Trends Survey; aOR, adjusted odds ratio. [a]c-Statistics: 0.72. [b]c-Statistics: 0.73.

Table 4b. Factors associated with mental health outcomes, HINTS 2024.[a]

Variable	Loneliness High vs Low		Loneliness Moderate vs Low	
	aOR (95% Confidence Limits)	Standard Error	aOR (95% Confidence Limits)	Standard Error
Intercept		0.28		0.17
Minutes per week of moderate-intensity exercise				
≥150 minutes/week vs <150 minutes/week	1.10 (0.71, 1.71)	0.11	0.88 (0.7, 1.11)	0.06
Strength training				
≥2 days/week vs <2 days/week	**0.65 (0.43, 0.98)**	**0.11**	0.96 (0.76, 1.21)	0.06
Weekday sleep				
7-9 hours of sleep per night vs <7 hours of sleep per night	**0.57 (0.37, 0.88)**	**0.16**	**0.67 (0.53, 0.84)**	**0.10**
>9 hours of sleep per night vs <7 hours of sleep per night	**3.21 (1.45, 7.11)**	**0.25**	0.67 (0.39, 1.17)	0.18
Weekend sleep				
7-9 hours of sleep per night vs <7 hours of sleep per night	**0.44 (0.27, 0.70)**	**0.13**	0.85 (0.62, 1.17)	0.09
>9 hours of sleep per night vs <7 hours of sleep per night	**0.52 (0.28, 0.98)**	**0.18**	1.21 (0.80, 1.83)	0.12
Body Mass Index				
Underweight vs Obese	0.92 (0.18, 4.63)	0.62	0.58 (0.21, 1.57)	0.38
Healthy weight vs Obese	0.81 (0.50, 1.32)	0.24	1.27 (0.98, 1.65)	0.14
Overweight vs Obese	0.80 (0.50, 1.26)	0.26	1.02 (0.79, 1.26)	0.15
Age, y				
18-34 vs ≥75	**26.28 (11.81, 58.49)**	**0.19**	**2.81 (1.88, 4.20)**	**0.11**
35-49 vs ≥75	**12.17 (5.52, 26.81)**	**0.18**	**1.67 (1.16, 2.41)**	**0.08**
50-64 vs ≥75	**8.85 (4.07, 19.23)**	**0.17**	**1.52 (1.06, 2.20)**	**0.09**
65-74 vs ≥75	**4.63 (1.81, 11.84)**	**0.29**	**1.04 (0.69, 1.56)**	**0.12**
Sex				
Female vs Male	0.86 (0.58, 1.28)	0.10	0.82 (0.64, 1.06)	0.06
Educational level				
Up to high school vs postgraduate	1.20 (0.60, 2.38)	0.20	**0.56 (0.35, 0.89)**	**0.14**
Post high school/some college vs postgraduate	1.06 (0.62, 1.81)	0.13	0.82 (0.58, 1.16)	0.10
College graduate vs postgraduate	0.72 (0.44, 1.21)	0.16	1.01 (0.74, 1.36)	0.09
Race and ethnicity				
Non-Hispanic Black vs Non-Hispanic White	**0.46 (0.28, 0.77)**	**0.21**	**0.68 (0.50, 0.93)**	**0.15**
Hispanic vs Non-Hispanic White	0.67 (0.41, 1.10)	0.19	**0.67 (0.51, 0.88)**	**0.11**
Non-Hispanic Asian vs Non-Hispanic White	0.32 (0.12, 0.85)	0.42	0.67 (0.36, 1.24)	0.25
Non-Hispanic Other vs Non-Hispanic White	1.55 (0.66, 3.64)	0.36	1.36 (0.86, 2.16)	0.18
Annual income, $				
20,000 to <35,000 vs <20,000	0.60 (0.33, 1.09)	0.23	1.11 (0.76, 1.62)	0.14
35,000 to <50,000 vs <20,000	0.84 (0.44, 1.61)	0.26	0.74 (0.47, 1.17)	0.14
50,000 to <75,000 vs <20,000	0.70 (0.40, 1.24)	0.19	**0.61 (0.42, 0.91)**	**0.13**
≥75,000 to 100,000 vs <20,000	0.64 (0.31, 1.33)	0.28	**0.55 (0.39, 0.78)**	**0.12**
>100,001 vs <20,000	**0.34 (0.17, 0.66)**	**0.23**	**0.42 (0.28, 0.61)**	**0.11**
Place of residence				
Urban vs Rural	0.75 (0.47, 1.17)	0.12	0.91 (0.69, 1.21)	0.07

Note: HINTS, Health Information National Trends Survey; aOR, adjusted odds ratio.
[a]Multinomial Logistic Regression Comparing High vs. Low Levels.

Table 4c. Factors associated with mental health outcomes, HINTS 2024.[a]

Variable	Social Loneliness High vs Low		Emotional Loneliness High vs Low	
	aOR (95% Confidence Limits)	Standard Error	aOR (95% Confidence Limits)	Standard Error
Intercept		0.21		0.35
Minutes per week of moderate-intensity exercise				
≥150 minutes/week vs <150 minutes/week	0.85 (0.65, 1.09)	0.07	0.91 (0.42, 1.97)	0.20
Strength training				
≥2 days/week vs <2 days/week	0.83 (0.64, 1.06)	0.06	0.86 (0.42, 1.76)	0.18
Weekday sleep				
7-9 hours of sleep per night vs <7 hours of sleep per night	**0.58 (0.44, 0.76)**	**0.11**	**0.56 (0.32, 0.97)**	**0.20**
>9 hours of sleep per night vs <7 hours of sleep per night	0.97 (0.50, 1.90)	0.21	5.67 (1.98, 16.24)	0.33
Weekend sleep				
7-9 hours of sleep per night vs <7 hours of sleep per night	0.71 (0.49, 1.01)	0.10	0.32 (0.17, 0.59)	0.18
>9 hours of sleep per night vs <7 hours of sleep per night	0.94 (0.57, 1.57)	0.14	0.36 (0.16, 0.82)	0.24
Body Mass Index[b]				
Underweight vs Obese	0.57 (0.14, 2.28)	0.52		
Healthy weight vs Obese	1.05 (0.78, 1.41)	0.19		
Overweight vs Obese	0.89 (0.68, 1.17)	0.19		
Age, y				
18-34 vs ≥75	**4.47 (2.78, 7.16)**	**0.12**	**52.09 (15.93, 170.39)**	**7.03**
35-49 vs ≥75	**2.61 (1.68, 4.05)**	**0.10**	**22.46 (7.01, 72.01)**	**0.26**
50-64 vs ≥75	**1.81 (1.22, 2.70)**	**0.10**	**6.74 (2.07, 21.88)**	**0.26**
65-74 vs ≥75	1.12 (0.69, 1.81)	0.14	2.34 (0.68, 8.04)	0.36
Sex				
Female vs Male	**0.77 (0.59, 0.99)**	**0.07**	1.05 (0.62, 1.79)	0.19
Educational level				
Up to high school vs postgraduate	**0.59 (0.36, 0.98)**	**0.15**	3.5 (0.98, 12.53)	0.34
Post high school/some college vs postgraduate	0.82 (0.54, 1.24)	0.11	2.19 (0.76, 6.32)	0.22
College graduate vs postgraduate	0.94 (0.66, 1.34)	0.11	1.15 (0.40, 3.30)	0.30
Race and ethnicity				
Non-Hispanic Black vs Non-Hispanic White	**0.43 (0.30, 0.61)**	**0.15**	**0.30 (0.15, 0.62)**	**0.27**
Hispanic vs Non-Hispanic White	**0.61 (0.45, 0.83)**	**0.12**	**0.29 (0.12, 0.68)**	**0.31**
Non-Hispanic Asian vs Non-Hispanic White	**0.45 (0.23, 0.88)**	**0.29**		
Non-Hispanic Other vs Non-Hispanic White	1.02 (0.59, 1.75)	0.23	0.42 (0.12, 1.50)	0.49
Annual income, $				
20,000 to <35,000 vs <20,000	0.85 (0.58, 1.25)	0.15	1.21 (0.51, 2.88)	0.34
35,000 to <50,000 vs <20,000	0.78 (0.49, 1.23)	0.15	1.46 (0.58, 3.67)	0.34
50,000 to <75,000 vs <20,000	**0.58 (0.40, 0.83)**	**0.12**	1.62 (0.65, 4.02)	0.28
≥75,000 to 100,000 vs <20,000	**0.59 (0.40, 0.87)**	**0.15**	0.91 (0.25, 3.28)	0.44
>100,001 vs <20,000	**0.32 (0.21, 0.48)**	**0.13**	0.87 (0.27, 2.82)	0.40
Place of residence				
Urban vs Rural	0.92 (0.68, 1.26)	0.08	1.96 (1.00, 3.84)	1.96

Note: HINTS, Health Information National Trends Survey; aOR, adjusted odds ratio. [a]Multinomial logistic regression comparing on low vs high levels. [b]There were insufficient observations to estimate the regression coefficient(s) for BMI.

emotional loneliness in unadjusted analyses (OR, 0.48; 95% CI, 0.31-0.73); however, this association was no longer statistically significant after adjustment. Obtaining 7-9 hours of sleep on weekdays was associated with lower odds of reporting high emotional loneliness in both unadjusted (OR, 0.25; 95% CI, 0.09-0.65) and adjusted analyses (aOR, 0.56; 95% CI, 0.32-0.97).

In multinomial models, non-Hispanic Black race/ethnicity was associated with lower odds of reporting high emotional loneliness (aOR, 0.30; 95% CI, 0.15-0.62). Conversely, adults aged 18-34 years had higher odds of reporting high emotional loneliness (aOR, 52.09; 95% CI, 15.93-170.39).

DISCUSSION

In this nationally representative sample of U.S. adults, most respondents screened negative for depression and anxiety and reported low levels of loneliness. Despite these generally favorable emotional health indicators, more than half of respondents did not meet the recommended levels of moderate-intensity physical activity or strength training.

