## Bijlage 7 Evidence tabellen en GRADE profielen

Evidence tabellen en GRADE profielen behorende bij de uitgangsvragen die via de GRADE methodiek zijn uitgewerkt.

**Onderzoeksvraag 1: Welke gevalideerde meetinstrumenten zijn beschikbaar om hartklachten, dyspneu/benauwdheid, epilepsie, dementie, gedragsverandering vast te stellen bij mensen met een verstandelijke beperking?**

### Dementie

Systematische reviews

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Arevalo 2019 | - Design: systematic review<br>- Funding: German Research Foundation (DFG; no. TH2137/3-1) and the Hans and Ilse Breuer Foundation; CoI: none<br>- Search date: Nov 2017<br>- Databases: PubMed, Web of Science<br>- Study designs: diagnostic accuracy studies<br>- N included studies: N=27 | 1. Eligibility criteria: general population aged 45 years and older | Assessment tools examining cognitive functioning in Hispanic / Latin population groups in the United States | 1. 13 instruments identified<br>2. MMSE: cut-off=21, sensitivity 74.5-100% and specificity 46-98%<br>3. Naming test:<br>a. Texas Spanish Naming Test: significant lower scores in clinical patient participants<br>b. Confrontation Naming Test: sensitivity 74%, specificity 77%<br>c. Boston Naming Test: sensitivity 39%, specificity 89%<br>4. Addenbrooke Cognitive Examination-Revised:<br>a. Peruvian version: cut-off 86, sensitivity 100%, specificity 100%<br>b. Chilean version: cut-off 76, sensitivity 92%, specificity 93%<br>c. Argentinean version: cut-off 86, sensitivity 92%, specificity 96%<br>5. Montreal Cognitive Assessment: with respect to dementia<br>a. One study in Chile used a cut-off of 21 that was adjusted for education (+1 point for 8-12 y of education, +2 points for <8 y of education) and revealed a sensitivity of 75% and a specificity of 90%<br>b. A second study in Mexico used a cut-off of 24 and showed a sensitivity of 98% and specificity of 93%<br>6. Clock-Drawing Test: sensitivity 99%, specificity 83%<br>7. Syndrom-Kurztest: significant differences in the scores between cognitively normal people and people with dementia | • Language restriction: English, Spanish<br>• Selection and quality appraisal by independent reviewers; unclear for data extraction<br>• Unclear which studies were done in population with cognitive impairment (probably none) |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | | | | 8. 10/66 Short Diagnostic Schedule: sensitivity 94%<br>9. Executive Battery 25: sensitivity 94%, specificity 100% (cut-off=15)<br>10. Phototest: sensitivity 89%, specificity 97% (cut-off=27)<br>11. Eurotest: sensitivity 91%, specificity 83% (cut-off=24) | |
| Arevalo-Rodriguez 2015 | - Design: systematic review<br>- Funding: Agencia de Calidad del Sistema Nacional de Salud, Ministry of Health, Madrid, Spain; CoI: none<br>- Search date: May 2014<br>- Databases: ALOIS, Medline, Embase, BIOSIS, PsycInfo, LILACS, Web of Science, MEDION, DARE, HTA, ARIF<br>- Study designs: longitudinal studies<br>- N included studies: N=11, 1569 patients | 2. Eligibility criteria: participants recruited from community, primary care and secondary care settings and clinically classified as individuals with MCI at baseline | MMSE<br><br>Reference standard: clinical diagnosis (DSM, ICD) | 12. For conversion from MCI to dementia in general, the accuracy of baseline MMSE scores ranged from sensitivities of 23% to 76% and specificities from 40% to 94%<br>13. In relationship to conversion from MCI to Alzheimer's disease dementia, the accuracy of baseline MMSE scores ranged from sensitivities of 27% to 89% and specificities from 32% to 90%<br>14. Only one study provided information about conversion from MCI to vascular dementia, presenting a sensitivity of 36%and a specificity of 80% with an incidence of vascular dementia of 6.2% | • High-quality review |
| Aslam 2018 | - Design: systematic review (PROSPERO CRD42015025410)<br>- Funding: National Institute for Health Research Health Technology Assessment programme; CoI: none<br>- Search date: 2005 – Aug 2015<br>- Databases: MEDLINE, EMBASE, The Cochrane Library, ISI Web of Science and PsycINFO<br>- Study designs: diagnostic accuracy studies | 3. Eligibility criteria: adults (aged > 18 years) with diagnosed MCI and early dementia | Automated computerised tests<br><br>Reference standard: clinical diagnosis (DSM, ICD) | 15. No studies met the review inclusion criteria for monitoring progression in MCI or early dementia | • Review in two parts: second part relevant for this research question<br>• High-quality review |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | - N included studies: N=16 | | | | |
| Chan 2018 | - Design: systematic review<br>- Funding: not reported; CoI: none<br>- Search date: Oct 2017<br>- Databases: MEDLINE, EMBASE, PsycINFO, and CINAHL<br>- Study designs: cross-sectional studies<br>- N included studies: N=58 | 4. Eligibility criteria: participants with MCI and dementia in any kind of setting | Computerized or paper-and-pencil memory tests | 16. For detection of dementia, 5 studies investigated computerized verbal memory tests, and the sensitivities ranged from 0.47 to 0.94 and specificities ranged from 0.56 to 0.97 across individual studies; the combined data with bivariate random-effects model gave a summary point of 0.85 sensitivity (95%CI 0.66-0.95) and 0.89 specificity (95%CI 0.690.96); the diagnostic odds ratio was 45.4, and the AUC was 93% (91%-95%)<br>17. Thirty-three studies investigated paper-and-pencil verbal memory tests, and the sensitivities ranged from 0.43 to 1.00 and specificities ranged from 0.52 to 0.99 across individual studies; a summary point of 0.90 sensitivity (95%CI 0.85-0.93) and 0.90 specificity (95%CI 0.86-0.93) was estimated; the diagnostic odds ratio was 78.5, and the AUC was 96% (93%-97%)<br>18. Seven studies investigated computerized visual memory tests, and the sensitivities ranged from 0.77 to 1.00 and specificities ranged from 0.77 to 0.96 across individual studies; a summary point of 0.89 sensitivity (95%CI 0.71-0.96) and 0.81 specificity (95%CI 0.68-0.90) was estimated; the diagnostic odds ratio was 33.2, and the AUC was 90% (88%-93%)<br>19. Two studies investigated paper-and-pencil visual memory tests, and the sensitivities ranged from 0.67 to 0.90 and specificities ranged from 0.76 to 1.00 across individual studies; the random-effects model of DerSimonian and Laird approach was applied because the Hessian matrix of bivariate random-effects approach was unstable; the estimated pooled sensitivity and specificity were 0.83 (95%CI 0.64-0.94) and 0.80 (95%CI 0.72-0.86), respectively | • Language restriction: unclear<br>• Review process in duplicate (although not completely clear for selection) |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Chen 2018 | - Design: systematic review<br>- Funding: none; CoI: none<br>- Search date: Apr 2017<br>- Databases: Medline, Embase, Cochrane Library, UpToDate, PsycInfo, PerioPath Indexto Taiwan Periodical Literature, Airiti Library, Google Scholar<br>- Study designs: diagnostic accuracy studies<br>- N included studies: N=7 | 5. Eligibility criteria: primary care setting in the community, clinics and hospitals | Ascertain Dementia 8 questionnaire | 20. Seven studies were pooled for differentiation between dementia and non-dementia<br>21. Pooled sensitivity: 0.91 (95%CI 0.89-0.92)<br>22. Pooled specificity: 0.78 (0.76-0.80)<br>23. Diagnostic odds ratio: 37.23 (21.34-64.94)<br>24. AUC: 0.92<br>25. Pooled LR+: 3.94 (1.97-7.87)<br>26. Pooled LR-: 0.13 (0.09-0.19) | • Language restriction: English, Chinese, Japanese, Spanish<br>• Review process by independent reviewers<br>• Unclear which studies were done in population with cognitive impairment (probably none) |
