Social support and vascular contributions to cognitive impairment

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Disclosures

- No disclosures

Research question

Among people with cardiovascular risk factors in midlife, does low social support independently predict the development of vascular cognitive impairment later in life?

Are there gender differences in this relationship?

Background

VCI= Cognitive impairment caused by vascular disease of the brain. Heterogeneous.

- Pathology: small vessel disease, infarcts, white matter lesions, reduced cerebral perfusion
- 20% of all dementia cases, likely underestimated
- Often coexists with other pathologies
- Vascular dysfunction -> inability to clear AB from brain
- Lowers threshold for pathology necessary for cognitive impairment
- Risk factors: HTN, T2DM, HLD, smoking, obesity, MI, CAD, physical inactivity
- Risk modification in midlife is essential

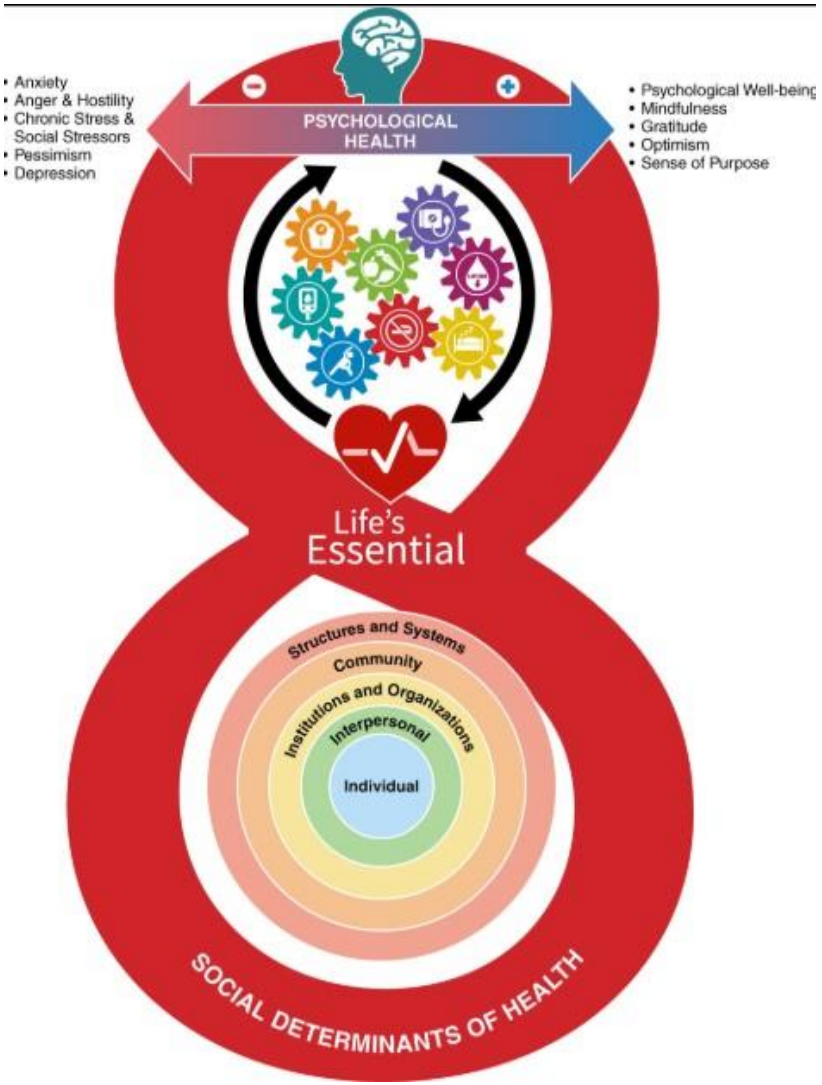
Background

- **FINGER**: Multidomain lifestyle intervention showed small improvement in cognition in older adults with risk of dementia
- **MAPT**: Multidomain intervention did not significantly slow cognitive decline, post hoc analyses showed benefit in high-risk individuals
- **PreDIVA**: Nurse-led, multidomain intervention did not decrease incidence of all cause dementia. Subgroup benefit for people with baseline untreated HTN