A key finding was that meeting strength-training recommendations (≥2 days/week) was associated with lower odds of screening positive for depression and lower odds of reporting high loneliness, whereas meeting moderate-intensity physical activity guidelines was not independently associated with depression, anxiety, or loneliness after adjustment. These findings are consistent with growing evidence that resistance exercise may provide unique mental health benefits beyond those associated with moderate-intensity aerobic activity.[14,61] Previous studies have linked resistance training and greater muscular strength with lower depressive symptoms, improved psychological well-being, and enhanced self-efficacy.[61-63]

Resistance exercise may influence mental health through neurobiological, psychological, and social pathways, including reduced inflammation, enhanced neuroplasticity, improved self-efficacy, and greater social engagement.[62,63] The absence of an independent association between moderate-intensity physical activity and emotional health after adjustment may reflect residual confounding, measurement limitations of self-reported physical activity, or overlap between aerobic activity and other lifestyle or socioeconomic factors included in the multivariable models.

The association between strength training and loneliness is particularly noteworthy. Although physical activity often is examined broadly, evidence suggests that activities involving structured participation and social interaction may be especially beneficial for reducing loneliness.[64,65] Many strength-training activities may occur in social settings, such as fitness centers, exercise classes, or organized programs, which can facilitate social connection while also providing physiological benefits.[63]

Sleep emerged as the most consistent predictor of emotional health. Obtaining the recommended 7-9 hours of sleep was consistently associated with lower odds of depression, anxiety, and loneliness, particularly for weekend sleep. Recommended weekday sleep also was associated with lower odds of overall, social, and emotional loneliness. These findings are consistent with extensive evidence linking adequate sleep with improved emotional regulation, psychological well-being, and social functioning.[21-30,66-69] Sleep deprivation has been shown to impair emotional processing and increase social withdrawal, whereas adequate sleep may promote resilience, interpersonal engagement, and emotional stability.[21-29,69]

Several demographic disparities also emerged. Lower household income was consistently associated with higher odds of depression, anxiety, and loneliness, highlighting the importance of social and economic determinants of emotional health.[70] Financial strain may increase chronic stress and reduce access to resources that support psychological well-being.[70] In addition, racial and ethnic differences were observed across several outcomes. These patterns may reflect differences in social support, coping strategies, cultural norms surrounding mental health, or experiences of structural disadvantage and discrimination.[71,72]

Younger adults (18-34 years) consistently had higher odds of depression, anxiety, and loneliness than older adults. These findings align with recent studies documenting elevated mental health concerns among younger adults in the United States.[73,74] Younger adulthood often is characterized by educational, occupational, and social transitions that may increase vulnerability to emotional distress and loneliness. However, the wide confidence intervals observed for some loneliness estimates suggest that these findings should be interpreted cautiously because of limited precision.

The distinction between social and emotional loneliness provided additional insight. Recommended weekday sleep

was associated with lower odds of both social and emotional loneliness, whereas physical activity showed few independent associations after adjustment. These findings suggest that sleep may be a more consistent correlate of loneliness than physical activity alone and underscore the interconnected nature of sleep, social relationships, and emotional well-being. Given the growing recognition of loneliness as a public health concern, interventions that promote healthy sleep behaviors may represent a promising strategy for improving both mental and social health.[1,2,67]

Limitations

Several limitations should be considered. First, the cross-sectional design precludes causal inference, and reverse causation cannot be excluded. Second, all measures were self-reported and therefore subject to recall and social desirability bias. Third, physical activity and sleep were assessed using brief survey measures rather than objective assessments. Fourth, residual confounding from unmeasured variables cannot be excluded despite adjustment for multiple demographic and health-related covariates. Finally, potentially important factors, including sleep quality, social support, chronic stress, and preexisting mental and physical health conditions, were not available in HINTS 7 and may have influenced the observed associations.

Despite these limitations, this study has several strengths, including a large nationally representative sample and the use of survey-weighted analyses that enhance the generalizability of the findings to the U.S. adult population. The findings suggest that strength training and adequate sleep were more consistently associated with favorable emotional health outcomes than moderate-intensity physical activity alone. Future longitudinal and intervention studies are needed to clarify causal pathways and determine whether interventions targeting strength training and healthy sleep behaviors can reduce depression, anxiety, and loneliness among U.S. adults.

CONCLUSIONS

In this nationally representative sample of U.S. adults, strength training and adequate sleep were more consistently associated with favorable emotional health outcomes than moderate-intensity physical activity alone. Meeting strength-training recommendations was associated with lower odds of depression and loneliness, whereas obtaining the recommended sleep duration was associated with lower odds of depression, anxiety, and both social and emotional loneliness. Younger adults and individuals with lower household incomes had higher odds of adverse emotional health outcomes. These findings highlight the potential value of promoting strength training and healthy sleep behaviors as modifiable strategies to support mental and social well-being. Longitudinal studies are needed to clarify causal relationships and inform targeted interventions.

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Elevated Circulating Fibroblast Growth Factor 21 in Lean Type 2 Diabetes: Evidence of Metabolic Dysregulation in the Absence of Adiposity

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ABSTRACT

Introduction. Lean type 2 diabetes mellitus (T2DM) is a form of diabetes that develops in persons with normal Body Mass Index (BMI) and considerable metabolic impairment. High levels of Fibroblast Growth Factor-21 (FGF21) can indicate disrupted metabolic signaling in this group. The study aimed to assess circulating FGF21 levels in lean T2DM and to examine their association with insulin resistance and hepatic steatosis, both biomarkers of metabolic dysregulation.

Methods. This cross-sectional study included 425 lean adults (body mass index 18.5–22.9 kg/m^2), comprising 200 lean T2DM patients and 225 non-diabetic controls. An enzyme-linked immunosorbent assay (ELISA) was used to measure serum FGF21 levels. Insulin resistance was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and ultrasonography was used to evaluate hepatic steatosis.

Results. Lean T2DM patients had significantly higher levels of glycated hemoglobin (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR), fasting glucose, fasting insulin, low-density lipoprotein (LDL) cholesterol, aspartate aminotransferase (AST), and total cholesterol, while high-density lipoprotein (HDL) cholesterol was lower than non-diabetic controls (all $p < 0.001$). In multivariable analyses of the lean T2DM cohort, serum FGF21 was independently associated with HOMA-IR ($\beta = 0.775$, $p < 0.001$) and hepatic steatosis (OR, 1.02; 95% CI, 1.01-1.03).

Conclusions. Circulating FGF21 levels are elevated in lean T2DM and may reflect compensatory upregulation or altered FGF21 signaling rather than confirmed tissue-level resistance. FGF21 was an independent predictor of insulin resistance and hepatic steatosis, suggesting its potential as a biomarker of metabolic dysfunction in the normal-BMI group.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has traditionally been associated with obesity and metabolic syndrome; however, a substantial proportion of individuals with T2DM have a lean body phenotype.[1] These individuals often are described as having lean T2DM and may exhibit distinct metabolic characteristics, including insulin resistance, altered lipid metabolism, and increased susceptibility to hepatic steatosis compared with individuals with obesity-related T2DM.[2,3] The pathophysiology of lean T2DM remains incompletely understood, and conventional risk factors such as body mass index (BMI) do not fully explain disease development in this population.[4]

Fibroblast growth factor 21 (FGF21) is an endocrine hormone primarily secreted by the liver that plays important roles in glucose and lipid metabolism, insulin sensitivity, and energy homeostasis.[5] Experimental and clinical studies suggest that FGF21 has protective metabolic effects, including improving insulin sensitivity and reducing hepatic steatosis, making it a potential therapeutic target for metabolic diseases.[6,7] Paradoxically, elevated circulating FGF21 levels are observed in metabolic disorders such as obesity, Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), and T2DM, suggesting the presence of impaired FGF21 signaling or a state of FGF21 resistance, in which target tissues become less responsive to the hormone despite increased circulating concentrations.[7,8]

Although FGF21 resistance has been extensively studied in obesity-related metabolic disorders, its role in lean T2DM remains poorly understood.[9,10] Recent studies have demonstrated elevated circulating FGF21 levels in individuals with T2DM and have associated higher FGF21 concentrations with metabolic dysfunction and diabetes-related vascular and microvascular complications, suggesting an important role for FGF21 in the pathophysiology of T2DM.[8,11] However, evidence linking elevated FGF21 levels to insulin resistance and hepatic abnormalities specifically in lean individuals with T2DM remains limited.[12]

Understanding the mechanisms underlying metabolic dysfunction in lean T2DM is clinically important, as these individuals may develop significant metabolic complications despite the absence of obesity. Therefore, we evaluated circulating FGF21 levels in individuals with lean T2DM and examined their associations with insulin resistance and hepatic steatosis, providing insight into metabolic dysregulation that occurs independently of excess adiposity.

METHODS

Study Design and Setting

This cross-sectional study assessed circulating FGF21 levels and their associations with insulin resistance and hepatic steatosis among lean individuals with T2DM. Participants were recruited from three cardiometabolic and endocrinology clinics at tertiary care centers in the United Kingdom. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[13]

Study Population

A convenience sample of 425 adults aged 18-45 years was enrolled, including 200 individuals with lean T2DM and 225 non-diabetic controls. The age range intentionally was restricted to younger adults to minimize the potential confounding effects of age-related metabolic changes, multimorbidity, and prolonged diabetes duration, thereby enabling a more homogeneous evaluation of the association between circulating FGF21 levels, insulin resistance, and hepatic steatosis in lean T2DM. Lean T2DM was defined as physician-diagnosed T2DM in individuals with a BMI of 18.5-22.9 kg/m^2, based on the Asian BMI classification proposed by the WHO Expert Consultation and consistent with published definitions of lean T2DM.[14] Controls had normal fasting glucose levels and no history of diabetes.

Individuals with chronic liver disease, alcohol use disorder, pregnancy, incomplete laboratory data, or use of medications known to significantly affect liver function were excluded. Participants receiving oral glucose-lowering therapy were eligible, whereas insulin users were excluded. The participant selection process is shown in Figure 1.

Data Collection

Demographic and Clinical Data. Age, sex, BMI, duration of diabetes (among participants with T2DM), family history of diabetes, hypertension, smoking status, physical activity, and dietary patterns were collected using a structured questionnaire.