| Diaz-Orueta 2018 | - Design: systematic review<br>- Funding: European Commission, under the program MSCA-IF (Marie Sklodowska Curie Actions-Individual Fellowship), Grant Number 654895 -E-SPACEH2020-MSCA-IF-2014; CoI: none<br>- Search date: 'last 10 years'<br>- Databases: PubMed, PsycInfo, Ingenta Connect<br>- Study designs: all<br>- N included studies: N=unclear | 6. Eligibility criteria: cognitive screening tools for MCI and dementia in primary and secondary care | Cognitive screening tools for MCI and dementia | Narrative overview, no detailed description of validity | • Goal is to identify tools that would benefit from modifications using a process-based approach<br>• Unclear if review process was done by independent reviewers<br>• Unclear which studies were done in population with cognitive impairment |
| Franzen 2019 | - Design: systematic review<br>- Funding: grant 733050834 from the Netherlands Organization of Scientific Research (ZonMw Memorabel); CoI: none<br>- Search date: Aug 2018 | 7. Eligibility criteria: patients with dementia and/or patients with MCI/Cognitive Impairment No Dementia (CIND) | Neuropsychological tests for the assessment of dementia | Narrative description of results | • Focus on non-Western populations<br>• 12 studies reported on reliability and validity of tests<br>• Unclear language restriction<br>• Selection by independent reviewers |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | - Databases: Medline, Embase, Web of Science, Cochrane, Psycinfo, and Google Scholar<br>- Study designs: all<br>- N included studies: N=44 | | | | • Unclear if data extraction and quality appraisal were done by independent researchers |
| Garcia-Casal 2017 | - Design: systematic review<br>- Funding: H2020 Grant 643566; CoI: none<br>- Search date: 2010 – Jul 2015<br>- Databases: Medline, PsycInfo<br>- Study designs: all<br>- N included studies: N=34<br>- | 8. Eligibility criteria: older adults | ICT-based instruments assessing or monitoring older adults with potential cognitive decline | 27. 31 screening tests identified<br>28. Only 5 validated in population with only patients with cognitive impairment<br>29. Narrative overview of results | • Unclear language restriction<br>• Selection and data extraction by independent reviewers<br>• Unclear if quality appraisal were done by independent researchers |
| Paddick 2017 | - Design: systematic review<br>- Funding: not reported; CoI: none<br>- Search date: Dec 2014<br>- Databases: Medline, Embase, PsycInfo, Cinahl<br>- Study designs: all<br>- N included studies: N=45 | 9. Eligibility criteria: individuals aged 45 years and over in a low-literacy setting; tests suitable for non-specialists to use in routine care | Cognitive screening tools for identification of dementia<br><br>Reference standard: standard criteria including ICD or DSM, or clinical diagnoses made by a specialist clinician | 30. 27 screening tests identified<br>31. 14 tests (12 multi-domain and 2 single domain) were specifically developed for use in low-literacy settings<br>32. Community or low prevalence studies:<br>a. Prevalence: illiteracy 25-91%, dementia 3-34%<br>b. Meta-analysis (9 tools together): sensitivity 0.869 (0.791-0.921), specificity 0.886 (0.823-0.923), DOR 50.529, AUC 0.937<br>c. The most accurate screening tests were 7MS, PCL, and KICA-Cog in Australia; the least accurate were the Hindi MMSE and VSID-P; no meta-analyses for individual tests<br>33. Higher prevalence or clinic-based studies:<br>a. Prevalence: illiteracy 5.3-65%, dementia 10.4-33%<br>b. Meta-analysis (12 tools together): sensitivity 0.845 (0.817-0.869), specificity 0.847 (0.805-0.882), DOR 35.681, AUC 0.881<br>c. The least accurate test was the Brazilian MMSE, and the most accurate were the CMT and PMIS in Thailand and India albeit | • Review process in duplicate<br>• Language restriction: English, Spanish, French, Italian, or Portuguese<br>• Meta-analyses of different pools together |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
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| | | | | with wide confidence intervals; no meta-analyses for individual tests<br>34. Studies of illiterate individuals:<br>a. Meta-analysis (6 tools together): sensitivity 0.818 (0.769-0.859), specificity 0.801 (0.745-0.848), DOR 18.753, AUC 0.869<br>b. The least accurate tests were the Brazilian MMSE and B-IMC in China with similar performance for the MMSE in another Brazilian study and for the Chinese MMSE; the most accurate tests were the KICA-Cog and SPMSQ; no meta-analyses for individual tests<br>35. Validation studies of the MMSE:<br>a. Meta-analysis: sensitivity 0.828 (0.789-0.862), specificity 0.817 (0.717-0.887), DOR 22.981, AUC 0.853 | |
| Rikkert 2011 | - Design: systematic review<br>- Funding: none; CoI: none<br>- Search date: 2009<br>- Databases: Medline, PsycInfo, Cinahl, and Cochrane library<br>- Study designs: prospective studies<br>- N included studies: N=23 | 10. Eligibility criteria: participants with cognitive impairment, dementia, or AD | Clinical staging scales for dementia | 36. 12 instruments identified<br>37. Narrative overview | • Language restriction: English<br>• Unclear how review process was done by three independent reviewers |
| Tavares-Junior 2019 | - Design: systematic review<br>- Funding: not reported; CoI: not reported<br>- Search date: Jun-Jul 2019?<br>- Databases: MEDLINE, LILACS, Cochrane, and SCOPUS<br>- Study designs: cross-sectional and prospective studies<br>- N included studies: N=36 | 11. Eligibility criteria: adults over 55 years of age with low education | Cognitive assessment tools | 38. 44 instruments identified<br>39. Narrative overview | • Unclear language restriction<br>• Selection and data extraction done by independent reviewers<br>• Unclear quality appraisal |
| Velayudhan 2014 | - Design: systematic review | 12. Eligibility criteria: patients with suspected dementia | Brief cognitive tests | 40. 22 instruments identified<br>41. Narrative overview | • Language restriction: English |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | - Funding: not reported; CoI: one author was one of the authors of the TE4D-cog validation paper<br>- Search date: May 2013<br>- Databases: Medline, Embase, PsychInfo, Web of Science, HMIC Health Management Information Consortium and the Cochrane library<br>- Study designs: all<br>- N included studies: N=23 | | | | • Review process in duplicate (although not completely clear for data extraction)<br>• Unclear which studies were done in population with cognitive impairment |

