The Delirium Subtyping Initiative

Emily Bowman, BSc (Hons), PhD

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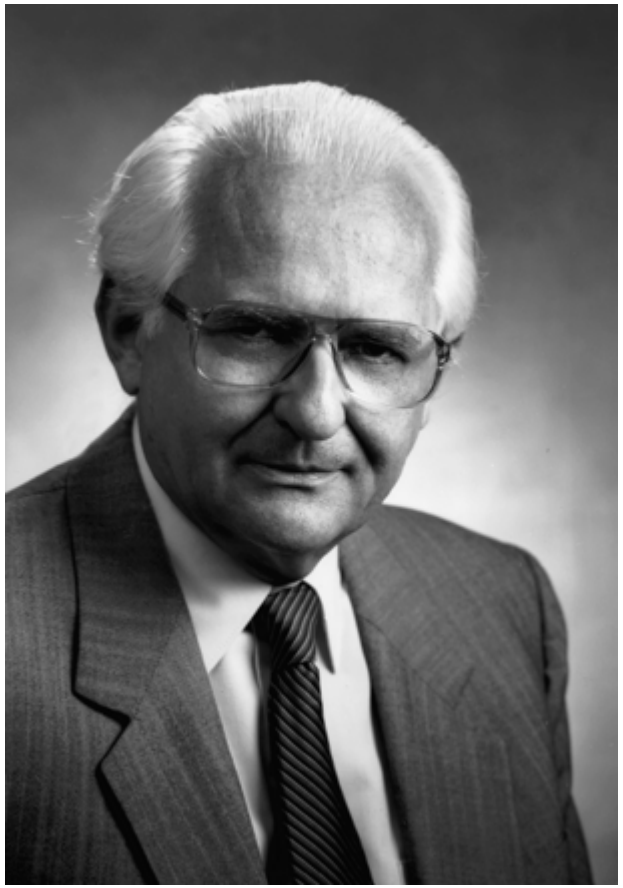
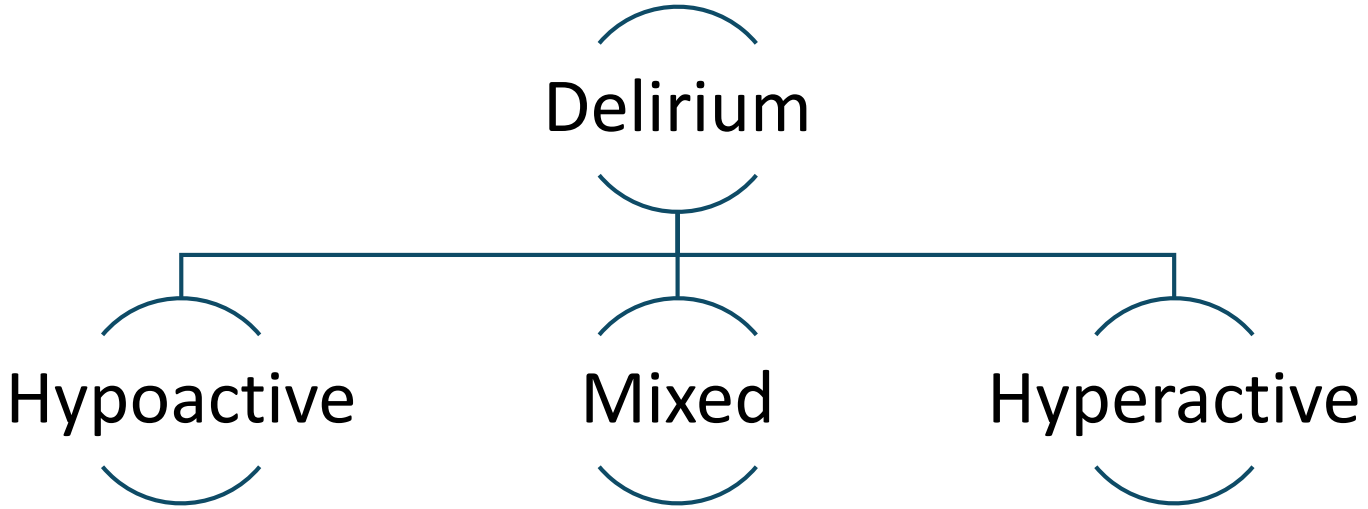
Department for the Economy



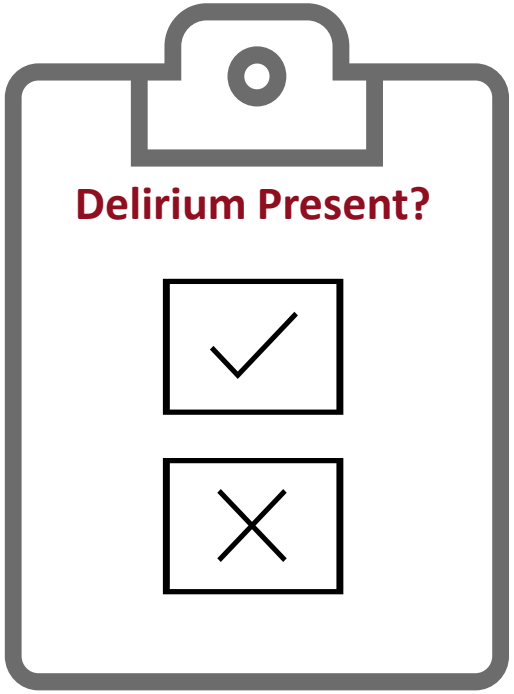
Zbigniew J. Lipowski
1924-1997

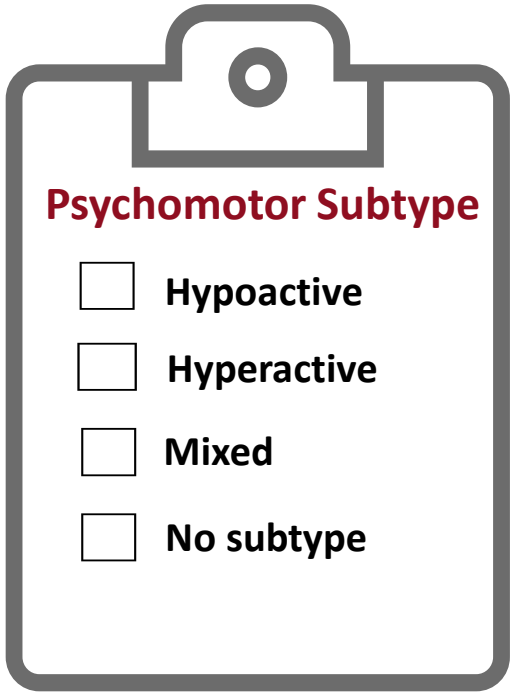
“Delirium, or ‘phrenitis,’ was one of the first mental disorders to be recognized by Western medical writers 2500 years ago.”