Laboratory Assessment. Venous blood samples were collected after an ≥8-hour overnight fast. Fasting blood glucose (mg/dL) was measured using an automated clinical chemistry analyzer (Cobas c702; Roche Diagnostics,

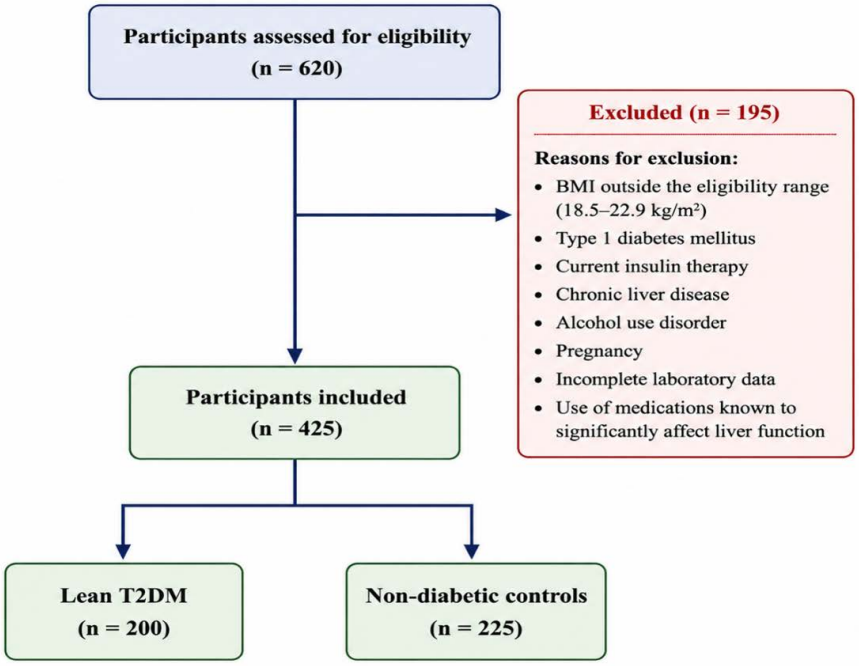

Figure 1. Participant flow diagram of study recruitment and selection.

Mannheim, Germany), and fasting serum insulin (μIU/mL) was measured using an electrochemiluminescence immunoassay analyzer (Cobas e801; Roche Diagnostics, Mannheim, Germany). Serum FGF21 concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Insulin resistance was estimated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) as follows:

HOMA-IR = [Fasting insulin (μIU/mL) × Fasting glucose (mg/dL)] / 405

Assessment of Hepatic Steatosis. Hepatic ultrasonography was performed by an experienced radiologist who was blinded to participants' clinical and biochemical data. Hepatic steatosis was graded on a scale of 0 to 3 based on hepatic echogenicity.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 26. Group comparisons were performed using the Mann–Whitney *U* test, chi-square test, or Fisher's exact test, as appropriate. Covariates were selected *a priori* based on their clinical relevance and biological plausibility for insulin resistance and hepatic steatosis. Multiple linear regression was used to identify factors independently associated with HOMA-IR, and binary logistic regression was used to identify factors independently associated with hepatic steatosis. For the binary logistic regression analysis, hepatic steatosis was dichotomized as absent (grade 0) and present (grades 1–3). Statistical significance was defined as a two-sided $p < 0.05$.

Ethical Considerations

The study was approved by the Institutional Review Board (IRB) of Lincoln County Hospital (LCH/REC/2026-0147). Written informed consent was obtained from all participants before enrollment, and all study procedures were conducted in accordance with the Declaration of Helsinki.

RESULTS

Participant Characteristics

The study included 425 participants, comprising 200 individuals with lean T2DM and 225 non-diabetic controls. Males and females were similarly distributed between the two groups, and most participants were 26-45 years of age. Among individuals with lean T2DM, the majority had a diabetes duration of 1-6 years. Additional demographic and clinical characteristics are summarized in Table 1.

Table 1. Comparison of baseline characteristics between lean T2DM and non-diabetic controls.

Variable	Lean T2DM (n = 200)	Non-diabetic Controls (n = 225)	*P*-value
Gender: Male, n (%)	107 (53.5)	112 (49.8)	0.496
Age Group, n (%)			
18–25 years	51 (25.5)	54 (24.0)	
26–35 years	75 (37.5)	80 (35.6)	
36–45 years	74 (37.0)	91 (40.4)	0.767
Duration of Diabetes (T2DM only, n = 200)			
<1 year	31 (15.5)	—	
1–3 years	71 (35.5)	—	
4–6 years	61 (30.5)	—	
>6 years	37 (18.5)	—	N/A
Family History of Diabetes Mellitus: Yes, n (%)	129 (64.5)	66 (29.3)	**<0.001**
History of Hypertension: Yes, n (%)	83 (41.5)	32 (14.2)	**<0.001**
Smoking Status, n (%)			
Current Smoker	51 (25.5)	24 (10.7)	
Former Smoker	27 (13.5)	31 (13.8)	
Never Smoked	122 (61.0)	170 (75.6)	**<0.001**
Physical Activity Level, n (%)			
Sedentary	111 (55.5)	36 (16.0)	
Moderate	63 (31.5)	81 (36.0)	
Active (4–5 days/week)	26 (13.0)	108 (48.0)	**<0.001**
Dietary Pattern, n (%)			
Mostly Carbohydrates	110 (55.0)	49 (21.8)	
Balanced Diet	62 (31.0)	121 (53.8)	
High-Protein / Low-Carb	28 (14.0)	55 (24.4)	**<0.001**

Note. Data are presented as n (%) unless otherwise indicated. Group comparisons were performed using the chi-square test or Fisher's exact test, as appropriate. Duration of diabetes was assessed only in the Lean T2DM group.
T2DM, Type 2 Diabetes Mellitus; BMI, Body Mass Index; HbA1c, Glycated Hemoglobin.

Comparison of Metabolic Parameters Between Lean T2DM and Non-diabetic Controls

As presented in Table 2, individuals with lean T2DM had significantly higher serum FGF21 concentrations than non-diabetic controls (median [IQR], 412.50 [315.00–560.00] pg/mL vs. 185.40 [140.00–250.00] pg/mL; p <0.001). They also had significantly higher levels of glycated hemoglobin (HbA1c), fasting glucose, fasting insulin, HOMA-IR, LDL cholesterol, total cholesterol, and aspartate aminotransferase (AST), and significantly lower HDL cholesterol levels than non-diabetic controls (all p <0.001). No significant differences were observed in age or body mass index (BMI), indicating that the groups were well matched for these characteristics.

Predictors of Insulin Resistance and Hepatic Steatosis

The multivariable regression analyses are presented in Table 3. In the multiple linear regression model, serum FGF21 was independently associated with HOMA-IR (β = 0.775, B = 0.03; 95% CI, 0.034-0.037, p <0.001). HbA1c was also independently associated with HOMA-IR (β = 0.19, B = 0.99; 95% CI, 0.56-1.43, p <0.001), whereas male sex was associated with lower HOMA-IR than female sex (β = –0.09, B = –0.45; 95% CI, –0.88 to –0.03, p = 0.04). In the binary logistic regression analysis, serum FGF21 (OR, 1.02; 95% CI 1.01-1.03, p = 0.003) and HOMA-IR (OR, 1.35; 95% CI, 1.06-1.72, p =

Table 2. Comparison of metabolic parameters between lean T2DM and non-diabetic controls (N = 425).

Variable	Lean T2DM Median (IQR) (n = 200)	Non-diabetic Controls Median (IQR) (n = 225)	*P*-value
Serum FGF21 (pg/mL)	**412.50 (315.00–560.00)**	**185.40 (140.00–250.00)**	**<0.001**
HbA1c (%)	6.50 (6.50–6.90)	5.20 (5.00–5.40)	**<0.001**
HOMA-IR	8.06 (6.62–10.30)	1.50 (1.14–1.82)	**<0.001**
Fasting Glucose (mg/dL)	159.25 (141.38–176.50)	85.60 (80.70–90.50)	**<0.001**
Fasting Insulin (μIU/mL)	21.38 (17.71–24.88)	7.05 (5.45–8.42)	**<0.001**
HDL Cholesterol (mg/dL)	36.35 (31.65–40.12)	54.50 (48.90–60.00)	**<0.001**
LDL Cholesterol (mg/dL)	124.85 (107.07–140.10)	95.60 (84.90–106.70)	**<0.001**
AST (U/L)	37.80 (27.58–47.02)	20.50 (16.40–24.30)	**<0.001**
Total Cholesterol (mg/dL)	203.75 (188.22–222.80)	178.10 (162.60–190.90)	**<0.001**
BMI (kg/m²)	21.20 (20.50–21.73)	20.93 (20.28–21.67)	0.067
Age (years)	31.00 (24.00–38.00)	32.00 (26.00–39.00)	0.398

Note. Values are presented as median (IQR) and compared using the Mann–Whitney *U* test. BMI and Age are shown to demonstrate comparable baseline characteristics between groups.
HbA1c, Glycated Hemoglobin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; AST, Aspartate Aminotransferase; BMI, Body Mass Index.

Table 3. Multiple regression analysis: full model of predictors of HOMA-IR (linear) and hepatic steatosis (logistic) in lean T2DM (N = 200).

Model A: Linear Regression: Predictors of HOMA-IR | R^2 = 0.695, Adjusted R^2 = 0.687, $F(5, 194)$ = 88.381, p <0.001 | N = 200						
Predictor	**B**	**SE**	**β / Wald**	***t* / OR**	***P*-value**	**95% CI**
Serum FGF21 (pg/mL)	0.034	0.002	0.775	17.894	**<0.001**	(0.030, 0.037)
HbA1c (%)	0.992	0.221	0.188	4.481	**<0.001**	(0.556, 1.429)
Gender (Male vs Female)	–0.454	0.216	–0.087	–2.102	**0.037**	(–0.881, -0.028)
BMI (kg/m²)	0.021	0.107	0.008	0.197	0.844	(–0.191, 0.233)
Triglycerides (mg/dL)	–0.003	0.002	–0.048	–1.201	0.231	(–0.007, 0.002)
Model B: Binary Logistic Regression: Predictors of Hepatic Steatosis | Nagelkerke R^2 = 0.432, H-L p = 0.085, Accuracy = 78.5% | N = 200						
Predictor	**B**	**SE**	**β / Wald**	***t* / OR**	***P*-value**	**95% CI**
Serum FGF21 (pg/mL)	0.017	0.006	9.028	1.017	**0.003**	(1.006, 1.028)
HOMA-IR	0.303	0.123	6.097	1.353	**0.014**	(1.064, 1.721)
ALT (U/L)	–0.026	0.013	3.833	0.975	0.050	(0.950, 1.000)
BMI (kg/m²)	–0.147	0.187	0.618	0.863	0.432	(0.598, 1.246)
HbA1c (%)	–0.127	0.382	0.111	0.881	0.739	(0.416, 1.862)
Gender (Male vs Female)	0.039	0.367	0.012	1.040	0.915	(0.507, 2.136)

Note. All variables entered into the regression models are presented regardless of statistical significance. B, unstandardized coefficient; β, standardized coefficient; Wald, Wald chi-square statistic; t, t-statistic; OR, odds ratio (Exp(B)); SE, standard error; CI, confidence interval.