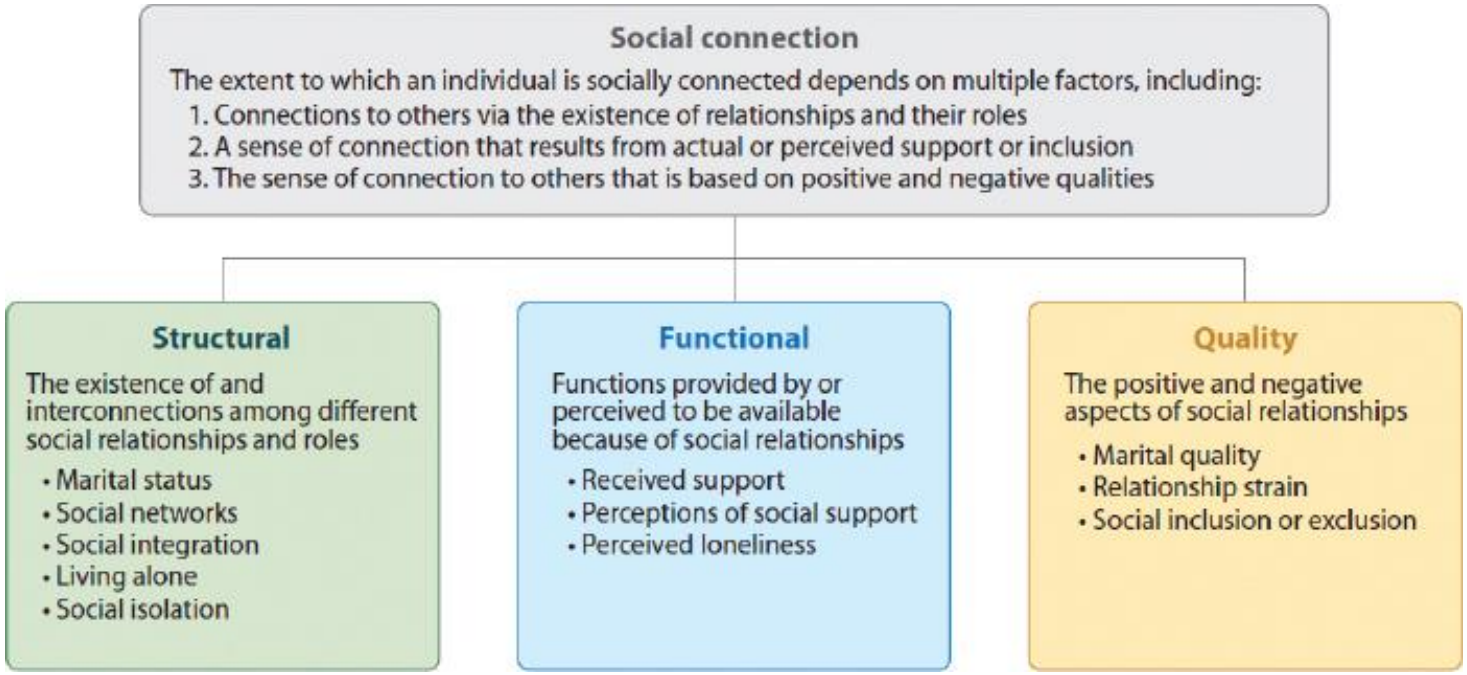
2, 3, 4

Background


Life's
Essential 8™
LIPIDS


• Anxiety
• Anger & Hostility
• Chronic Stress & Social Stressors
• Pessimism
• Depression
PSYCHOLOGICAL HEALTH
• Psychological Well-being
• Mindfulness
• Gratitude
• Optimism
• Sense of Purpose
Life's Essential
Structures and Systems
Community
Institutions and Organizations
Interpersonal
Individual
SOCIAL DETERMINANTS OF HEALTH