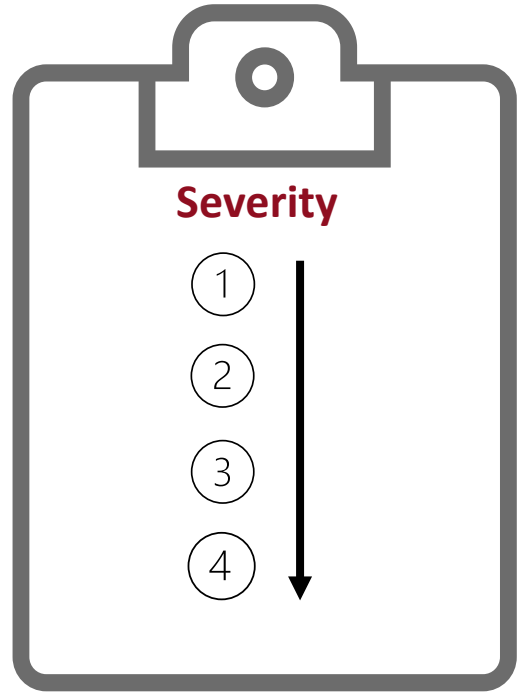
– Lipowski, 1990



Delirium Characterisations





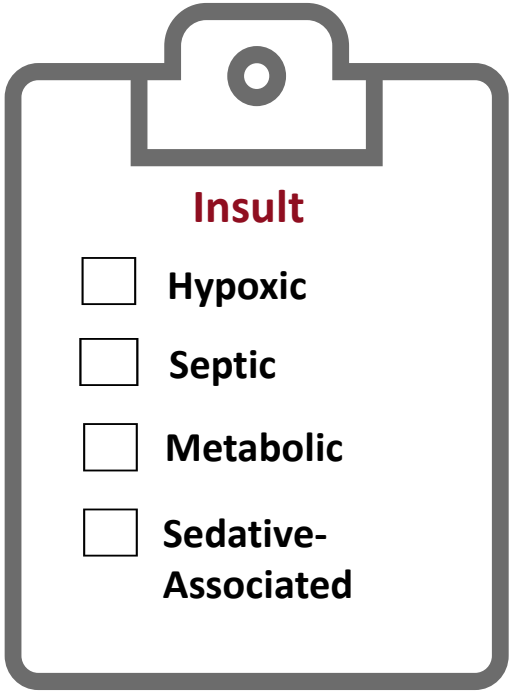


More accurate classification is required

Published in final edited form as:
Lancet Respir Med. 2018 March ; 6(3): 213–222. doi:10.1016/S2213-2600(18)30062-6.

Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study

Timothy D Girard, MD, MSCI[1,2], Jennifer L Thompson, MPH[1,8], Pratik P Pandharipande, MD, MSCI[1,3,4,13], Nathan E Brummel, MD MSCI[1,4,5,7], James C Jackson, PsyD[1,4,5,9,14], Mayur B Patel, MD, MPH[1,4,10,11,15], Christopher G Hughes, MD[1,3,4,13], Rameela Chandrasekhar, PhD[1,8], Brenda T Pun, DNP, RN[1], Leanne M Boehm, PhD[1,12], Mark R Elstad, MD[17,18], Richard B Goodman, MD[19,20], Gordon R Bernard, MD[1,3], Robert S Dittus, MD, MPH[1,4,6,7,16], E Wesley Ely, MD, MPH[1,4,5,7,16]



Tieges et al. BMC Geriatrics (2021) 21:162
https://doi.org/10.1186/s12877-021-02095-z

BMC Geriatrics

RESEARCH ARTICLE Open Access

Association between components of the delirium syndrome and outcomes in hospitalised adults: a systematic review and meta-analysis

Zoë Tieges[1,2*], Terence Quinn[3], Lorn MacKenzie[4], Daniel Davis[5], Graciela Muniz-Terrera[6], Alasdair M. J. MacLullich[1] and Susan D. Shenkin[1]

Todd et al. BMC Geriatrics (2017) 17:283
DOI 10.1186/s12877-017-0661-7

BMC Geriatrics

RESEARCH ARTICLE Open Access

Reduced level of arousal and increased mortality in adult acute medical admissions: a systematic review and meta-analysis

Amy Todd[1], Samantha Blackley[1], Jennifer K. Burton[2,3,7], David J. Stott[4], E. Wesley Ely[5,6], Zoë Tieges[3,7], Alasdair M. J. MacLullich[3,7] and Susan D. Shenkin[3,7*]

Heterogeneity of symptoms and their description

OXFORD JOURNALS Age and Ageing

Age Ageing. 2024 Apr 18;53(4):afae077. doi: 10.1093/ageing/afae077

Assessment and report of individual symptoms in studies of delirium in postoperative populations: a systematic review

Emily M L Bowman [1,2,✉], Aoife M Sweeney [3], Danny F McAuley [4], Chris Cardwell [5], Joseph Kane [6], Nadine Badawi [7], Nusrat Jahan [8], Halla Kiyan Iqbal [9], Callum Mitchell [10], Jessica A Ballantyne [11], Emma L Cunningham [12]