0.014) were independently associated with hepatic steatosis. Complete multivariable regression models, including variables that were not statistically significant, are presented in Table 3 to provide the full set of covariates evaluated.

As shown in Table 4, hepatic steatosis was significantly more prevalent among individuals with lean T2DM than among non-diabetic controls (p <0.001). Only 31.0% of participants with lean T2DM had no evidence of hepatic steatosis

Table 4. Distribution of hepatic steatosis grades between lean T2DM and non-diabetic controls.

Hepatic steatosis grade	Lean T2DM n (%)	Controls n (%)	*P*-value
No steatosis (Grade 0)	62 (31.0)	155 (68.9)	
Mild steatosis (Grade 1)	84 (42.0)	55 (24.4)	
Moderate steatosis (Grade 2)	42 (21.0)	14 (6.2)	
Severe steatosis (Grade 3)	12 (6.0)	1 (0.4)	
Total	200 (100.0)	225 (100.0)	**<0.001**

Note. Values are presented as n (%). Hepatic steatosis was graded (Grades 0–3) using ultrasonography. Group comparisons were performed using the chi-square test.

(Grade 0), compared with 68.9% of controls. Mild steatosis (Grade 1) was the most common grade among individuals with lean T2DM (42.0% vs. 24.4%), while moderate (21.0% vs. 6.2%) and severe steatosis (6.0% vs. 0.4%) were also considerably more frequent in the lean T2DM group than in controls, indicating a substantially greater burden of hepatic steatosis despite normal BMI.

DISCUSSION

The present study examined circulating FGF21 concentrations in lean individuals with T2DM and their associations with insulin resistance and hepatic steatosis. Serum FGF21 levels were significantly higher in individuals with lean T2DM than in non-diabetic controls, consistent with previous studies reporting elevated circulating FGF21 levels in T2DM and their association with metabolic and vascular complications.[11]

In addition, aspartate aminotransferase (AST) levels were significantly higher in the lean T2DM group, consistent with previous evidence showing that elevated AST and other liver enzymes are independently associated with diabetes and reflect underlying metabolic abnormalities.[15]

Unlike many previous studies that focused primarily on obesity-related T2DM, our study specifically evaluated metabolic abnormalities in lean individuals with T2DM. Although comparisons with overweight or obese individuals with T2DM may provide additional clinical insight, our primary objective was to characterize metabolic dysfunction associated with lean T2DM while minimizing the confounding effects of excess adiposity. Future studies directly comparing lean and overweight or obese individuals with T2DM are warranted to further define the distinct metabolic characteristics of these populations.

Individuals with lean T2DM also exhibited significantly higher fasting insulin levels and HOMA-IR, indicating substantial insulin resistance despite having a normal BMI. Abnormalities in lipid profiles and liver enzymes further support the presence of metabolic and hepatic dysfunction in this population, consistent with previous reports.[16-18] Collectively, these findings suggest that lean T2DM is characterized by metabolic disturbances that extend beyond hyperglycemia alone.

In the multivariable analyses, serum FGF21 was independently associated with HOMA-IR, whereas HbA1c and sex were also independently associated with insulin resistance. These findings are consistent with a previous study linking elevated FGF21 levels to insulin resistance and poor glycemic control.[19] The independent association between sex and HOMA-IR also is consistent with evidence suggesting that sex-related differences in insulin resistance may be influenced by variations in body fat distribution and sex hormones.[20] Furthermore, both FGF21 and HOMA-IR were independently associated with hepatic steatosis. Similar associations have been reported in individuals with MASLD.[21,22] However, because of the cross-sectional study design, these findings should be interpreted as associations rather than evidence of causal relationships.

Overall, lean T2DM was characterized by elevated circulating FGF21 levels, insulin resistance, and hepatic abnormalities despite normal BMI. Elevated FGF21 may represent a compensatory response to metabolic stress or impaired FGF21 signaling; however, circulating FGF21 concentrations alone cannot confirm tissue-level FGF21 resistance. Together, these findings suggest that FGF21 may serve as a biomarker of metabolic dysfunction in lean T2DM and highlight the need for further investigation into its role in disease pathophysiology.

Limitations

This study has several limitations. First, its cross-sectional design precludes causal inference and does not establish the temporal relationship between elevated FGF21 levels and metabolic dysfunction. Second, hepatic steatosis was assessed using ultrasonography rather than histologic confirmation, and tissue-level FGF21 signaling was not

evaluated. Although all ultrasonographic examinations were performed by a single experienced radiologist who was blinded to participants' clinical and biochemical data, inter- and intra-observer reliability were not formally assessed, which may have introduced measurement variability. Third, participants were recruited through convenience sampling from three tertiary care centers, which may limit the representativeness of the study population and the generalizability of the findings. In addition, restricting enrollment to adults aged 18-45 years may further limit the applicability of the findings to older individuals with lean T2DM. Additionally, information regarding the specific classes of oral glucose-lowering medications used by participants with T2DM was not collected or analyzed. Because several glucose-lowering agents may directly influence circulating FGF21 concentrations, the potential confounding effects of medication use could not be assessed. Finally, the multivariable regression models were not externally validated. Prospective, multicenter studies incorporating direct measures of FGF21 signaling, broader and more representative populations, and external validation of predictive models are needed to confirm and extend these findings.

CONCLUSIONS

Lean T2DM was associated with elevated circulating FGF21 levels, insulin resistance, and hepatic dysfunction despite normal BMI. These findings suggest that FGF21 may serve as a biomarker of metabolic dysfunction in lean T2DM. Longitudinal and mechanistic studies are needed to determine whether elevated FGF21 contributes to disease progression or primarily reflects underlying metabolic stress.

ARTICLE INFORMATION

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Keywords: *Type 2 diabetes mellitus; fibroblast growth factor 21; insulin resistance; hepatic steatosis; body mass index*

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Widespread Skin Lesions in an Adult Patient

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INTRODUCTION

Impetigo is a contagious, superficial skin infection mostly caused by *Staphylococcus aureus* and beta-hemolytic streptococci. It is classified into non-bullous and bullous forms, with non-bullous impetigo accounting for approximately 70% of cases.[1,2] Although the disease can occur at any age, it is more common in children than in adults.[2] Risk factors include poor hygiene, crowded living conditions, lower socioeconomic status, immunodeficiency, atopic dermatitis, scabies, and malnutrition.[1,2] Empiric antibiotic therapy should provide coverage against *S. aureus* and beta-hemolytic streptococci.[3] While topical antibiotics are appropriate for limited disease, oral antibiotic therapy is preferred for extensive disease or during outbreaks.[3]

Here, we present a case of extensive skin lesions in an adult patient that initially prompted a broad infectious differential diagnosis but were ultimately identified as non-bullous impetigo.

CASE REPORT

A man in his 40s with a history of diabetes mellitus (hemoglobin A1c 6.7% on hospital admission), methamphetamine use (smoked), and unstable housing (living in an outdoor encampment in a wooded area) presented with a two-week history of scattered, painful skin lesions involving primarily the upper and lower extremities. Some lesions intermittently produced purulent drainage. He did not have associated systemic symptoms. The patient reported that another individual residing in the same encampment had developed similar skin lesions.

Physical examination revealed multiple annular erythematous plaques on the bilateral upper and lower extremities, several with overlying golden crust. Additional findings included a crusted plaque on the ventral abdomen and a pustule on the left knee (Figures 1-4). Given the extent of the lesions and the patient's outdoor exposures, a broad differential diagnosis was considered, including infectious etiologies such as histoplasmosis, blastomycosis, sporotrichosis, bacterial impetigo, and syphilis. Noninfectious conditions, including pustular psoriasis and subcorneal pustular dermatosis, also were considered but were thought to be less likely.

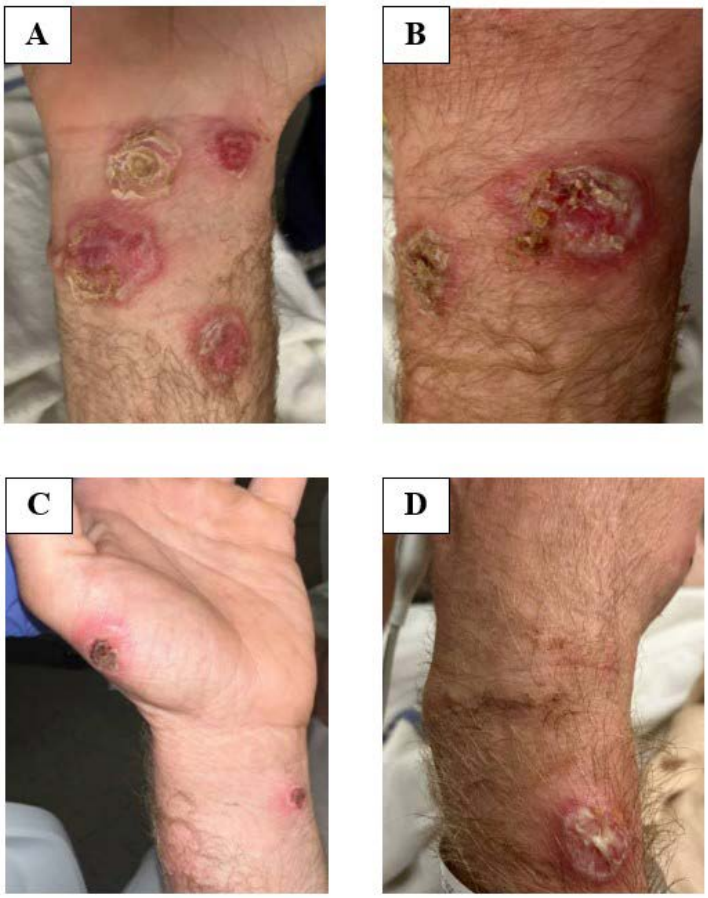

Figure 1. Upper extremity skin lesions. (A) Right ventral wrist. (B) Right dorsal wrist. (C) Left hand and ventral wrist. (D) Left dorsal wrist.