Background


Social connection
The extent to which an individual is socially connected depends on multiple factors, including:
1. Connections to others via the existence of relationships and their roles
2. A sense of connection that results from actual or perceived support or inclusion
3. The sense of connection to others that is based on positive and negative qualities
Structural
The existence of and interconnections among different social relationships and roles
• Marital status
• Social networks
• Social integration
• Living alone
• Social isolation
Functional
Functions provided by or perceived to be available because of social relationships
• Received support
• Perceptions of social support
• Perceived loneliness
Quality
The positive and negative aspects of social relationships
• Marital quality
• Relationship strain
• Social inclusion or exclusion

Background

Epidemiology

- Aging does not independently cause loneliness
- 43% of adults age 60+ report feeling lonely
- 19% of adults 92-91 report frequent loneliness
- Loneliness decreases with age through early 70s, then increases
- Stable overall level of social support between middle age and late life (size decreases but interactions become more quality)

Background

Mortality outcomes

- **Social isolation**:
  - > Robust for significantly increased risk for premature mortality from all causes

- **Loneliness**:
  - > Rico-Uribe et al 2018 meta-analysis found loneliness significantly increases the risk for all cause mortality by 22% independent of depression

- **Social support**:
  - > Holt-Lunstad et al showed stronger social connection was associated with a 50% greater odds of survival and specifically perceived social support predicted 35% increased odds of survival

1, 5, 14, 15

Background

Vascular outcomes

- **Stroke:**
  - > Valtora et al found poor social relationships were associated with a 32% increase in stroke risk
- **MI**:
  - > UK Biobank found that lonely people were at increased risk of MI
- **HTN**:
  - > Social support, particularly for older adults, is linked with a lower resting blood pressure
  - > Social isolation and loneliness are associated with elevated vascular resistance, high blood pressure, and higher rates of metabolic syndrome.
- **CSVD**:
  - > Poor social relationships associated with WMH progression in community-dwelling older adults
  - > Mid-life social relationships significantly modified the relationship between WMH volume and dementia risk

1, 12, 13

Background

Dementia and cognition outcomes

- Loneliness at a single time point is independently associated with cognitive decline and dementia
- Loneliness, infrequent social contacts, and low-level group participation increased risk of dementia by 50%
- Meta-analysis of 2.3 million participants - poor social support was a risk factor for dementia and even stronger when adjusting for depression
- Possible protective effects of high social engagement

Background

Proposed physiological mechanisms

- **Structural**:
  - > Individuals reporting both loneliness and social isolation have higher brain age
  - > In older adults, greater emotional support is associated with higher levels of BNP
- **Pathological**:
  - > Loneliness is associated with higher amyloid burden and regional tau accumulation in cognitively normal older adults
- **Cardiovascular:**
  - > Loneliness is associated with activation of the HPA axis and sympathetic nervous system
- **Inflammatory:**
  - > Midlife in US study - positive relationship between loneliness and IL-6, fibrinogen, and CRP
- **Genetics:**
  - > Research emerging
- **Cognitive reserve**:
  - > Social interactions may enhance cognitive capacity by activating and maintaining brain networks