## Apathie

### Systematische reviews

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Clarke 2011 | - Design: systematic review<br>- Funding: American Psychiatric Association; CoI: not reported<br>- Search date: 1980-2008<br>- Databases: PubMed, Psycinfo, Medline, Embase, Cinahl<br>- Study designs: all<br>- N included studies: N=unclear | 13. Eligibility criteria: adults aged 18y | Assessment tools for apathy | 42. 7 instruments identified that were validated in population with cognitive impairment (narrative description):<br>a. AES<br>b. AI<br>c. DAIR<br>d. IAS<br>e. FrSBe<br>f. KBCI<br>g. NPI | • Limited to English<br>• Limited information about selection process, data extraction and quality appraisal |
| Radakovic 2015 | - Design: systematic review<br>- Funding: Anne Rowling Regenerative Neurology Clinic, Alzheimer Scotland Dementia Research Centre; CoI: none<br>- Search date: 1980-2013<br>- Databases: PubMed, Psycinfo, Medline, | 14. Eligibility criteria: adults aged 18y | Assessment tools for apathy | 43. 4 instruments (in different versions) identified that were validated in population with cognitive impairment (narrative description):<br>a. AES<br>b. AI<br>c. DAIR<br>d. NPI | • Limited to English<br>• Review process in duplicate (although unclear for data extraction) |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | Embase, Google Scholar<br>- Study designs: all<br>- N included studies: N=16 | | | | |

Primaire studies: observationele studies

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Jao 2016 | - Design: observational study<br>- Funding: Honor Society of Nursing, Sigma Theta Tau (STT) International and the STT Gamma Chapter (PI: Ying-Ling Jao); CoI: none<br>- Setting: 22 nursing homes and 6 assisted living facilities, US<br>- Sample size: N=185<br>- Duration: 2000-2004 | 15. Assessors: two trained raters<br>16. Patients: (1) English-speaking, (2) diagnosis of dementia, (3) score of less than 24 for the MMSE, (4) ambulatory, and (5) stable regime of psychotropic medications<br>17. *A priori* characteristics:<br>e. Mean age: 82.4y<br>f. Female: 78.8%<br>g. MMSE <10: 72.8% | PEAR scale | Environment subscale<br>44. Inter-rater reliability:<br>a. 74.0-89.6% agreement<br>b. Weighted kappa: 0.49-0.94<br>45. Intra-rater reliability:<br>a. 79.2-92.7% agreement<br>b. Weighted kappa: 0.63-0.94<br>46. Internal consistency: Cronbach's alpha 0.84<br>47. Construct validity: Spearman's rank-order correlations<br>a. Crowding Index score: 0.266<br><br>Apathy subscale<br>48. Inter-rater reliability:<br>a. 63.5-85.4% agreement<br>b. Weighted kappa: 0.66-0.86<br>49. Intra-rater reliability:<br>a. 75.0-89.6% agreement<br>b. Weighted kappa: 0.74-0.89<br>50. Internal consistency: Cronbach's alpha 0.85<br>51. Construct validity: Spearman's rank-order correlations<br>a. PDS: 0.814<br>b. NPI-Apathy: 0.710 | • Each participant was recorded in 14 videos: 12 randomly distributed between 8 am and 8 pm over two days, separated by at least 48 hours, one during mealtime, and one during a care event<br>• 96 videos were selected from 24 randomly selected participants; four videos over two days were selected for each participant |