Laboratory studies showed a white blood cell count of 11.6 × 10^3/μL, an absolute neutrophil count of 7.66 × 10^3/μL, hemoglobin of 13.7 g/dL, platelet count of 383 × 10^3/μL, C-reactive protein of 3.96 mg/dL, and an erythrocyte sedimentation rate of 46 mm/hr. Testing for human immunodeficiency virus types 1 and 2 and syphilis was negative. Evaluation for endemic fungal infections, including Histoplasma urine and serum antigens, Blastomyces serum antigen, and Blastomyces antibody, also was negative.

On hospital day 1, a dermatology consultant performed a biopsy of a left forearm lesion for histopathology and culture (routine, anaerobic, and fungal). Histopathology demonstrated a neutrophil-predominant infiltrate involving the papillary dermis and epidermis, with Gram stain highlighting surface bacterial cocci. Grocott's methenamine silver and acid-fast stains were negative. Routine cultures yielded heavy growth of both methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus*

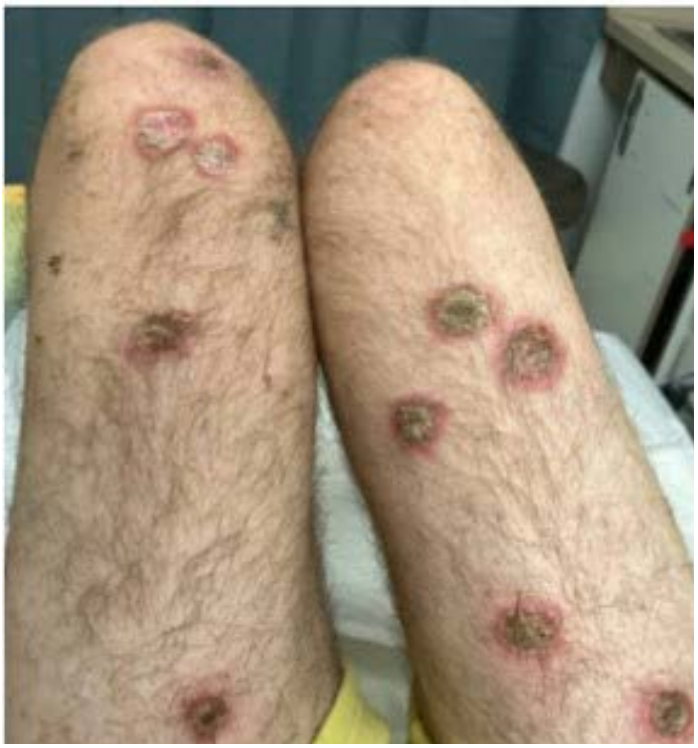

Figure 2. Bilateral anterior thigh skin lesions.

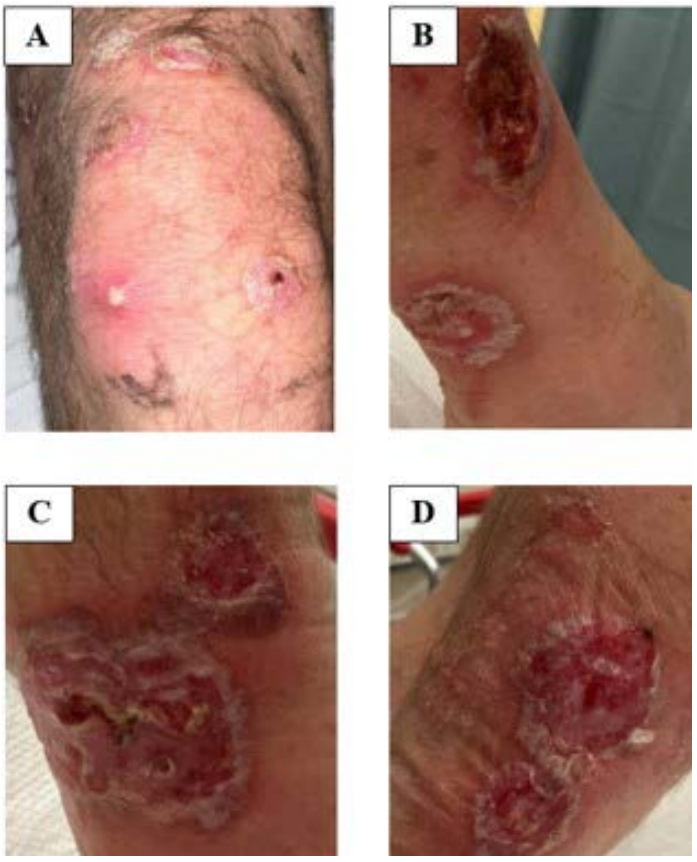

Figure 3. Knee and lower leg skin lesions. (A) Left anterior knee. (B) Right lateral lower leg. (C) Left medial lower leg. (D) Left lateral lower leg.

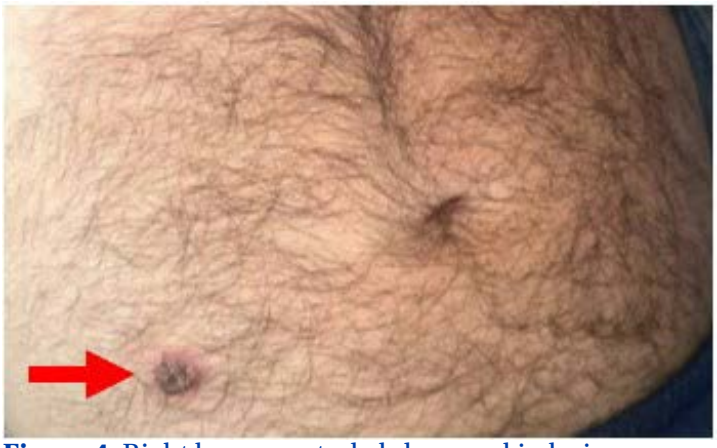

Figure 4. Right lower ventral abdomen skin lesion.

pyogenes, anaerobic culture demonstrated light growth of *Finegoldia magna*, and fungal cultures remained negative after four weeks.

The patient was diagnosed with extensive non-bullous impetigo and treated with intravenous vancomycin during hospitalization, with clinical improvement in the skin lesions. He was discharged on hospital day 5 with oral doxycycline and amoxicillin to complete a seven-day course of antibiotic therapy.

DISCUSSION

Although impetigo classically is associated with pediatric patients, this case highlights that extensive non-bullous impetigo also can occur in adults, as previously reported.[4] Impetigo should be strongly considered in adult patients with predisposing risk factors, several of which were present in our patient. He was experiencing homelessness, a condition associated with increased risk of impetigo because of factors such as malnutrition, crowded living conditions, and limited access to hygiene resources.[5,6] Although scabies was not specifically evaluated, it is a recognized risk factor for impetigo and occurs more frequently among individuals experiencing homelessness.[2,6]

The patient also reported that another individual living in the same encampment had similar skin lesions, suggesting possible disease transmission and emphasizing the importance of obtaining a thorough social history when evaluating skin and soft tissue infections.

Although impetigo typically is a clinical diagnosis that does not require biopsy or culture, this case demonstrates the value of skin biopsy and microbiologic evaluation when the presentation is atypical or the diagnosis is uncertain. In such cases, culture results can help confirm the diagnosis and guide antimicrobial therapy, including the need for coverage against methicillin-resistant MRSA.[1,3]

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Recurrent Hypoglycemia Secondary to Pancreatic Insulinoma

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INTRODUCTION

Insulinomas are insulin-secreting pancreatic neuroendocrine tumors arising from pancreatic islet cells and are the most common cause of endogenous hyperinsulinemic hypoglycemia.[1] They produce hypoglycemia through autonomous insulin secretion that is independent of normal glucose-mediated regulation, resulting in increased peripheral glucose uptake and suppression of hepatic glucose production.[2] Although insulinomas are the most common functional pancreatic neuroendocrine tumors, they are rare, with an annual incidence of approximately one to four cases per million people.[3] Most are solitary lesions measuring less than 2 cm in diameter and often present with nonspecific symptoms, including visual disturbances, altered mental status, diaphoresis, and weakness, making diagnosis challenging.[1,4,5] Diagnosis is confirmed by demonstrating inappropriate insulin secretion during a supervised 72-hour fast, followed by imaging studies to localize the tumor.[6] Surgical resection remains the definitive treatment, with the operative approach determined by the tumor's size and anatomical location.[7,8] We report a case of recurrent hypoglycemia caused by an insulinoma arising in the pancreatic uncinate process that was successfully treated with pancreaticoduodenectomy.

CASE REPORT

A 61-year-old man with a history of paroxysmal atrial fibrillation and chronic lymphocytic leukemia (not receiving treatment) presented with recurrent severe hypoglycemia. He reported a one-year history of episodic hypoglycemia confirmed by home blood glucose monitoring. One week before presentation, he developed progressive nausea, fatigue, weakness, lightheadedness, and blurred vision, culminating in a fall that resulted in minor injuries. On admission, his serum glucose level was 33 mg/dL, requiring continuous intravenous dextrose infusion. Attempts to discontinue the infusion were unsuccessful, as his glucose level declined to 40 mg/dL after cessation, prompting further evaluation.

Laboratory testing showed a hemoglobin A1c of 5.2%, with normal cortisol (16.81 µg/dL) and thyroid-stimulating hormone (2.4 mU/L)

levels. Because of persistent hypoglycemia, a supervised 72-hour fast was initiated. The patient developed symptomatic hypoglycemia approximately two hours after discontinuation of intravenous dextrose. At the time of hypoglycemia, C-peptide (4.1 ng/mL), insulin (7.5 μU/mL), and proinsulin (23 pmol/L) levels were inappropriately elevated. Beta-hydroxybutyrate was suppressed at 0.1 mmol/L, consistent with endogenous hyperinsulinemia. Screening for exogenous hypoglycemic agents was negative.