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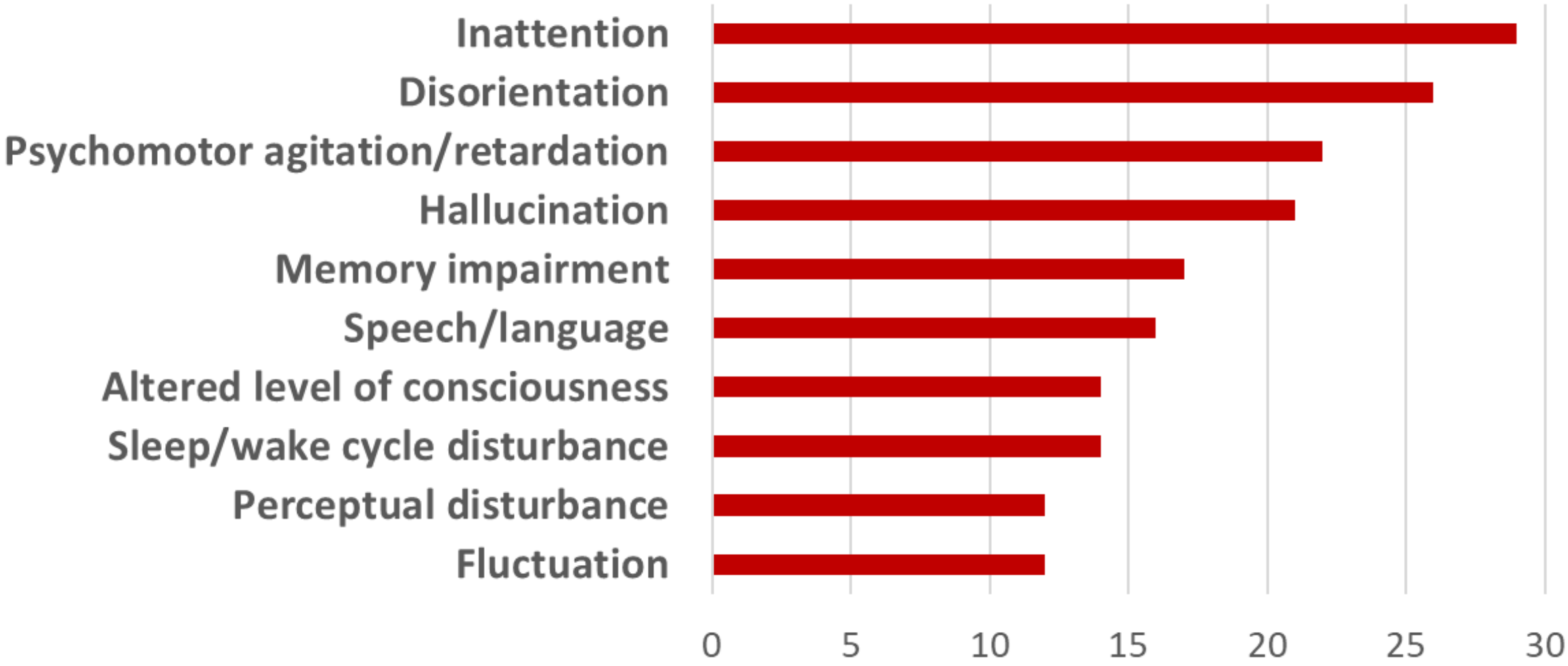
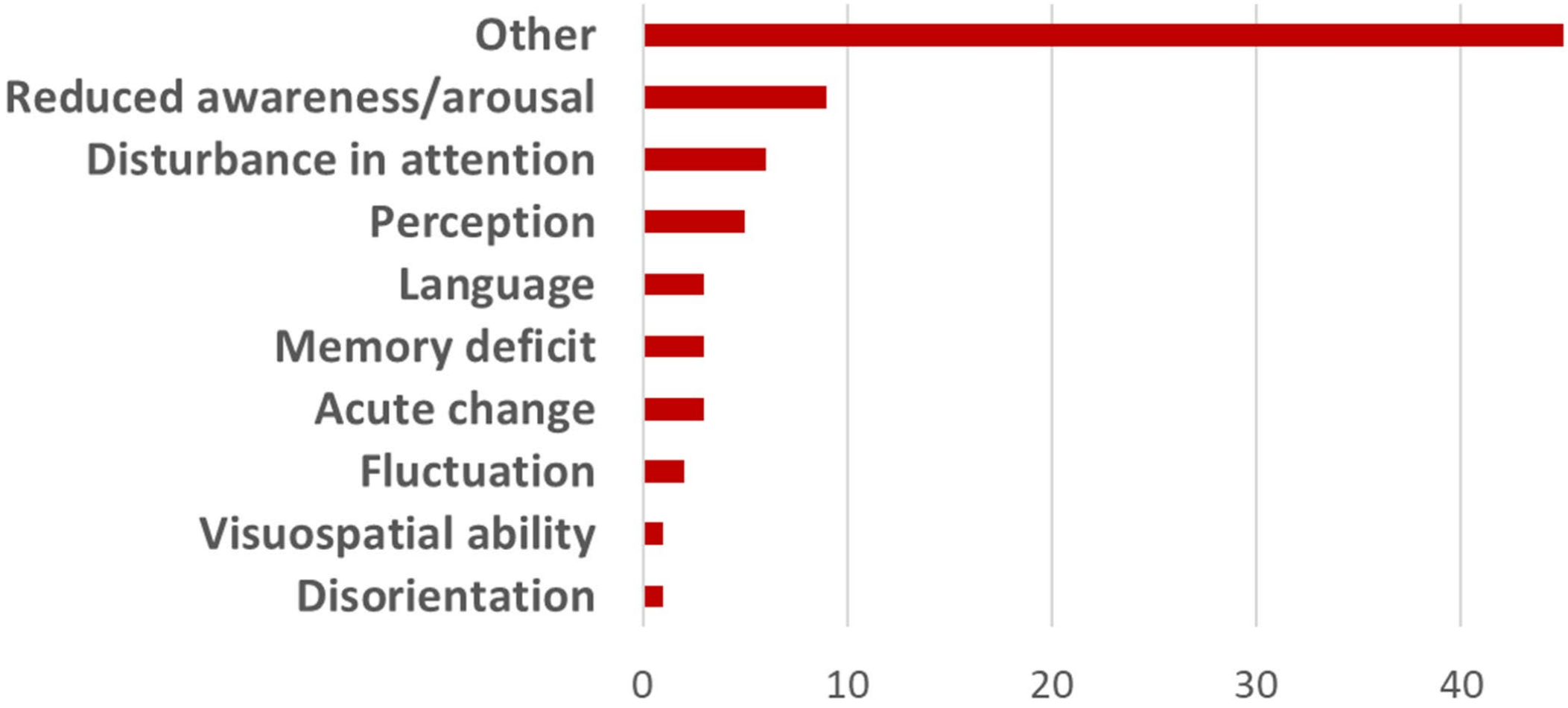
PMCID: PMC11028403 PMID: 38640126

Ten Most Reported Symptoms



Total patients= 12,442 **Total delirious patients= 2,243** **Reported symptoms= 78**

N Symptoms falling under each DSM-5-TR Symptom Category



Total patients= 11,377 **Total delirious patients= 2,049** **Reported symptoms= 78**

Integration Required

ELSEVIER

The American Journal of Geriatric Psychiatry

Volume 26, Issue 9, September 2018, Pages 913-924

Regular Research Articles

Refining Delirium: A Transtheoretical Model of Delirium Disorder with Preliminary Neurophysiologic Subtypes

Mark A. Oldham M.D. [a], Joseph H. Flaherty M.D. [b], Jose R. Maldonado M.D. [c]

July 28, 2020; 95 (4) CONTEMPORARY ISSUES

Delirium disorder

Integrating delirium and acute encephalopathy

Mark A. Oldham, Robert G. Holloway

First published June 9, 2020, DOI: https://doi.org/10.1212/WNL.0000000000009949

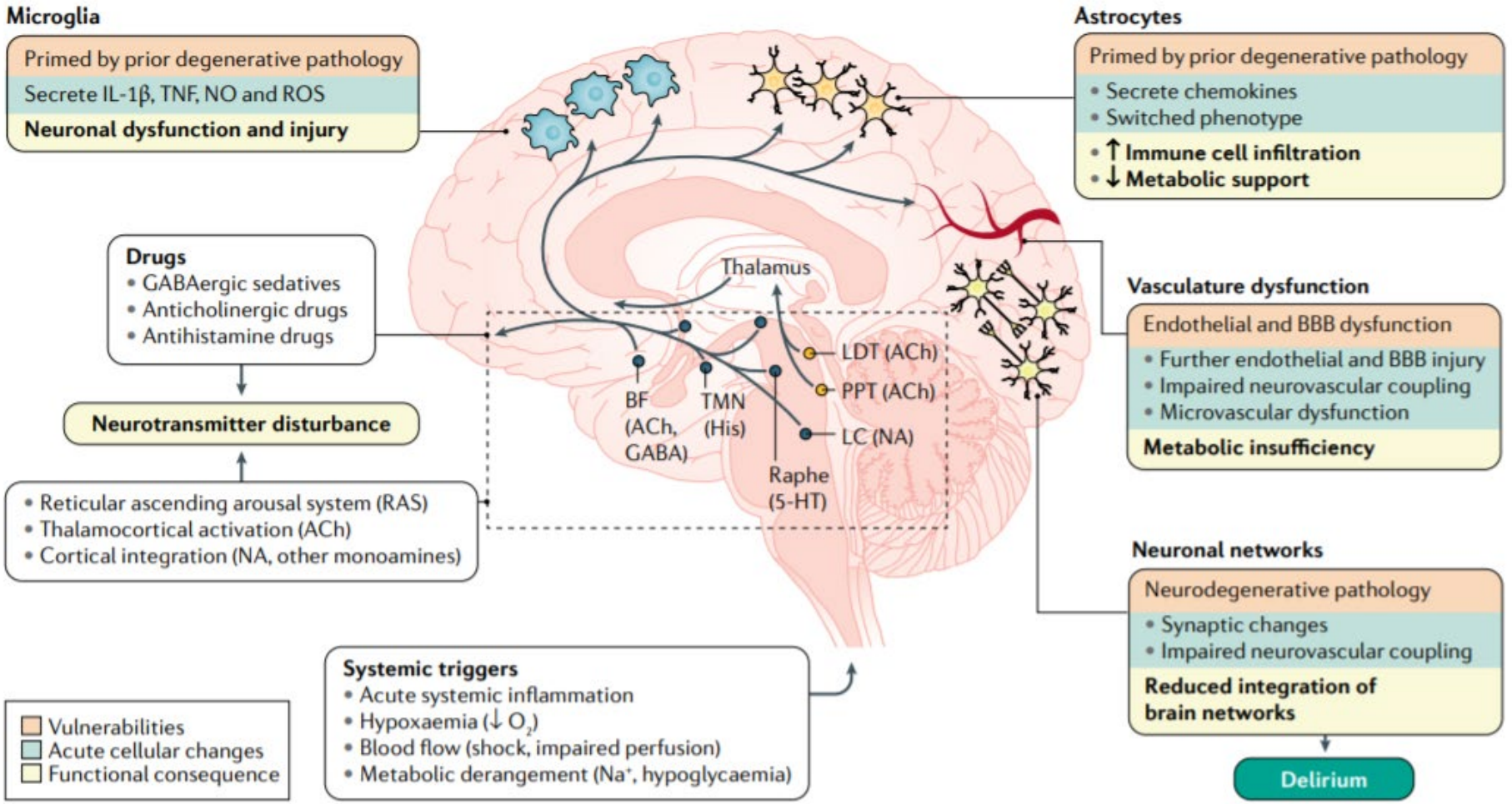
Journal of the Academy of Consultation-Liaison Psychiatry 2023:64:248–261