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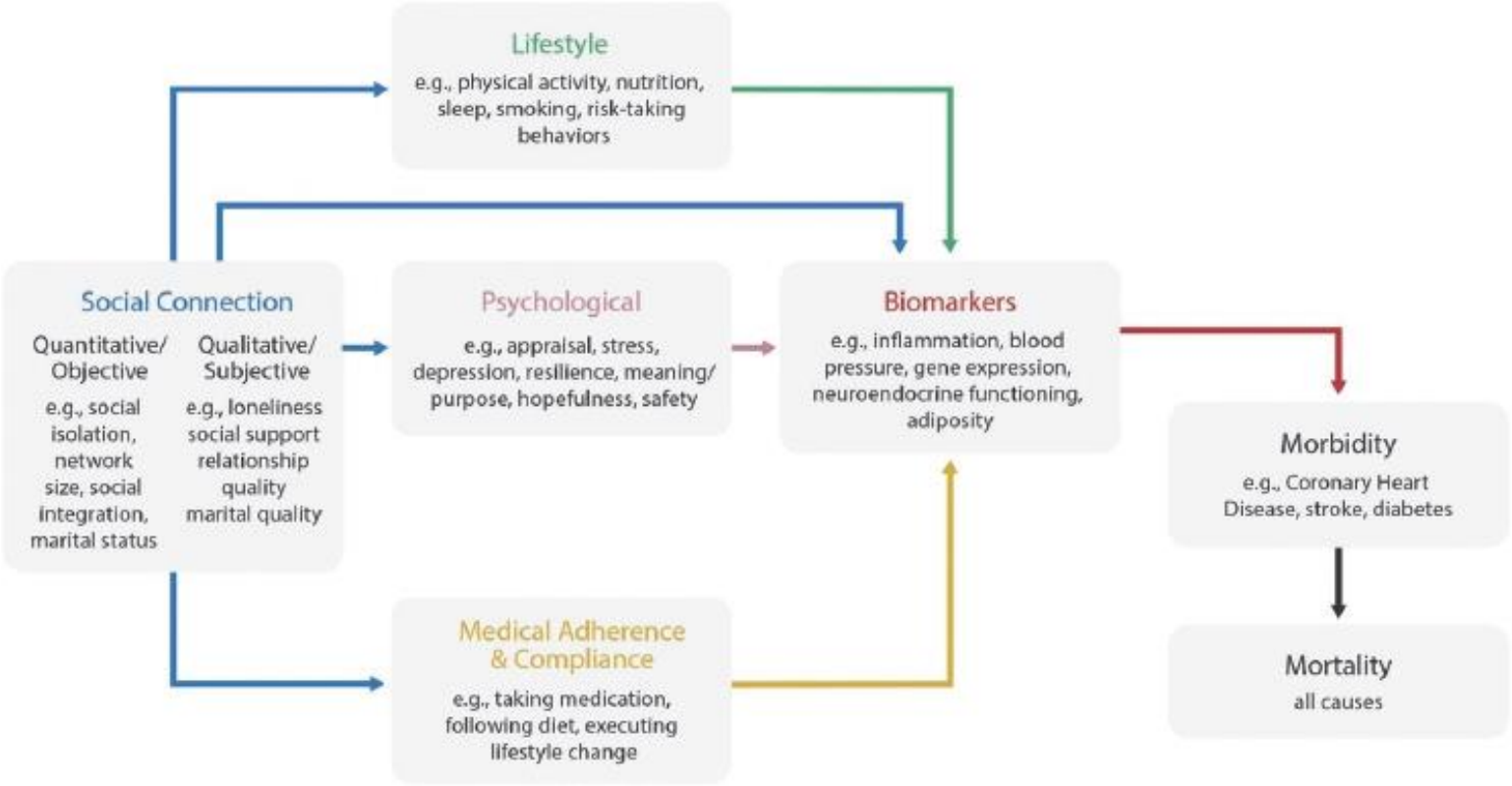
Background


Lifestyle
e.g., physical activity, nutrition, sleep, smoking, risk-taking behaviors
Social Connection
Quantitative/ Objective
e.g., social isolation, network size, social integration, marital status
Qualitative/ Subjective
e.g., loneliness social support relationship quality marital quality
Psychological
e.g., appraisal, stress, depression, resilience, meaning/ purpose, hopefulness, safety
Biomarkers
e.g., inflammation, blood pressure, gene expression, neuroendocrine functioning, adiposity
Morbidity
e.g., Coronary Heart Disease, stroke, diabetes
Mortality
all causes
Medical Adherence & Compliance
e.g., taking medication, following diet, executing lifestyle change

Research question

Among people with cardiovascular risk factors in midlife, does low social support independently predict the development of vascular cognitive impairment later in life?

Hypothesis 1

Poor social support as a risk factor for VCID in ACT cohort

- Low social support is an independent predictor of vascular cognitive impairment later in life among individuals with cardiovascular risk factors.

Background

Gender differences

- No differences in loneliness between genders across the lifespan
- Loneliness and all cause dementia risk is not moderated by gender
- Gender is not a significant moderator in the relationship between social support and mortality
- Protective effects of social relationships are similar for women and men
- Women may report higher levels of loneliness and may have larger social networks
- Men - higher risk of VCID up until age 85
- Women - unique vascular risk factors including pregnancy, menopause, and HRT

Research question

Are there gender differences in the relationship between social support and VCI risk?