Computed tomography (CT) of the abdomen and pelvis demonstrated a small enhancing lesion in the pancreatic head, raising concern for a pancreatic neuroendocrine tumor (Figure 1). Dedicated pancreatic imaging confirmed the lesion. The patient's hypoglycemia was medically managed with diazoxide while definitive surgical treatment was planned. He subsequently underwent exploratory laparotomy with pancreaticoduodenectomy (Whipple procedure), cholecystectomy, appendectomy, and regional lymph node sampling. Intraoperatively, a 1-cm lesion was identified in the uncinate process of the pancreas, and frozen section analysis confirmed a neuroendocrine tumor. Blood glucose levels normalized during the procedure without the need for additional dextrose administration, and sampled lymph nodes were negative for metastatic disease.

Gross examination revealed a well-circumscribed pancreatic mass measuring 0.8 × 0.6 × 0.4 cm that was confined to the pancreas. Histopathologic evaluation demonstrated a well-differentiated pancreatic neuroendocrine tumor, World Health Organization (WHO) Grade 1. No lymphovascular invasion, perineural invasion, or tumor necrosis was identified (Figures 2-4). Immunohistochemical staining was positive for synaptophysin, chromogranin, and INSM1, confirming the diagnosis. A Ki-67 proliferation index of <3% was consistent with low-grade disease (Figures 4 and 5).

At outpatient follow-up, the patient remained euglycemic without recurrent hypoglycemic episodes. His hemoglobin A1c increased to 6.1%, within the prediabetic range, warranting continued monitoring. Four months after surgery, positron emission tomography demonstrated no evidence of residual or metastatic disease.

DISCUSSION

Whipple's triad, (1) symptoms of hypoglycemia, (2) documented low plasma glucose at the time of symptoms, and (3) resolution of symptoms following glucose administration, was first described by Whipple and Frantz in 1935 and remains the cornerstone for diagnosing suspected insulinoma.[1] Our patient fulfilled all three criteria, presenting with recurrent hypoglycemic symptoms, including dizziness, blurred vision, and falls; documented episodes of severe hypoglycemia; and prompt symptom resolution following dextrose administration.

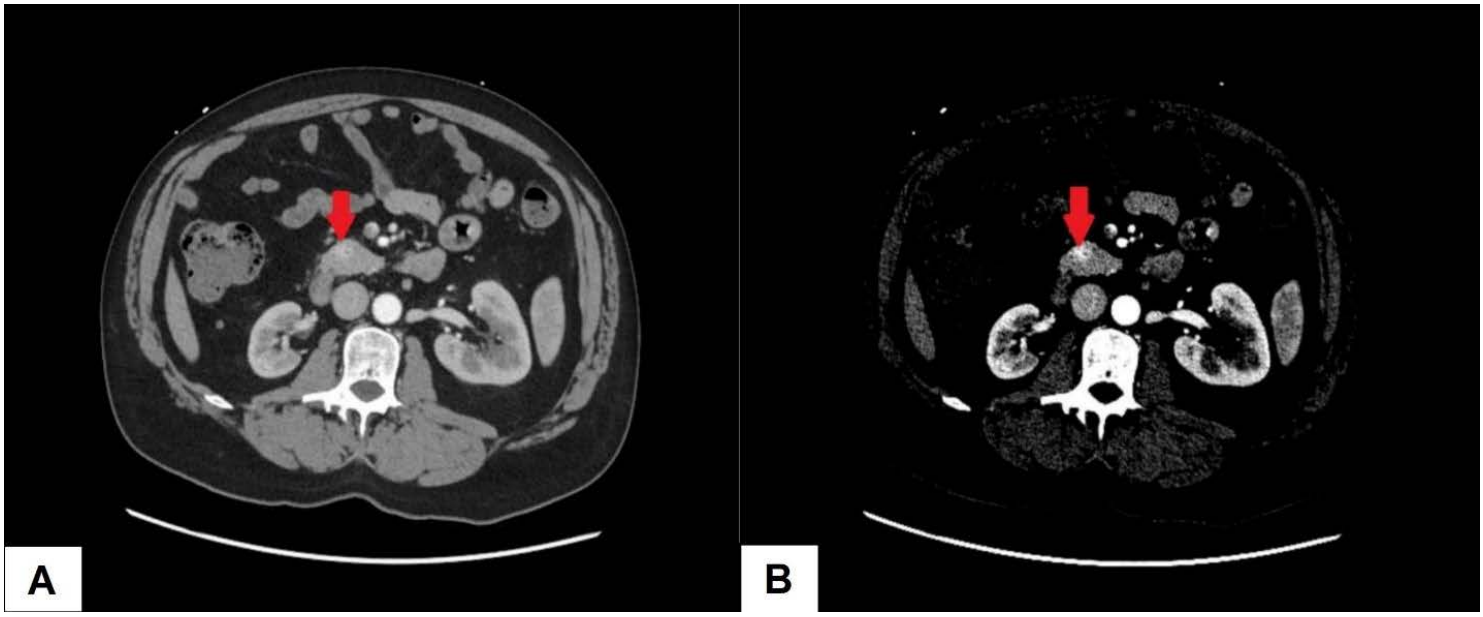

Figure 1. Contrast enhanced CT of the abdomen and pelvis demonstrating an enhancing lesion of the pancreatic head measuring approximately 1.4 x 1.3 cm, suspicious for a pancreatic neuroendocrine tumor. (A) Abdominal window. (B) Liver window.

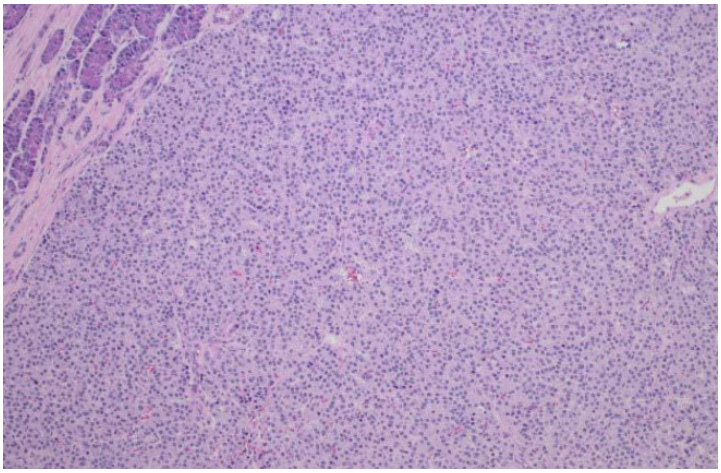

Figure 2. 4x histologic view showing a well-circumscribed tumor within the pancreatic parenchyma.

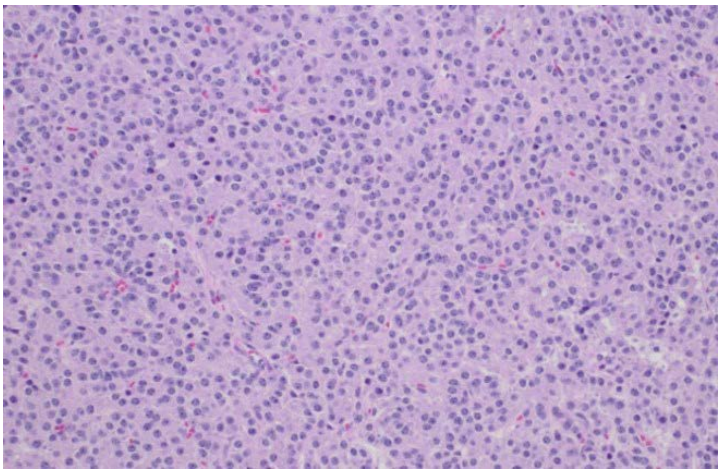

Figure 3. 20x histologic view showing nests and cords of uniform cells with round nuclei and speckled "salt and pepper" chromatin, characteristic of neuroendocrine tumors.

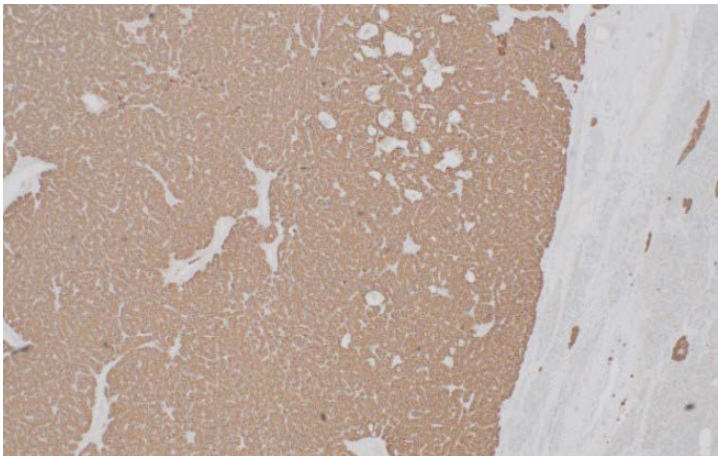

Figure 4. Immunohistochemical stain synaptophysin highlighting tumor cells, supporting neuroendocrine differentiation.

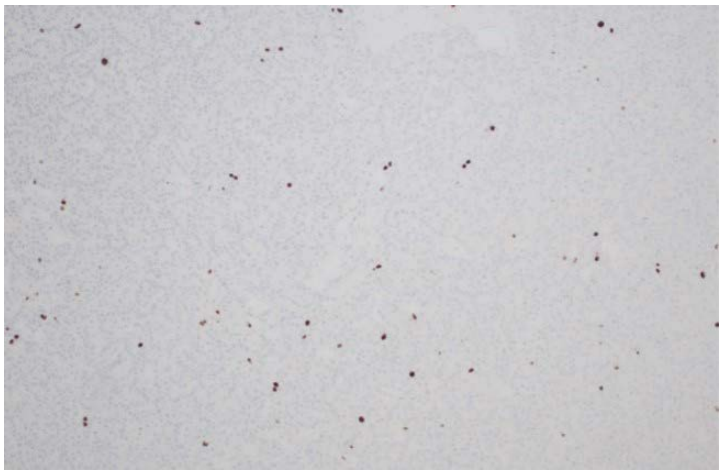

Figure 5. Immunohistochemical stain Ki-67 demonstrating a proliferation index of <3%. In combination with a mitotic rate of <2 mitoses per 2mm2, this pancreatic neuroendocrine tumor was classified as a WHO Grade 1.