Special Article

An Interdisciplinary Reappraisal of Delirium and Proposed Subtypes

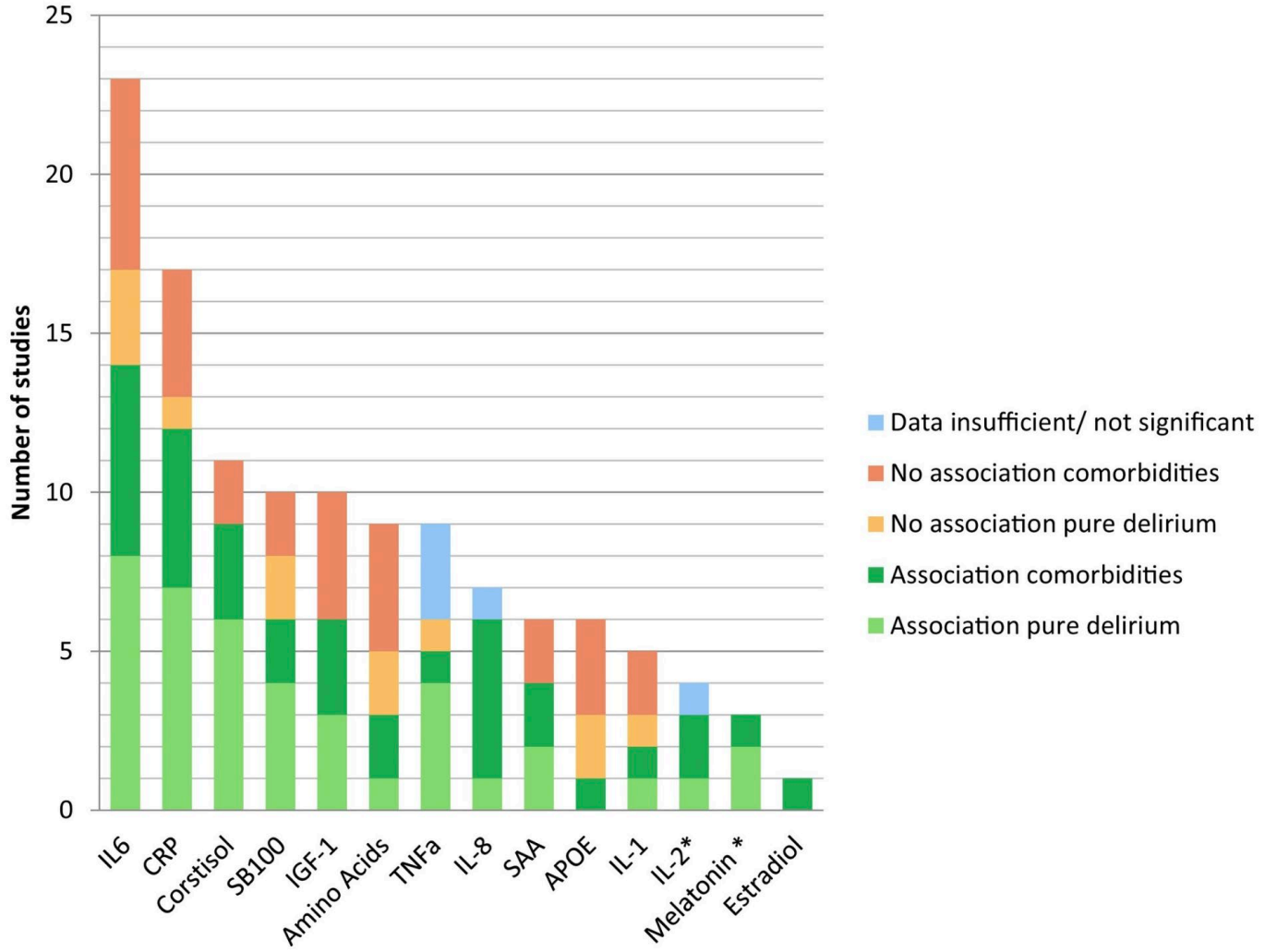
Mark A. Oldham, M.D., Arjen J.C. Slooter, M.D., Ph.D., E. Wesley Ely, M.D., M.P.H., Cathy Crone, M.D., José R. Maldonado, M.D., Lisa J. Rosenthal, M.D.

Pathophysiology



Wilson et al, 2020

Heterogeneity of biomarkers



*** Although graph indicates a high proportion of associations found, these findings were contradictory. Associations were with both high and low levels of these markers.**

Dunne et. al, 2021

nature portfolio

Nat Med. 2024 Jun 17;30(7):2076–2087. doi: 10.1038/s41591-024-03057-9

Personalized brain circuit scores identify clinically distinct biotypes in depression and anxiety

Leonardo Tozzi [1], Xue Zhang [1], Adam Pines [1], Alisa M Olmsted [1,2], Emily S Zhai [1], Esther T Anene [3], Megan Chesnut [1], Bailey Holt-Gosselin [4], Sarah Chang [5], Patrick C Stetz [1,2], Carolina A Ramirez [6], Laura M Hack [1,2], Mayuresh S Korgaonkar [7,8], Max Wintermark [9], Ian H Gotlib [10], Jun Ma [11], Leanne M Williams [1,2,✉]

ohrenia Bulletin

Schizophr Bull. 2021 Aug 19;48(1):56–68. doi: 10.1093/schbul/sbab090

Psychosis Biotypes: Replication and Validation from the B-SNIP Consortium

Brett A Clementz [1,✉], David A Parker [1], Rebekah L Trotti [1], Jennifer E McDowell [1], Sarah K Keedy [2], Matcheri S Keshavan [3], Godfrey D Pearlson [4,5], Elliot S Gershon [2], Elena I Ivleva [6], Ling-Yu Huang [1], S Kristian Hill [7], John A Sweeney [8], Olivia Thomas [1], Matthew Hudgens-Haney [6], Robert D Gibbons [2], Carol A Tamminga [6]

Author information Article notes Copyright and License information

PMCID: PMC8781330 PMID: 34409449

THE LANCET
Respiratory Medicine
Volume 8, Issue 6, June 2020, Pages 631-643

Review

Subphenotypes in critical care: trans… into clinical practice

Kiran Reddy MB [a], Pratik Sinha PhD [b], Prof Cecilia M O'Kane PhD [c], Prof Anthor… MD [d], Prof Carolyn S Calfee MD [b], Prof Daniel F McAuley MD [c, e]

Published in final edited form as:
Lancet Respir Med. 2014 August ; 2(8): 611–620. doi:10.1016/S2213-2600(14)70097-9.