Hypothesis 2

Gender differences in relationship between social support and VCI in the ACT cohort

- There will be no gender related difference in the relationship between social support and the development of VCI.

Study design

Population

Participants age 65+ at baseline visit with at least one cardiovascular risk factor in midlife and an MRI at least 10 years after baseline visit.

Study proposal

Exposure

- Social support- ACT form 73, psychosocial health at baseline visit
  - When I feel lonely, there are several people I can talk to
  - I often meet or talk with family or friends
  - If I needed help, I could easily find someone to help me with my daily chores
  - When I need suggestions on how to deal with personal problem, I know someone I can turn to
  - There is at least one person I know whose advice I really trust
  - If I had to go out of town for a few weeks, it would be possible to find someone who would look after my house or apartment (plants, pets, garden, etc.)

Study design

Outcome

- Diagnosis of vascular cognitive impairment based on The Vascular Impairment of Cognition Classification Consensus Study (VICCCS) criteria at follow up exam or on pathology
- VICCCS criteria:
  - > Neuroimaging evidence of cerebrovascular disease
  - > Mild vascular cognitive impairment= impairment in at least one cognitive domain and one ADL
  - > Major vascular cognitive impairment= deficits in at least one cognitive domain and severe disruption to ADL or iADL independent of stroke-related impairment

Study proposal

Covariates/confounders

- Age, sex, education, race, HTN, HLD, DMT2, medication use, OSA, smoking, alcohol use, depression, anxiety, physical activity, BMI

Study design

Statistical analysis

- Logistic regression or Cox proportional hazards model
- Interaction term included for gender
- Stratify by gender if significant

Importance

- Fills research gap
- Focuses on high-risk population
- Explores a modifiable risk factor
- Supports prevention/treatment strategies
- Investigates gender differences

Limitations

- Do not have measure of social support in midlife
- Psychosocial questions are not validated to measure social support, loneliness, or social isolation
- May miss some participants with vascular contributions to cognitive impairment
- Sample size- participants with MRIs, diagnostic criteria

References

1. National Academies of Sciences, Engineering, and Medicine; Division of Behavioral and Social Sciences and Education; Health and Medicine Division; Board on Behavioral, Cognitive, and Sensory Sciences; Board on Health Sciences Policy; Committee on the Health and Medical Dimensions of Social Isolation and Loneliness in Older Adults. Social Isolation and Loneliness in Older Adults: Opportunities for the Health Care System. Washington (DC): National Academies Press (US); 2020 Feb 27. PMID: 32510896.Silbert LC. Vascular Cognitive Impairment. Continuum (Minneap Minn). 2024 Dec 1;30(6):1699-1725. doi: 10.1212/CON.0000000000001508. PMID: 39620840.Holt-Lunstad J. Why Social Relationships Are Important for Physical Health: A Systems Approach to Understanding and Modifying Risk and Protection. Annu Rev Psychol. 2018 Jan 4;69:437-458. doi: 10.1146/annurev-psych-122216-011902. Epub 2017 Oct 16. PMID: 29035688.
2. Holt-Lunstad J, Smith TB. Loneliness and social isolation as risk factors for CVD: implications for evidence-based patient care and scientific inquiry. Heart. 2016 Jul 1;102(13):987-9. doi: 10.1136/heartjnl-2015-309242. Epub 2016 Apr 18. PMID: 27091845; PMCID: PMC4941164.
3. Valtorta NK, Kanaan M, Gilbody S, Ronzi S, Hanratty B. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. Heart. 2016 Jul 1;102(13):1009-16. doi: 10.1136/heartjnl-2015-308790. Epub 2016 Apr 18. PMID: 27091846; PMCID: PMC4941172.
4. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, Rosamond W; American Heart Association. Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. Circulation. 2022 Aug 2;146(5):e18-e43. doi: 10.1161/CIR.0000000000001078. Epub 2022 Jun 29. PMID: 35766027; PMCID: PMC10503546.
5. de Lange AG, Kaufmann T, Quintana DS, Winterton A, Andreassen OA, Westlye LT, Ebmeier KP. Prominent health problems, socioeconomic deprivation, and higher brain age in lonely and isolated individuals: A population-based study. Behav Brain Res. 2021 Sep 24;414:113510. doi: 10.1016/j.bbr.2021.113510. Epub 2021 Aug 4. PMID: 34358570.
6. Düzel S, Drewelies J, Gerstorf D, Demuth I, Steinhagen-Thiessen E, Lindenberger U, Kühn S. Structural Brain Correlates of Loneliness among Older Adults. Sci Rep. 2019 Sep 19;9(1):13569. doi: 10.1038/s41598-019-49888-2. PMID: 31537846; PMCID: PMC6753249.
7. Donovan NJ, Okereke OI, Vannini P, Amariglio RE, Rentz DM, Marshall GA, Johnson KA, Sperling RA. Association of Higher Cortical Amyloid Burden With Loneliness in Cognitively Normal Older Adults. JAMA Psychiatry. 2016 Dec 1;73(12):1230-1237. doi: 10.1001/jamapsychiatry.2016.2657. PMID: 27806159; PMCID: PMC5257284.
8. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005 Jan 25;64(2):277-81. doi: 10.1212/01.WNL.0000149519.47454.F2. PMID: 15668425.