## Delirium

Systematische reviews

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| De 2015 | - Design: systematic review | 18. Eligibility criteria: hospitalized adult inpatients, | Delirium screening tools, evaluated against standardized | 52. 21 tools identified<br>53. Narratively reported | • Unclear if review process in duplicate<br>• Unclear language restriction |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | - Funding: not reported; CoI: not reported<br>- Search date: Jul 2014<br>- Databases: Medline, Cinahl, Psycinfo<br>- Study designs: all<br>- N included studies: N=31 | including those with dementia or terminal illness | diagnosis of delirium using DSM or ICD criteria | | |
| Morandi 2012 | - Design: systematic review<br>- Funding: see article; CoI: one author holds patents on instruments for assessment of attentional deficits in delirium<br>- Search date: Jan 2012<br>- Databases: PubMed, Embase, Web of Sciense<br>- Study designs: all<br>- N included studies: N=9 | 19. Eligibility criteria: adult patients, with inclusion of patients with dementia | Delirium screening tools, evaluated against standardized diagnosis of delirium using DSM | 54. 6 tools identified<br>55. Narratively reported | • Review process in duplicate (although unclear for quality appraisal)<br>• Unclear language restriction |

Primaire studies: observationele studies

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Hendry 2016 | - Design: observational study<br>- Funding: not reported; CoI: none<br>- Setting: urban teaching hospital, UK<br>- Sample size: N=500<br>- Duration: 8 months | 20. Assessors: clinicians<br>21. Patients: non-elective elderly care hospital inpatients, 65+<br>22. *A priori* characteristics:<br>a. Mean age: 83y<br>b. Female: 87% | Index tests:<br>AMT<br>4AT<br>bCAM<br>SQiD<br>MOTYB<br><br>Reference standard: clinical diagnosis (DSM) | 56. For diagnosis of definite delirium, AMT-4 (cut-point < 3/4) had a sensitivity of 92.7% (95%CI 84.8–97.3), with a specificity of 53.7% (95%CI 48.1–59.2); AMT-10 (<4/10), MOTYB (<4/12) and SQiD showed similar performance. bCAM had a sensitivity of 70.3% (95%CI 58.5–80.3) with a specificity of 91.4% (95%CI 87.7–94.3). 4AT (>4/12) had a sensitivity of 86.7% (95%CI 77.5–93.2) and specificity of 69.5% (95%CI 64.4–74.3) | • Consecutive patients<br>• Blinded assessments<br>• Potential differential verification |
| Morandi 2016 | - Design: prospective observational study<br>- Funding: not reported; CoI: none<br>- Setting: acute geriatric wards, inhospital rehabilitation, emergency department<br>- Sample size: N=645 | 23. Patients: patients 65 years and older with dementia<br>24. *A priori* characteristics:<br>a. Median age: 84y<br>b. Female: 64.1% | RASS<br>m-RASS<br><br>Reference standard: clinical diagnosis (DSM) | 57. RASS other than 0: sensitivity 70.5% (95%CI 65.9-75.1), specificity 84.8% (95%CI 80.5-89.1), LR+ 5.00 (3.68-6.79), LR- 0.35 (0.30-0.41)<br>58. The specificity of the RASS/m-RASS incrementally increased with higher degrees of impairment increasing to 95.5% with a RASS/m-RASS value >+1 or <−1 but at the expense of sensitivity | • Secondary analysis of previous cohort studies<br>• Unclear blinding<br>• Potential differential verification<br>• Not all patients were included in the analysis |

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Teale 2018 | - Design: prospective observational study (ISRCTN 14608554)<br>- Funding: National Institute for Health Research (PBPG-1112-29068); CoI: none<br>- Setting: nine UK residential and nursing care homes<br>- Sample size: N=216<br>- Duration: Mar 2015 – Jun 2016 | 25. Patients: residents over 65 years, except those approaching end of life or unable to complete delirium assessments<br>26. *A priori* characteristics:<br>a. Mean age: 84.9y<br>b. Female: 61%<br>c. 50% had cognitive impairment | DOSS<br><br>Reference standard: CAM | 59. Inter-rater reliability:<br>a. DOSS: ICC 0.71<br>b. CAM: kappa 0.80<br>60. Diagnostic accuracy:<br>a. DOSS: cut-off 5, sensitivity 61% (39-80), specificity 71% (70-73), AUC 0.66, DOR 3.9, PPV 1.3%, NPV, 99.5%, LR+ 2.1, LR- 0.55<br>b. Cognitive impairment, DOSS cut-off 7: sensitivity 60% (30-90), specificity 72% (70-74), DOR 3.9 | • Unclear blinding<br>• Multiple assessments per patient included in analysis |