Latent Class Analysis of ARDS Subphenotypes: Analysis of Data From Two Randomized Controlled Trials

Carolyn S. Calfee, M.D., MAS[1], Kevin Delucchi, PhD.[2], Polly E. Parsons, M.D.[3], B. Taylor Thompson, M.D.[4,5], Lorraine B. Ware, M.D.[6], Michael A. Matthay, M.D.[1,7], and **the NHLBI ARDS Network**

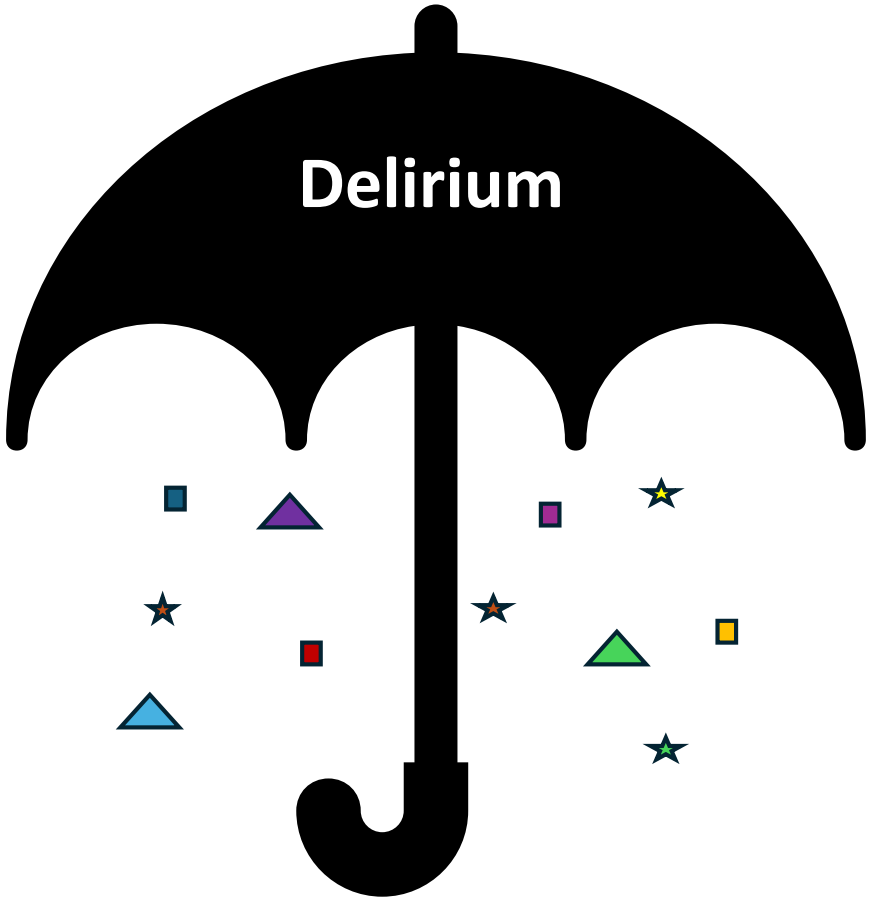
T-helper Type 2–driven Inflammation Defines Major Subphenotypes of Asthma

Prescott G. Woodruff[1,2], Barmak Modrek[3], David F. Choy[4], Guiquan Jia[4], Alexander R. Abbas[3], Almut Ellwanger[1], Joseph R. Arron[4]*, Laura L. Koth[1,5], and John V. Fahy[1,2]*

[1]Division of Pulmonary and Critical Care Medicine and [2]Cardiovascular Research Institute, Department of Medicine, Cardiovascular Research Institute, University of California, San Francisco, San Francisco, California; [3]Department of Bioinformatics and [4]ITGR Biomarker Group, Genentech, Inc., South San Francisco, California; and [5]Lung Biology Center, Department of Medicine, Cardiovascular Research Institute, University of San Francisco, San Francisco, California

The Problem

- Delirium research
- Understanding low
- Delirium is common



CRITICAL CARE

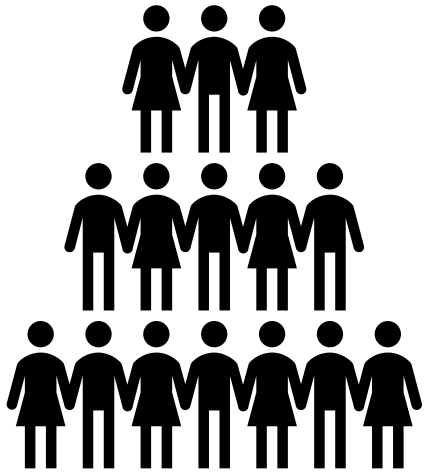
REVIEW Open Access

Phenotypes and subphenotypes of delirium: a review of current categorisations and suggestions for progression

Emily M. L. Bowman[1*], Emma L. Cunningham[1], Valerie J. Page[2] and Daniel F. McAuley[3]

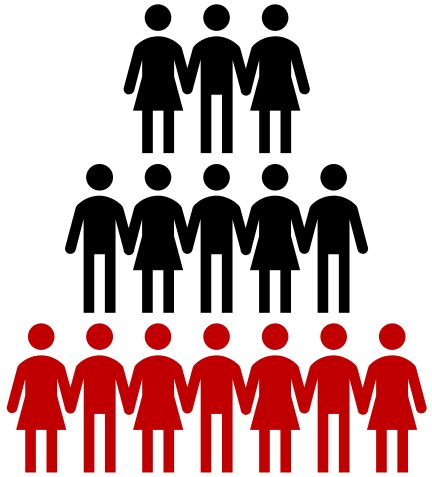
Definitions

Phenotypes



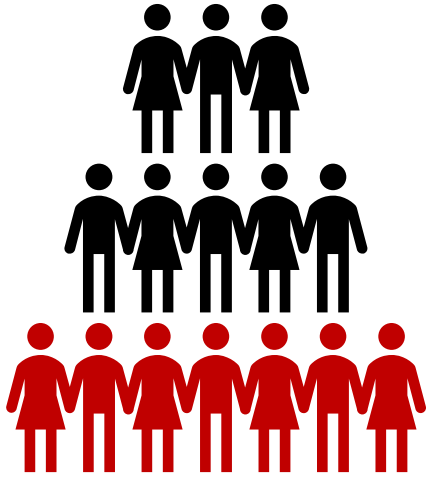
All have delirium (based on clinical features)