Despite a year-long history of episodic hypoglycemia, the diagnosis was likely delayed because of the nonspecific nature of the patient's symptoms. Progressive, recurrent hypoglycemia requiring continuous dextrose infusion prompted a comprehensive endocrine evaluation. A supervised 72-hour fast was initiated but terminated early because of symptomatic hypoglycemia. During hypoglycemia, insulin, C-peptide, and proinsulin levels were inappropriately elevated, while screening for exogenous hypoglycemic agents was negative, supporting endogenous hyperinsulinemia. Subsequent imaging identified a pancreatic lesion, and the diagnosis of insulinoma was definitively confirmed by postoperative histopathology.

The differential diagnosis of hyperinsulinemic hypoglycemia includes insulinoma, factitious hypoglycemia, insulin autoimmune syndrome, and non-insulinoma pancreatogenous hypoglycemia syndrome.[7,9,10] In this case, the biochemical findings obtained during the supervised fast, together with negative screening for exogenous hypoglycemic agents and subsequent imaging and pathologic findings, strongly supported insulinoma as the underlying cause.

Most insulinomas are small, solitary, benign pancreatic neuroendocrine tumors that present with nonspecific neuroglycopenic and autonomic symptoms, frequently contributing to delayed diagnosis.[5,8,11] Clinical evaluation begins with confirmation of Whipple's triad, followed by biochemical testing to determine whether hypoglycemia

is insulin-mediated. A supervised fasting study demonstrated inappropriately elevated insulin, C-peptide, and proinsulin levels during hypoglycemia, together with suppressed beta-hydroxybutyrate and exclusion of exogenous hypoglycemic agents, strongly supports endogenous hyperinsulinism.[11] Imaging studies are then used to localize the lesion before surgery.[9] This diagnostic sequence closely mirrored our patient's clinical course. Malignant insulinomas have been associated with more rapid symptom onset and higher insulin, proinsulin, and C-peptide concentrations at the glucose nadir than benign tumors.[11,12]

The small size of most insulinomas, with the majority measuring less than 2 cm at diagnosis, can make localization challenging.[1,7] In this patient, contrast-enhanced computed tomography successfully identified an enhancing lesion within the pancreatic head that was subsequently confirmed intraoperatively. Although conventional imaging was sufficient in this case, equivocal lesions may require additional localization techniques, including endoscopic ultrasound or selective arterial calcium stimulation.[7,10] Previous study has reported localization rates of approximately 84% for CT and 79% for magnetic resonance imaging (MRI).[13] When combined, these imaging modalities achieve localization rates approaching 97%, suggesting that complementary imaging may improve preoperative localization when initial studies are inconclusive.[13]

Although most insulinomas occur sporadically, approximately 5% are associated with inherited endocrine syndromes, most commonly multiple endocrine neoplasia type 1 (MEN1).[3,14] MEN1 is an autosomal dominant disorder characterized by primary hyperparathyroidism, pancreatic neuroendocrine tumors, and pituitary adenomas.[8,14] It most commonly results from pathogenic variants in the *MEN1* gene, which encodes the tumor suppressor protein menin, a key regulator of cellular growth and genomic stability.[1] Compared with sporadic tumors, insulinomas associated with MEN1 are more likely to recur, metastasize, and be larger at diagnosis.[3,8,14] They also tend to present at a younger age, with approximately 25% occurring before 20 years of age.[14] Because pancreatic neuroendocrine tumors account for a substantial proportion of MEN1-related mortality, screening for pancreatic neuroendocrine tumors is recommended in both symptomatic and asymptomatic patients with MEN1.[14] Although MEN1 testing was not documented for our patient, evaluation for MEN1 should be considered in patients diagnosed with insulinoma, particularly those with early-onset disease, multifocal tumors, or a suggestive family history.[3,8,14]

Surgical resection remains the definitive treatment for localized insulinoma and is associated with excellent long-term outcomes.[1,7,15] Our patient underwent pancreaticoduodenectomy with complete tumor excision, resulting in intraoperative normalization of blood glucose levels and sustained postoperative resolution of hypoglycemia. Histopathologic examination demonstrated a well-differentiated pancreatic neuroendocrine tumor, WHO Grade 1, without lymphovascular invasion, perineural invasion, or tumor necrosis. These findings are consistent with the favorable prognosis observed in most localized insulinomas.[9] Studies have shown that the majority of insulinomas are localized at diagnosis and that surgical resection results in complete resolution of hypoglycemic symptoms in most patients.[8,16] Benign insulinomas typically are small, solitary lesions associated with low recurrence rates, whereas malignant tumors are more commonly characterized by larger size, metastatic disease, and poorer long-term outcomes.[9-12]

Although the tumor in this case was small, its location within the uncinate process placed it in close proximity to critical vascular and biliary structures. The operative approach was therefore determined based on anatomic considerations and intraoperative findings. While parenchyma-sparing procedures such as enucleation are preferred for appropriately located small insulinomas, pancreaticoduodenectomy may be necessary when local excision cannot be performed safely.[17]

Medical therapy remains an important option for patients who are poor surgical candidates, have unresectable disease, or require symptom control before surgery. Treatment options include frequent carbohydrate intake, diazoxide to suppress insulin secretion, and somatostatin analogs in selected patients.[18] Although our patient received diazoxide during hospitalization, persistent hypoglycemia necessitated continued intravenous dextrose infusion until definitive surgical resection.

A 60-year Mayo Clinic experience demonstrated that recurrence following complete resection of benign insulinoma is uncommon and that long-term survival is excellent.[6] Improved localization techniques have further contribut-

ed to favorable surgical outcomes. Consistent with these findings, our patient experienced complete resolution of hypoglycemia following surgery and remained euglycemic without the need for dextrose supplementation or antihypoglycemic therapy. At follow-up, the hemoglobin A1c had increased to the prediabetic range (6.1%), warranting continued metabolic surveillance.

This case underscores the importance of maintaining a high index of suspicion for insulinoma in patients with recurrent, unexplained hypoglycemia. Early recognition, appropriate biochemical evaluation, timely localization, and definitive surgical management are essential to prevent recurrent neuroglycopenic events and reduce the morbidity associated with delayed diagnosis.

CONCLUSIONS

This case highlights the importance of considering insulinoma in patients with recurrent, unexplained hypoglycemia accompanied by biochemical evidence of endogenous hyperinsulinism. Because symptoms often are intermittent and nonspecific, diagnosis may be delayed without a structured endocrine evaluation. Confirmation of Whipple's triad, appropriate biochemical testing, and timely tumor localization are essential for establishing the diagnosis and guiding management. Although surgical resection remains the definitive treatment for most localized insulinomas, this case also illustrates the importance of multidisciplinary collaboration in the evaluation and management of pancreatic neuroendocrine tumors. Prompt diagnosis and definitive treatment can result in complete resolution of hypoglycemia, reduce the risk of recurrent neuroglycopenic events, and provide excellent long-term outcomes.

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Keywords: *insulinoma; neuroendocrine tumors; hypoglycemia; pancreaticoduodenectomy; endogenous hyperinsulinemia*

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Isolated, Unilateral Lower Eyelid Mass Presenting as a Delayed Ocular Complication of Dermal Filler

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INTRODUCTION

With the increasing use of minimally invasive cosmetic procedures, including dermal fillers, ophthalmic complications associated with these treatments are becoming increasingly recognized.[1] We present a case of nontender, unilateral lower eyelid edema that developed years after dermal filler injection, which the patient had not disclosed at the initial evaluation. This case highlights the diagnostic challenge posed by the delayed presentation of a nonspecific symptom that may be attributed to several underlying etiologies.

CASE REPORT

A 64-year-old woman with a medical history of hypertension and an ocular history of dry eye presented with a 1-year history of left lower eyelid swelling. The swelling was neither painful nor pruritic and did not improve with warm or cold compresses. She had discarded her old makeup products and washcloths to identify a potential cause, without improvement. She also reported increasing strain in her left eye and questioned whether it was related to the eyelid swelling.

External examination revealed a prominent, protruding, soft, and slightly rubbery lower eyelid fat pad on the left (Figure 1). A similar finding was present on the right, although the herniated lower eyelid fat pad was less prominent. There was no proptosis or palpable mass along the orbital rim. Ocular motility and pupillary examination were normal. Slit-lamp examination and the remainder of the ocular examination were unremarkable bilaterally. The differential diagnosis included allergic reaction, insect bite, chalazion, hordeolum, preseptal cellulitis, orbital cellulitis, fluid imbalance, sarcoidosis, and lymphoma. The patient subsequently underwent an open biopsy of the left lower eyelid lesion. Intraoperatively, clear, granular, gelatinous material was identified within the subcutaneous tissue, orbicularis muscle, and postseptal space. Two specimens were obtained: the first consisted of orbital fat with associated gelatinous material, and the second consisted of subcutaneous tissue containing gelatinous material.

Histopathologic examination revealed no evidence of malignancy

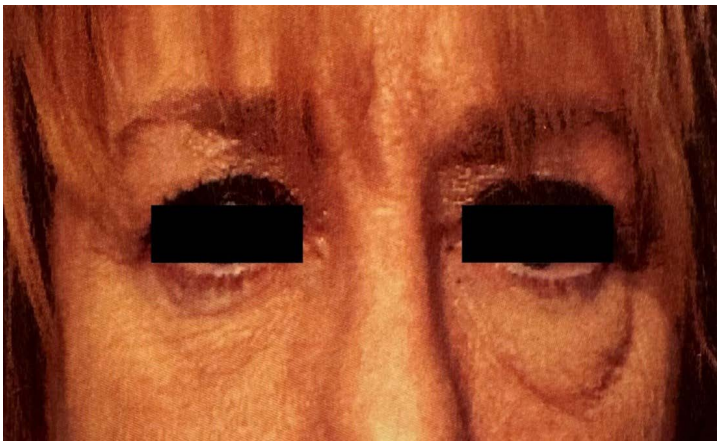

Figure 1. External photograph demonstrating left lower eyelid fullness.

and demonstrated fibroadipose tissue with acellular foreign material, suspected to represent dermal filler, in both specimens. At her 1-week postoperative visit for suture removal, the patient reported a history of Voluma® (hyaluronic acid; HA) filler injections to the mid-cheek 3 years earlier.

At the 1-month postoperative visit, the infraciliary incision was well healed, although some firmness persisted in the left lower eyelid region. We administered 1 mL of hyaluronidase, resulting in moderate improvement in the left lower eyelid swelling. Given the clinical response, close observation and surveillance were elected.