## Dyspneu

Primaire studies: observationele studies

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Campbell 2010 | - Design: observational study<br>- Funding: not reported; CoI: none<br>- Setting: palliative care service, US<br>- Sample size: N=89 | 27. Patients: eligible adult patients were terminally ill and referred for palliative care consultation; chronic obstructive pulmonary disease, congestive heart failure, pneumonia, or lung cancer<br>28. *A priori* characteristics:<br>c. Mean age: 72y | Revised RDOS | 61. Internal consistency: Cronbach's alpha 0.64<br>62. 'Perfect interrater reliability for all parameters', but data not reported<br>63. Correlation with VAS: r=0.404 | • Consecutive patients<br>• 99 were eligible, but 10 were excluded<br>• Blinded scoring |
| Kiely 2012 | - Design: observational study<br>- Funding: NIH-NIA R01 AG024091 and NIH-NIA K24AG033640 (SLM); CoI: not reported<br>- Setting: 22 nursing homes with moren tan 60 beds, Boston, US<br>- Sample size: N=323 | 29. Patients: (1) age over 60 years, (2) dementia (any type, determined from medical record), (3) Global Deterioration Scale score of 7 (ascertained by nurse interview), (4) an available English-speaking proxy to provide informed consent<br>30. *A priori* characteristics:<br>a. Mean age: 85.3y<br>b. Female: 85.5% | SM-EOLD | 64. Discriminant validity: mean score for patients with dyspnoea 30.6 vs. no dyspnoea 33.3; MD -2.7 (SD 7.2), p=0.0001 | • Data from CASCADE study<br>• Possible selection bias |

## Gedrag

Primaire studies: observationele studies

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Dekker 2018 | - Design: observational study<br>- Funding: UMCG Alzheimer Research Center, the Research School for Behavioral and Cognitive Neu-rosciences of the University of Groningen (RUG), the Gratama-Stichting/Stichting Groninger Universiteitsfonds (2015-04), Research Foundation Flanders (FWO, G053218N), Carlos III National Institute of Health of Spain (PI13/01532 to Rafael Blesa and PI14/01126 to Juan Fortea) jointly funded by the European Regional Development Fund, the European Union Integrated Operational Programme, the Fundacio´ Marato´ TV3 (project 20141210 to Juan Fortea), a grant from the La Caixa Banking Foundation and a grant from Griffols Foundation, Catalan Government (2014SGR-0235) and the Catalan Down Syndrome Foundation; CoI: none<br>- Setting: multicentre, Europe<br>- Sample size: N=… | 31. Assessors:<br>32. Patients: phenotypical diagnosis of Down syndrome, aged ≥30 years, intellectual disability in the mild-severe range, and stable dosage of psychoactive medication<br>33. *A priori* characteristics:<br>a. Mean age:<br>b. Female: | BPSD-DS | Construction of scale, no validation of final instrument | |

## Welzijn

Systematische review

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Flynn, 2017 | - Design: systematic review<br>- Funding: funded by the Baily Thomas Charitable Fund (Reference number: TRUST/RNA/AC/SG/3543/6297), and was spon- sored by the University of Warwick<br>- Search date: July 2015<br>- Databases: CINAHL, ERIC, EMBASE, MEDLINE, ASSIA, PsycINFO, PsycTESTS, CENTRAL, and the Social Sciences and Science Citation Indices<br>- Study designs: not reported<br>- N included studies: N=32 | 34. Eligibility criteria: at least 70% of the sample in the study were re- ported as having severe or profound ID (although in some senses an arbitrary criterion, this was to ensure that there was a majority of people with severe or profound ID in the study samples) or the data for participants with severe or profound ID were reported separately<br>35. the study focused on the development, adaptation, or evaluation of a measure of mental health or well-being | 36. Autism Spectrum Disorders-Comorbidity for Adults (ASD-CA)<br>37. Depression Scale for Severe Disability (DEPRESSED)<br>38. Diagnostic Assessment for the Severely Handicapped Scale (DASH)<br>39. Diagnostic Assessment for the Severely Handicapped Scale-II (DASH-II)<br>40. Aberrant Behavior Checklist (ABC)<br>41. Interact Short Form<br>42. Mini Psychiatric Assessment Schedule for Adults with a Developmental Disability (Mini PAS-ADD)<br>43. Psychiatric Assessment Schedule for Adults with a Developmental Disability (PAS-ADD)<br>44. Physiological Measure of Subjective Well-being<br>45. Anxiety, De- pression and | 65. Narrative description of results | • Language restriction: English, Dutch, French or German<br>• Review process by independent reviewers<br>• Unclear which studies were done in population with cognitive impairment (probably none) |

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | | | Mood Scale (ADAMS)<br>46. Mood, Interest and Pleasure Questionnaire (MIPQ)<br>47. Reiss Screen for Maladaptive Behaviour (Reiss Screen) | | |

## Welzijn

Primaire studies: observationele studies

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| De Vries, 2018 | - Design: observational study<br>- Funding: Novartis Pharmaceuticals Corporation<br>- Setting: multicentre, international<br>- Sample size: N= 366 | 48. Patients: with Tuberous sclerosis complex. 265 patientscould be analyzed. Of them, 124 had ID and for 95 patients the intellect was unknown.<br>49. *A priori* characteristics:<br>a. Median age: 10.1; range 2.2 – 56.3<br>b. Female: not reported | 66. Quality of Life in Childhood Epilepsy (QOLCE),<br>67. Quality of Life in Epilepsy Inventory for Adolescents-48 (QOLIE-AD-48)<br>68. Quality of Life in Epilepsy Inventory-31-Problems (QOLIE-31-P) | Construction of scale, no validation of final instrument | |