References

9. 9. Skrobot OA, Black SE, Chen C, DeCarli C, Erkinjuntti T, Ford GA, Kalaria RN, O'Brien J, Pantoni L, Pasquier F, Roman GC, Wallin A, Sachdev P, Skoog I; VICCCS group; Ben-Shlomo Y, Passmore AP, Love S, Kehoe PG. Progress toward standardized diagnosis of vascular cognitive impairment: Guidelines from the Vascular Impairment of Cognition Classification Consensus Study. Alzheimers Dement. 2018 Mar;14(3):280-292. doi: 10.1016/j.jalz.2017.09.007. Epub 2017 Oct 19. PMID: 29055812.
10. 10. Del Brutto OH, Mera RM, Recalde BY, Rumbea DA, Del Brutto VJ. High Social Risk Influence Progression of White Matter Hyperintensities of Presumed Vascular Origin: A Prospective Study in Community-Dwelling Older Adults. Stroke. 2022 Aug;53(8):2577-2584. doi: 10.1161/STROKEAHA.122.038561. Epub 2022 May 4. PMID: 35506386.
11. 11. Eswaran S, Knopman DS, Koton S, Kucharska-Newton AM, Liu AC, Liu C, Lutsey PL, Mosley TH Jr, Palta P, Sharrett AR, Sullivan KJ, Walker KA, Gottesman RF, Groechel RC. Psychosocial Health and the Association Between Cerebral Small Vessel Disease Markers With Dementia: The ARIC Study. Stroke. 2024 Oct;55(10):2449-2458. doi: 10.1161/STROKEAHA.124.047455. Epub 2024 Aug 28. PMID: 39193713.
12. 12. Rico-Uribe LA, Caballero FF, Martín-María N, Cabello M, Ayuso-Mateos JL, Miret M. Association of loneliness with all-cause mortality: A meta-analysis. PLoS One. 2018 Jan 4;13(1):e0190033. doi: 10.1371/journal.pone.0190033. PMID: 29300743; PMCID: PMC5754055.
13. 13. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Med. 2010 Jul 27;7(7):e1000316. doi: 10.1371/journal.pmed.1000316. PMID: 20668659; PMCID: PMC2910600.
14. 14. Kuiper JS, Zuidersma M, Oude Voshaar RC, Zuidema SU, van den Heuvel ER, Stolk RP, Smidt N. Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev. 2015 Jul;22:39-57. doi: 10.1016/j.arr.2015.04.006. Epub 2015 May 5. PMID: 25956016.
15. 15. Nersesian PV, Han HR, Yenokyan G, Blumenthal RS, Nolan MT, Hladek MD, Szanton SL. Loneliness in middle age and biomarkers of systemic inflammation: Findings from Midlife in the United States. Soc Sci Med. 2018 Jul;209:174-181. doi: 10.1016/j.socscimed.2018.04.007. Epub 2018 Apr 30. PMID: 29735350; PMCID: PMC6013269.