Subphenotypes



Red all have delirium and a shared risk factor, eg sepsis

Endotypes

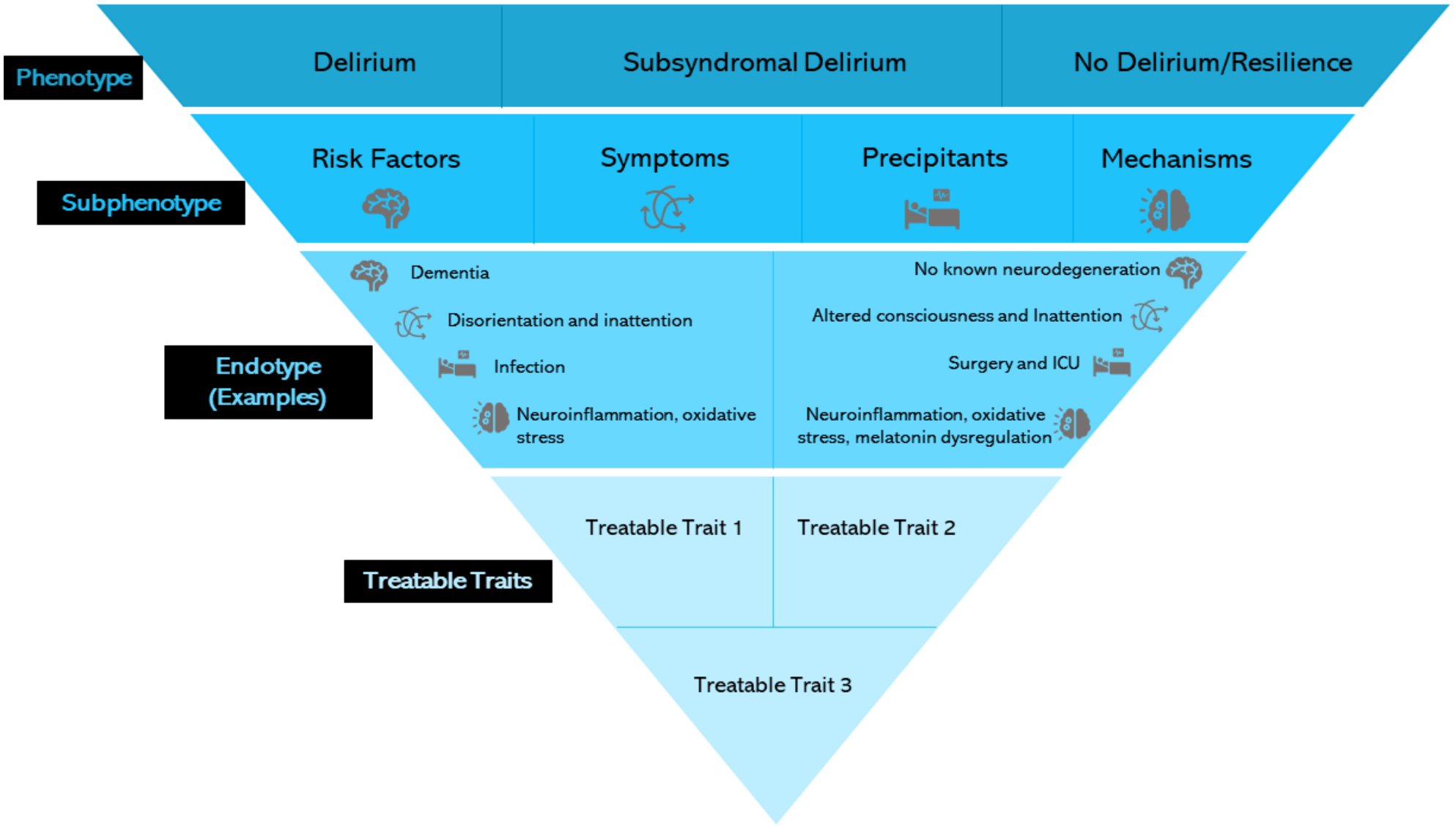


Red all share a mechanism, eg neuroinflammation

Treatable Traits

Characteristics targeted by an intervention.

Lötvall et al, 2011



Bowman et al. 2021

Delirium Subtyping Initiative Steering Committee

Overall Meeting Aims

Reach consensus on:

1. Methods for selecting primary symptoms to be considered/recorded in delirium diagnosis.
2. Definitions for subtyping
3. Which clinical and biomarker features should be considered with most importance

Discuss ideas on:

1. How to update and validate new subtypes.
2. What we can learn from previous subtyping works.
3. A plan to conquer logistical challenges in data sharing and combination.

Session 1- Clinical Features

Problems

Indexical approach- ***DSM-5-TR*** *is* a partial picture.

Delirium normally recorded as a **binary outcome**.

How to **define and operationalise core features**, eg inattention.

Boundaries between clinical syndromes, e.g., delirium and dementia, can be **indistinct.**

Variability in **outcomes assessment** make study comparison difficult- even in similar populations.

Currently defined by **clinical features only**.

How to describe those unable to engage with delirium assessment? **Possible/probable delirium?**

Is the **number of delirium symptoms** predictive of outcomes?

Session 1- Clinical Features

Recommendations

Operationalisation of features must be standardised across studies for combination and comparison of results.

Delirium subtyping methods should consider including all “delirium-spectrum syndromes”.

Delirium screening should involve a patient’s level of communication and reasoning.

Creation of distinct research and clinical criteria should be considered.

Session 1- Clinical Features

Future Aims

- ✓ Robust collection of **individual, routine and well-classified clinical features**.
- ✓ Delirium identification and severity assessment tools for all **medical settings and communicative abilities.**
- ✓ **Consistent** collection of **clinical feature data** and **biomarker data** in both clinical and research settings.

Session 2- Refinement and Validation

Problems

Potentially limited **translatability** of statistical clustering methods **into clinical practice** (imputation).

Categories of clinical and biomarker features are **not consistently measured.**

Subtyping success requires **establishing validation and** methods for regular updates.

Session 2- Refinement and Validation

Recommendations

Use of large datasets incorporating **clinical and biomarker** variables.

Analysis of similar and different cohorts, with caution, for understanding **variability and validity**.

Session 2- Refinement and Validation

Future Goals

- ✓ Application of **cluster analysis techniques** (e.g., latent class analysis)
- ✓ **Data complexity** and **feature quality** should dictate clinical phenotypes.
- ✓ Methods used must be **replicable** and **easily understood.**
- ✓ Strong phenotypes must be **discrete, consistent, reproducible, validated and clinically useful**.
- ✓ Multivariable phenotyping and **prognostic enrichment** needed to identify groups of patients with specific treatment responses or treatable traits.

Session 3- Methods for handling data & statistics

Problems

Heterogeneity in medical setting, clinical features, demographics, precipitants, insults, cognition and outcomes.

Transiency, patient **multimorbidity** and treatment response.

Ensuring ease of **data sharing**.

Variability in data records and thresholds used.

Potential differences between **hypothesis driven** studies and **data/sample driven** studies**.**