## Angst

Systematische review

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Hermanns, 201 | - Design: systematic review<br>- Funding: funded by ZonMw<br>- Search date: February, 2010<br>- Databases: Embase, PubMed and PsychInfo | | 50. ADAMS<br>51. ADD<br>52. DASH<br>53. DASH-II<br>54. FSAMR<br>55. GAS-ID<br>56. MASS<br>57. Mini PAS-ADD | 69. GAS: Test–retest: Þ=0.95, p < 0.0001, CI: 0.87–0.99 (interval: 4 weeks)<br>70. GAS: convergent validity Þ =0.75, p<0.001 (Beck Anxiety Scale)<br>71.<br>72. PIMRA-SR: Test–retest: r=0.54, p < 0.01, CI: 0.15–0.79 (interval: 23 weeks, SD 4.3) | • Language restriction: English, Dutch, French, Spanish or German<br>• Review process by independent reviewers<br>• Unclear which studies were done in population with |

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | - Study designs: not reported<br>- N included studies: N=17 | | 58. PAS-ADD Interview<br>59. PAS-ADD checklist<br>60. PAC<br>61. P-AID<br>62. PIMRA<br>63. ZAS | 73. PIMRA-SR: convergent validity r=0.32, p < 0.001, CI: 0.16–0.46 (FSAMR)<br>74. ZAS: r=0.40, p<0.001, CI: 0.25–0.53 (FSAMR) r=0.59, p < 0.05, CI: 0.41–0.73 (GHQ anxiety subscale)<br>75. FSAMR: r=0.40, p<0.001,CI: 0.25–0.53 (ZAS), r=0.32, p < 0.001, CI: 0.16–0.46 (PIMRA-SR) | cognitive impairment (probably none) |

## Allerlei

Systematische reviews

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Bentvelzen 2017 | - Design: systematic review<br>- Funding: Australian National<br>- Health and Medical Research Council-funded Dementia Collaborative Research Center Assessment and Better Care at UNSW Australia, Dementia Collaborative Research Center (Assessment and Better Care) PhD scholarship (UNSW), Center of Excellence in Population Ageing Research (CEPAR) Supplementary Scholarship, Mary Frances Stephens Scholarship (University of Sydney); CoI: one author with several competing interests<br>- Search date: unclear<br>- Databases: CINAHL, ProQuest, Scopus, PsychARTICLES, Biomed Central, | 64. Eligibility criteria: not clearly stated | Dementia-related tools | Narrative overview, no detailed description of validity | • Language restriction: English<br>• Few details on methodology |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | EMBASE, PubMed, PsychINFO, MEDLINE, ScienceDirect, Web of Science, Cochrane Reviews<br>- Study designs: all<br>- N included studies: N=unclear | | | | |
| Ellis-Smith 2016 | - Design: systematic review<br>- Funding: Cicely Saunders International and The Atlantic Philanthropies, and National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care Funding scheme; CoI: none<br>- Search date: Jun 2015<br>- Databases: Medline, EMBASE, PsycInfo, CINAHL, ASSIA<br>- Study designs: unclear<br>- N included studies: N=40 | 65. Eligibility criteria: people with dementia in long-term care settings; measures were included if they assessed symptoms using proxy-observed behaviors or signs in people whose verbal communication was compromised due to dementia, were validated in English, and were for use in routine care without the requirement of formal clinical training | Measures to assess commonly experienced symptoms | Multiple neuropsychiatric symptoms<br>76. Two instruments: Neuropsychiatric Inventory Questionnaire and California Dementia Behavior Questionnaire; both not validated in long-term care setting<br><br>Discomfort<br>77. Discomfort Behavior Scale: internal consistency: Cronbach's alpha 0.77<br>78. DS-DAT: strong inter-rater reliability (ICC 0.83 at rest and 0.85 during exercise) | • English literature only<br>• Review process partly in duplicate (selection not) |
| McKenzie 2018 | - Design: systematic review<br>- Funding: NHS Lothian; CoI: none<br>- Search date: unclear<br>- Databases: Proquest, Web of Science and Scopus<br>- Study designs: all<br>- N included studies: N=43 | 66. Eligibility criteria: people with intellectual disability | Tools designed or adapted for the purpose of helping to diagnose dementia in people with intellectual disability | 79. 22 tools identified: 12 cognitive and 10 behaviour<br>80. Narrative overview | • Language restriction: English<br>• Unclear if review process was done by independent reviewers |
| Zeilinger 2013 | - Design: systematic review<br>- Funding: not reported; CoI: not reported<br>- Search date: unclear<br>- Databases: CINAHL, PsycInfo, PubMed, | 67. Eligibility criteria: persons with intellectual disabilities | Assessments instruments for dementia | 81. 114 instruments identified + 4 test batteries<br>82. Narrative overview, but no data on validity | • Unclear language restriction<br>• Selection by two independent reviewers<br>• Unclear if data extraction and quality appraisal were |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | Scopus, and Web of Science<br>- Study designs: all<br>- N included studies: N=97 | | | | done by independent researchers |

Abbreviations: 4AT: 4 A's test; 95%CI: 95% confidence interval; AES: Apathy Evaluation Scale; AI: Apathy Inventory; AMT: Abbreviated Mental Test; AUC: area under the curve; BPSD-DS: Behavioral and psychological symptoms of dementia – Down Syndrome; CAM: Confusion Assessment Method; CI: cognitive impairment; CoI: conflict of interest; DAIR: Dementia Apathy Interview and Rating; DOR: diagnostic odds ratio; DOSS: Delirium Observation Screening Scale; DS-DAT: Discomfort scale-dementia of the Alzheimer type; DSM: Diagnostic and Statistical Manual of Mental Disorders; FrSBe: Frontal System Behavior Scale; HR: hazard ratio; IAS: Irritability-Apathy Scale; ICC: intra-class coefficient; ICD: International Classification of Diseases; LR: likelihood ratio; LTC: long-term care; MCI: mild cognitive impairment; MD: mean difference; MMSE: mini-mental state examination; MOTYB: Months of the year backwards; NPI: Neuropsychiatric Inventory; NPV: negative predictive value; NRS: numeric rating scale; PEAR: Person-Environment Apathy Rating; PPV: positive predictive value; RASS: Richmond Agitation Sedation Scale; RDOS: Respiratory Distress Observation Scale; SD: standard deviation; SQID: Single Question in Delirium; SM-EOLD: Symptom Management End-of-Life in Dementia; VAS: visual analogue scale.