DISCUSSION

This case emphasizes the importance of maintaining a broad differential diagnosis when evaluating patients with lower eyelid masses. Common eyelid masses include chalazia, hordeola, epidermal inclusion cysts, hidrocystomas, and malignant lesions such as basal cell carcinoma, squamous cell carcinoma, sebaceous carcinoma, and malignant melanoma.[2] Given the increasing use of periocular soft tissue fillers, complications related to these injections also should be considered in the differential diagnosis. According to the American Society of Plastic Surgeons, 6,219,152 (5,294,603 HA and 924,549 Non-HA) dermal filler procedures were performed in the United States in 2023.[3] This figure reflects procedures performed by plastic surgeons and therefore does not capture the full volume of filler injections performed by other qualified clinicians. Multiple commercial filler materials are available for use in the periocular region, with HA being among the most commonly used because of its favorable safety profile and reversibility.[4-6] Other materials include autologous fat, collagen, poly-L-lactic acid, and calcium hydroxyapatite.[4] Our patient had previously received Voluma, an HA-based dermal filler designed for midface volumization. Voluma contains a combination of low- and high-molecular-weight HA and uses cross-linking technology that contributes to its durability, with clinical effects lasting up to 2 years.[7]

Ocular complications of dermal filler injections range from mild, transient effects to severe, permanent vision loss.[5,8] These complications can be categorized as early or delayed based on their time of onset.[6,8] Early complications include periorbital or eyelid edema, ocular pain, ptosis, and vascular occlusion, which can result in unilateral or bilateral vision loss.[1,5,8] HA fillers can cause transient swelling because of their water-binding properties, although this typically resolves within several days.[5,8] Persistent lower eyelid edema may occur when filler is placed too superficially or in excessive volume, particularly in the tear trough region.[5]

Delayed complications are less common but can present months or even years after filler injection. In a systematic review of 28 articles comprising 52 cases of delayed complications following tear trough filler injections, swelling was the most common complication, occurring in 20 cases, with an average onset of 14.8 months.[9] Delayed unilateral swelling also may reflect an inflammatory nodule or granuloma. Such reactions typically present as firm subcutaneous nodules and may be associated with tenderness or other signs of inflammation.[5,6] Histopathologic examination may demonstrate foreign-body giant cells and inflammatory infiltrates. The reported incidence of granuloma formation with modern HA fillers is approximately 0.01-0.1%.[5] In contrast, our patient presented 3 years after filler injection with a unilateral lower eyelid mass without a discrete nodule or tenderness. Histopathologic examination demonstrated acellular foreign material without an inflammatory infiltrate or other evidence of a granulomatous reaction. These findings made a delayed inflammatory or granulomatous response less likely.

Filler migration, defined as the presence of filler material at a site distant from the original injection site, is another potentially delayed complication. Although HA fillers are biodegradable, filler material may persist and migrate to distant sites months or years after injection.[10,11] Nathoo et al.[11] described three patients with filler material in locations

distant from the original injection site, including cases presenting with lower eyelid swelling or a noninflammatory mass. Similarly, Hamed-Azzam et al.[10] reported seven cases of delayed orbital complications following facial dermal filler injections, including patients with lower eyelid swelling and painless lower eyelid masses. As in our patient, these cases demonstrate how delayed filler migration can mimic other orbital or eyelid pathology and lead to diagnostic uncertainty, particularly when the history of cosmetic filler use is not initially disclosed. Treatment of filler-related complications depends on the type and location of the filler and may include hyaluronidase for HA fillers, intralesional corticosteroids or 5-fluorouracil for inflammatory reactions, and surgical excision when conservative treatment is unsuccessful or the diagnosis remains uncertain.[1,5,11]

CONCLUSIONS

This case highlights the importance of obtaining a thorough history and specifically asking about prior cosmetic injections and aesthetic treatments when evaluating patients with facial edema or new-onset orbital or eyelid masses. Patients may not consider previous cosmetic procedures relevant to their current ocular symptoms and therefore may not volunteer this information. However, a history of filler injections can substantially alter the differential diagnosis, guide appropriate diagnostic evaluation, and influence treatment. In this case, knowledge of the patient's prior HA filler injection might have raised the possibility of delayed filler migration earlier and potentially allowed an initial trial of hyaluronidase before surgical biopsy. Clinicians should therefore recognize that delayed filler-related complications can mimic more serious pathology and should be considered when evaluating unexplained periorbital swelling or masses, even when the original injection occurred years earlier and at a site distant from the presenting lesion.

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Keywords: *dermal filler; eyelid disease*

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Presenting Research During Residency Interviews: A Framework for Explaining the *Why*, *How*, *What*, *So What*, and *Your Role*

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INTRODUCTION

One of the most effective ways to present research during a residency interview is to organize your presentation around five simple questions: (1) Why was the study conducted? (2) How was it conducted? (3) What did we find through the study? (4) What are the implications of the findings? (5) What was my role? This approach helps interviewers quickly understand the significance of your work while demonstrating your ability to communicate scientific information clearly. The figure summarizes a framework for presenting research during residency interviews.

Why Was the Study Conducted?

Begin by explaining the clinical or scientific problem that motivated the study. Describe the knowledge gap or unmet need that prompted the research and state the study objective or hypothesis. Keep this section concise and emphasize why the research matters to you, patients, clinicians, or the healthcare system.

Example:

"Previous studies showed inconsistent evidence regarding the relationship between strength training and mental health among U.S. adults. We conducted this study to determine whether meeting national physical activity recommendations was associated with depression, anxiety, and loneliness in a nationally representative sample."[1]

How Was the Study Conducted?

Provide a brief overview of the study design and methodology. Explain the study population, data source, key variables, and analytical approach without overwhelming your audience with excessive technical details. Focus on the methods that are essential for understanding the validity of the findings.

Example:

"We conducted a cross-sectional analysis using nationally representative survey data. We assessed physical activity behaviors

PRESENTING RESEARCH DURING RESIDENCY INTERVIEWS

The Why, How, What, So What, and Your Role

1 WHY
Why was the study conducted?

- Explain the clinical or scientific problem and knowledge gap.
- State the study objective or hypothesis.
- Emphasize why the research matters to patients, clinicians, or the healthcare system.

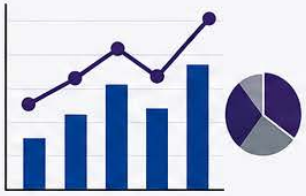
Key question: *Why was this study important?*

2 HOW
How was it conducted?

- Briefly describe the study design (cross-sectional, cohort, RCT, etc.).
- Identify the study population and data source.
- Describe key variables and measures.
- Explain the statistical/analytical methods used.

Key question: *How was the study done?*

3 WHAT
What did the study find?



- Present the main findings clearly and concisely.
- Focus on results that directly answer the research question.
- Use key statistics or effect sizes—avoid listing every numerical result.

Key question: *What did the study find?*

4 SO WHAT
What are the implications?

- Explain the clinical, research, or policy implications.
- Discuss how findings can influence patient care or practice.
- Acknowledge limitations and suggest next steps.

Key question: *So what does this mean?*

5 WHAT WAS MY ROLE?
What was my specific contribution?

- Clearly describe your specific role in the project (e.g., recruited patients, built the REDCap® database, performed analyses, wrote the first draft).
- Be honest, even if your role was modest (e.g., "I was one of four chart abstractors and contributed to the discussion section.").
- Discuss what you learned, the challenges you encountered, what didn't go as planned, and what you'd do differently.
- Interviewers want to know if you have the skills, initiative, and perseverance to complete scholarly work in residency.

Key question: *What was my contribution and what did I learn?*

TAKE-HOME MESSAGE: A clear, well-organized presentation that addresses the *Why, How, What, So What, and Your Role* shows that you can think critically, communicate effectively, and are ready to contribute as a future physician–scholar.

Figure. A Framework for presenting research during residency interviews: Organizing your presentation around the *Why, How, What, So What* and *Your Role*. Figure created with AI.

using standardized questionnaire items, and we measured mental health outcomes with validated instruments. We used multivariable logistic regression models to evaluate the associations while adjusting for relevant demographic and health-related factors."[1]

What Did You Find Through the Study?

Present the major findings **clearly** and **objectively**. Highlight the results that directly answer the research question using simple language and only the most important statistics. Avoid reading tables or listing every numerical result.

Example:

"We found that adults who met the recommended strength-training guidelines had significantly lower odds of screening positive for depression and experiencing loneliness, even after adjusting for potential confounders. However, meeting aerobic physical activity recommendations alone was not independently associated with these mental health outcomes."[1]

What Are the Implications of the Findings? (The *So What?*)

Conclude by explaining why the findings are important. Discuss how the results may influence clinical practice, future research, health policy, or patient care. Acknowledge important study limitations up front and suggest logical next steps.

Example:

These findings suggest that strength training may play an important role in promoting mental well-being and should be considered alongside aerobic exercise when counseling patients." [1]

What Was My Role?

Be prepared to clearly describe your specific role in the project. Did you recruit patients, build the REDCap® database, perform the statistical analyses, or write the first draft of the manuscript? Be honest, even if your contribution was modest. For example, you might say, "*I was one of four chart abstractors, and I contributed to writing the discussion section.*"

Do not hesitate to discuss what you learned from the project, the challenges you encountered, what did not go as planned, and what you would do differently in future research. It is also perfectly acceptable to discuss smaller scholarly projects, such as case reports, quality improvement initiatives, or even unpublished chart review projects. Ultimately, interviewers are interested in understanding whether you have the skills, initiative, and perseverance to successfully complete scholarly work during residency.

CONCLUSIONS

Structuring your research presentation around the ***why***, ***how, what***, ***so what,*** and ***your role*** provides a logical and engaging framework that is easy for interviewers to follow. This format demonstrates not only your understanding of the research itself but also your ability to critically interpret findings, communicate effectively, and appreciate their relevance to clinical practice; qualities that most residency programs highly value.

REFERENCES

1. Ofei-Dodoo et al. Associations of Physical Activity and Sleep with Depression, Anxiety, and Loneliness Among U.S. Adults: A Population-Based Cross-Sectional Study. Kan J Med, In press. https://doi.org/10.17161/kjm.vol19.25605.

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