Session 3- Methods for handling data & statistics

Recommendations

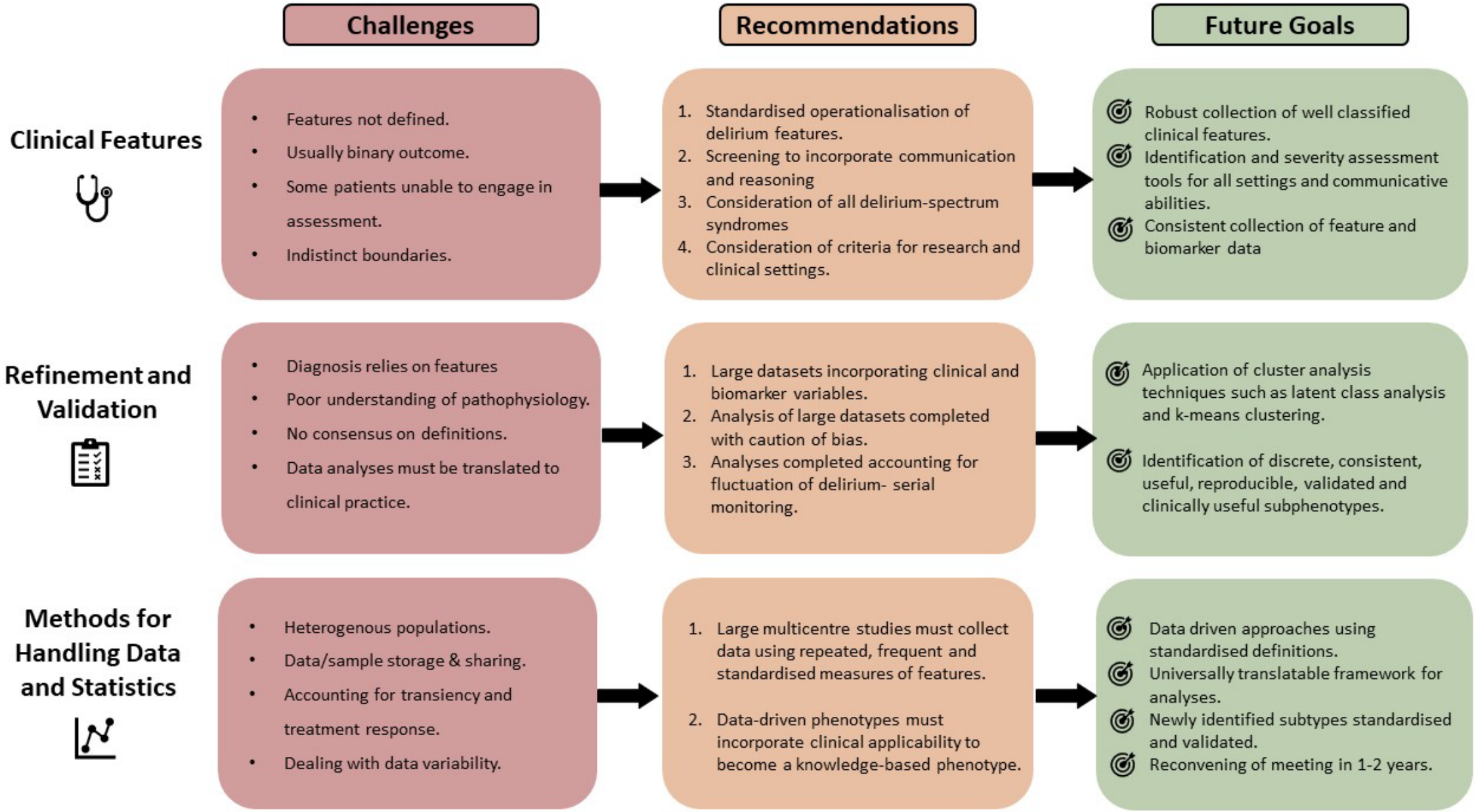
Large multicentre studies should collect data using **repeated**, **frequent** and **standardised** measures of clinical features.

Data-driven phenotypes must incorporate **clinical applicability** to become a knowledge-based phenotype.

Session 3- Methods for handling data & statistics

Future Goals

- ✓ **Data collection** (notes and samples) must be robust, consistent, and statistical protocols shared among all.
- ✓ **Operationalisation** and **standardisation** of all recommendations,
- ✓ A **universally translatable language** within which we are collecting data based on a framework.
- ✓ Newly identified subtypes must be **standardised** and **validated**.
- ✓ **Reconvening** of the Delirium Subtyping Initiative in 1-2 years for progress updates and review of goals.



Bowman et al. 2023

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Alzheimers Dement. 2023 Jul 31;20(1):183–194. doi: 10.1002/alz.13419

Advancing specificity in delirium: The delirium subtyping initiative

Emily M L Bowman [1,2,✉], Nathan E Brummel [3], Gideon A Caplan [4], Colm Cunningham [5], Lis A Evered [6,7,8], Kirsten M Fiest [9,10,11,12,13], Timothy D Girard [14], Thomas A Jackson [15], Sara C LaHue [16,17,18], Heidi L Lindroth [19,20], Alasdair M J Maclullich [21], Daniel F McAuley [2], Esther S Oh [22], Mark A Oldham [23], Valerie J Page [24], Pratik P Pandharipande [25], Kelly M Potter [14], Pratik Sinha [26], Arjen J C Slooter [27,28], Aoife M Sweeney [1], Zoë Tieges [21,29], Edwin Van Dellen [27,28], Mary Elizabeth Wilcox [30], Henrik Zetterberg [31,32,33,34,35,36], Emma L Cunningham [1]

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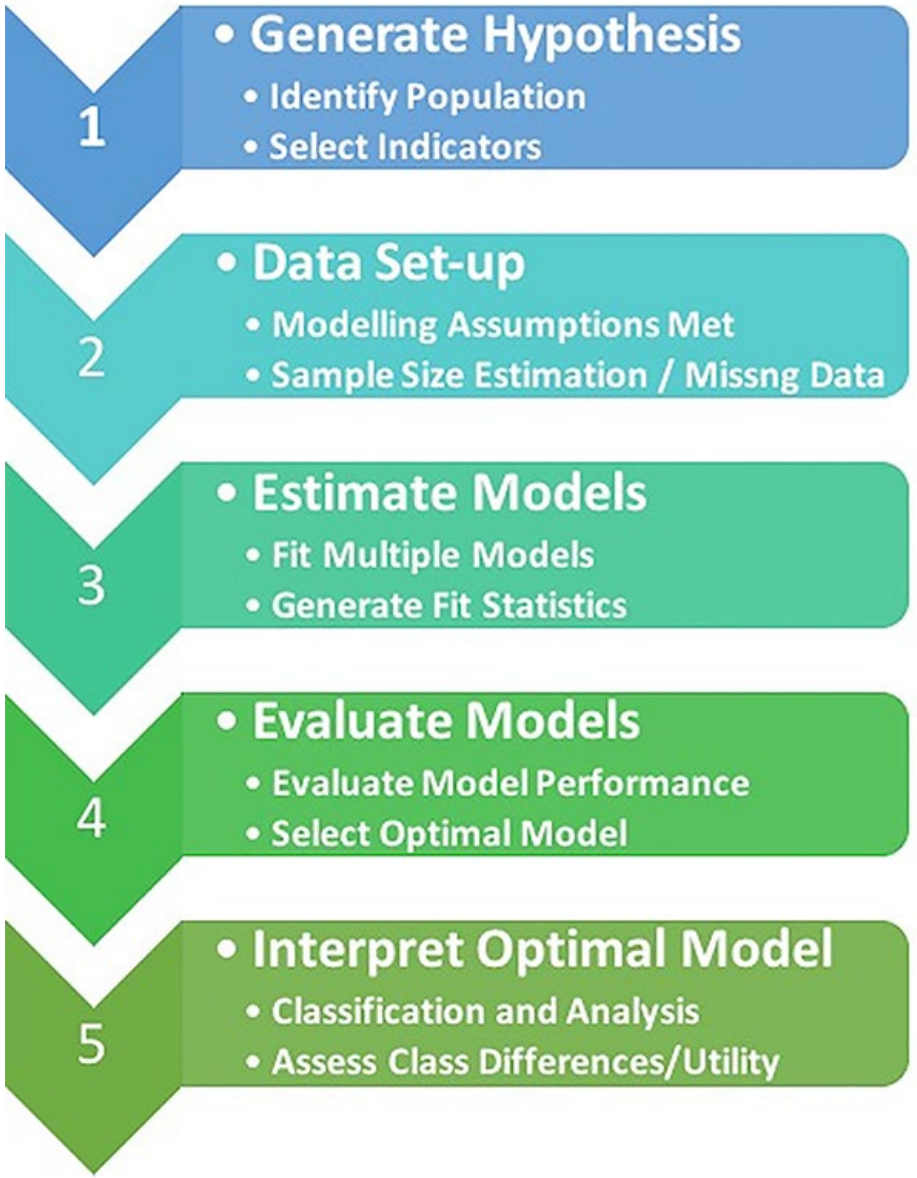
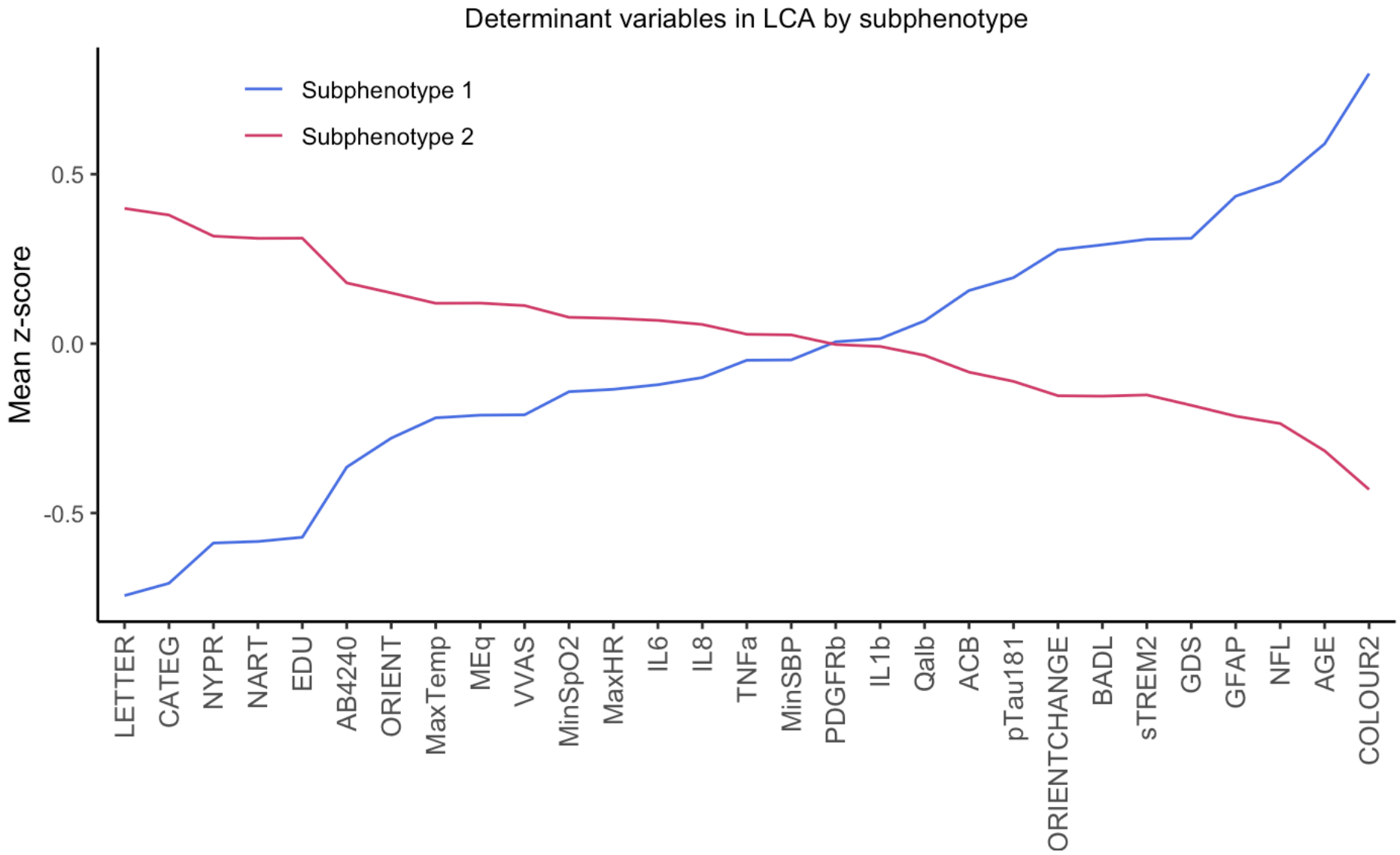
PMCID: PMC10917010 PMID: 37522255

Latent Class Analysis - Methods



Sinha et al., 2021.

Latent Class Analysis – PoDB Results



ery patients

based on

s?

Two Subphenotypes of PoDB participants

Class 1	Class 2
N = 110 28% Delirium Average age 78 Shorter education More depression and dependency in ADL Higher levels of pain Worse preoperative and postoperative cognition More postoperative inattention and altered consciousness Lower oxygen saturation, temperature and numbers of morphine equivalents Higher CSF GFAP, NfL, and sTREM2, indicating higher levels or neuronal injury or neurodegeneration. Slightly higher levels plasma pTau181, a marker of AD. More likely to have died, have dementia or be institutionalised at 8-year follow up.	N = 205 6.3% Delirium Average age 71 Slightly higher CSF Aβ4240 ratios, a marker of AD.

Acknowledgements

Delirium Subtyping Initiative Steering Committee

Dr Emma Cunningham

Prof Danny McAuley

Prof Chris Cardwell

Dr Aoife Sweeney

Dr Valerie Page

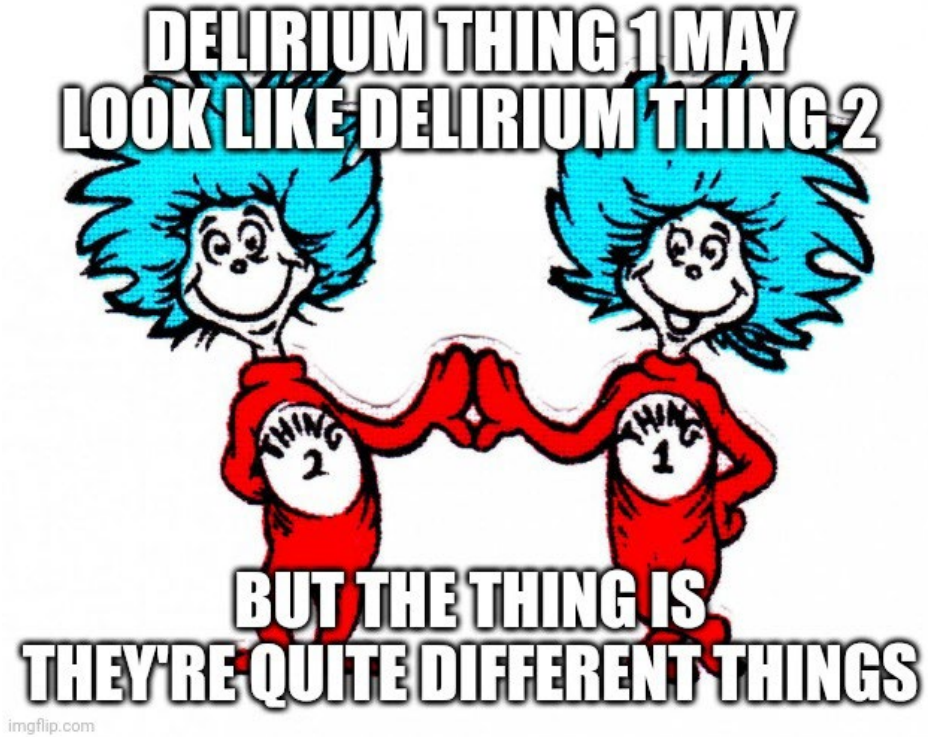
Prof Rich Jones

Dr Kiran Reddy

Mr John Conlon

CPH Ageing Research Forum

WWIEM Critical Care & Respiratory Research Group



(Credits to M. Oldham)

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