**Onderzoeksvraag 2: Welke gevalideerde meetinstrumenten zijn beschikbaar om pijn vast te stellen bij menen met een verstandelijke beperking of met dementie?**

Vraag 2: Welke gevalideerde meetinstrumenten zijn beschikbaar om pijn vast te stellen bij mensen met een verstandelijke beperking of met dementie?

Systematische reviews

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Coca 2020 | - Design: systematic review (CRD42019133892)<br>- Funding: none; CoI: none<br>- Search date: 2012-2018<br>- Databases: PubMed, BIREME, and Scielo databases<br>- Study designs: quantitative studies, clinical trials, cases and<br>- controls, cohorts, cross-sectional studies<br>- N included studies: N=10 | 68. Eligibility criteria: elderly people diagnosed with dementia (Alzheimer's, vascular dementia, dementia with Lewy bodies); sample size at least 20 patients | Instruments for assessing pain in non-communicative patients | 83. 7 pain instruments evaluated: PAINAD (5 studies), Abbey (1 study), McGill (2 studies), PACSLAC (1 study), VAS (3 studies), Colored Pain Scale (1 study), Faces Pain Scale (1 study)<br>84. No numeric data reported<br>85. Abbey (15/20) and PACSLAC (14/20) scored the best | • Language restriction: English, Spanish, or Portuguese<br>• Focus on studies conducted in Latin American countries (Latin America, Spain, and Portugal)<br>• Quality appraisal: Mixed Methods Appraisal Tool<br>• Review process by two independent reviewers, although not completely clear for data extraction<br>• Evaluation of included tools: instrument of Zwakhalen et al. (score 0-20) |
| Corbett 2014 | - Design: systematic review<br>- Funding: COST program (European Cooperation in the field of Scientific and Technical Research) for COST Action TD 1005, Pain Assessment in Patients with Impaired Cognition, especially Dementia; CoI: none<br>- Search date: Sep 2012<br>- Databases: PubMed, EMBASE, Cochrane Library<br>- Study designs: systematic reviews<br>- N included studies: N=11 | 69. Eligibility criteria: patients with dementia | Pain assessment tools | 86. 12 tools identified: Abbey, ADD, CNPI, DS-DAT, DOLOPLUS-2, EPCA-2, MOBID-2 Pain Scale, NOPPAIN, PACSLAC, PAINAD, PADE and PAINE<br>87. No numeric data reported | • Review as a first step to create the PAIC meta-tool<br>• Review process done by expert panels, but process unclear<br>• No quality appraisal |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Crosta 2014 | - Design: systematic review<br>- Funding: National Institute of Nursing Research, NR 012734-01, T32 NR007106, NR08136, Center for Research on Management of Sleep Disturbances, NR011400; CoI: none<br>- Search date: 2012<br>- Databases: PubMed, CINAHL<br>- Study designs: all<br>- N included studies: N=7 | 70. Eligibility criteria: children with cognitive impairment who are unable to self-report pain in acute care settings | Pain measures | 88. 4 pain measures identified: Non-Communicating Child's Pain Checklist – Postoperative Version (NCCPC-PV), Individualized Numeric Rating Scale (INRS), Pediatric Pain Profile (PPP), revised Face, Leg, Activity, Cry and Consolability scale (r-FLACC)<br>89. Narrative overview | • English literature only<br>• No information on selection process, data extraction or quality appraisal |
| Ellis-Smith 2016 | - Design: systematic review<br>- Funding: Cicely Saunders International and The Atlantic Philanthropies, and National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care Funding scheme; CoI: none<br>- Search date: Jun 2015<br>- Databases: Medline, EMBASE, PsycInfo, CINAHL, ASSIA<br>- Study designs: unclear<br>- N included studies: N=40 | 71. Eligibility criteria: people with dementia in long-term care settings; measures were included if they assessed symptoms using proxy-observed behaviors or signs in people whose verbal communication was compromised due to dementia, were validated in English, and were for use in routine care without the requirement of formal clinical training | Measures to assess commonly experienced symptoms | 90. 12 pain measures identified: Abbey Pain Scale (APS), Checklist of Nonverbal Pain Indicators (CNPI), CNA Pain Assessment Tool, Doloplus-2, Mahoney Pain Scale, Non-communicative Patient's Pain Assessment Instrument (NOPPAIN), PAINAD, PACSLAC and PACSLAC-II, Pain Assessment in Communicatively Impaired, Pain Assessment for Dementing Elderly (PADE), and Pain Behaviors for Osteoarthritis Instrument for Cognitively Impaired Elders<br>91. PAINAD:<br>a. Good internal consistency: Cronbach's alpha of 0.70 and greater<br>b. Inter-rater reliability strong: kappa=0.87, ICC ≥0.87 in two studies, although one study reported an ICC of 0.24 when administered in rest situations and 0.80 during movement situations<br>c. Good construct validity against APS, PACSLAC, CNPI, NOPPAIN, and PADE at rest and during exercise (r ≤0.62)<br>92. PACSLAC:<br>a. Good construct validity against the NOPPAIN, CNPI, PADE, APS, and PAINAD at rest and during exercise (r ≤0.56)<br>b. Inter-rater reliability at rest and movement situations was consistently high (ICC ≥0.76)<br>93. PACSLAC-II: | • English literature only<br>• Review process partly in duplicate (selection not) |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | | | | a. Strong correlations with PACSLAC, CNPI, PADE, and PAINAD in pain and non-pain conditions (r ≥0.56)<br>b. Weak correlations with the Cornell Scale for Depression in Dementia (CSDD) (non-pain condition: r=–0.05, vaccination: r=0.10, movement: r=–0.06)<br>c. Ability to discriminate between non-pain and painful conditions (p<0.01)<br>d. Internal consistency was strong (Cronbach's alpha ≥0.74) and interrater reliability kappa was 0.63<br>94. NOPPAIN:<br>a. High correlation (r ≤0.70) against CNPI, PACSLAC, PADE, and PAINAD with an inter-rater reliability kappa of 0.73 when administered by trained research assistants | |
| Lichtner 2014 | - Design: systematic review<br>- Funding: National Institute for Health Research HS&DR Programme (11/2000/05).; CoI: none<br>- Search date: Mar 2013<br>- Databases: Medline, All EBM Reviews (including Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED), Embase, PsycINFO, and CINHAL<br>- Study designs: systematic reviews<br>- N included studies: N=23 (8 with data for extraction) | 72. Eligibility criteria: patients with dementia or cognitive impairment in an acute care setting | Pain assessment tools | 95. 28 tools assessed<br>96. Inter-rater reliability:<br>a. Percentage agreement: FACS (43-93%), CNPI (93%), DS-DAT (84-94%), PACSLAC (94%), PATCOA (56.5-100%), NOPAIN (82-100%), and ADD protocol (86-100%)<br>b. Kappa coefficients: FLACC (0.404), Mahoney Pain Scale (0.55-0.77), CNPI (0.625-0.819), MOBID (0.05-0.90), MOBID-2 (0.44-0.90), NOPAIN (0.70-0.87)<br>c. Correlation coefficients: FACS (0.82-0.92), PAINE (0.711-0.999), RaPID (0.97), DS-DAT (0.61-0.98), PAINAD (0.72-0.97)<br>d. Intra-class correlations: CPAT (0.71), PBM (0.10-0.87), DS-DAT (0.74), Doloplus-2 (0.77-0.90 total scale, 0.60-0.96 subscales), PACSLAC (0.77-0.96), PADE (range from 0.54-0.96), ECPA (0.80), EPCA-2 (0.852-0.897), MOBID (0.70-0.96), and Abbey pain scale (0.44-0.845)<br>97. Test-retest and intra-rater reliability:<br>a. Percentage agreement: FACS (79-93%)<br>b. Correlation: FACS (0.88-0.97), PAINE (0.711-0.999) and RaPID (>0.75), DS-DAT (0.6)<br>c. Kappa coefficients: MOBID-2 (0.41-0.83 (pain behaviour), 0.48- 0.93 (visual pain recordings))<br>d. Nygard test-retest: CNPI (0.23-0.66) | • English literature only<br>• Review process by multiple reviewers |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | | | | e. Intra-class correlations: CPAT (0.67), REPOS (0.90-0.96), PACSLAC (0.72-0.96), PADE (0.70-0.98), MOBID (0.60-0.94), and Abbey Pain Scale (0.657)<br>98. Internal consistency:<br>a. Mahoney Pain Scale (total scale a=0.76, subscales range 0.68-0.75), PAINE (0.75-0.78), RaPID (0.79), REPOS (0.49), CNPI (0.54-0.64), Doloplus-2 (0.668- 0.82), PACSLAC (0.74-0.92), PADE (0.24-0.88), PAINAD (0.5-0.74, PATCOA (0.44), ECPA (0.70), EPCA-2 (0.73- 0.79), MOBID (0.82-0.91), MOBID-2 (0.82-0.84), and Abbey Pain Scale (0.645-0.81)<br>99. Concurrent and criterion validity:<br>a. CPAT was compared to DS-DAT (rs=22, p=0.076, rs=0.25, p=0.048)<br>b. PAINAD compared to the DS-DAT (0.56-0.76)<br>c. DS-DAT compared to the Pittsburgh Agitation Scale (0.51) and the Cohen-Mansfield Assessment Inventory (0.25)<br>d. Doloplus 2 compared with the PAINAD (0.34) and PACSLAC (0.29-0.38)<br>e. REPOS compared to PAINAD (0.61-0.75)<br>f. FACS was compared to PBM (0.02-0.41)<br>g. PAINE compared with PADE (r=0.65)<br>h. PADE compared to CMAI (0.30 – 0.42)<br>i. PPI compared with the Memorial pain Subscale (0.67), Verbal scale (0.54), RAND Health Survey and Dartmouth COOP chart (0.72)<br>j. RaPID compared to McGill pain scale (0.8-0.86)<br>k. Comparisons to proxy pain reports (doctor or nurse); Mahoney pain scale (k=0.86), PAINAD (0.84), the PBM (0.62-0.73), MOBID (0.41-0.64), Abbey Pain Scale (0.586), PACSLAC (0.35-0.54), and REPOS (−0.12-0.39)<br>l. Comparison to self-report (using a VAS): RaPID (0.8-0.86), EPCA-2 (0.846), DS-DAT (0.56-0.81), PAINAD (0.75 pain VAS and 0.76 discomfort VAS), ECPA (0.67), Doloplus 2 (0.31-0.65), PPI (0.55), CNPI (0.30-0.50), PATCOA (0.41), and PBM (r=0.11-0.30) | |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Rostad 2017 | - Design: systematic review (CRD42016049697)<br>- Funding: Oslo and Akershus University College of Applied Sciences funds, Canadian Institutes of Health Research New Investigator Award; CoI: none<br>- Search date: 1990 – Apr 2017<br>- Databases: CINAHL, Medline and PsycINFO<br>- Study designs: all<br>- N included studies: N=24 | 73. Eligibility criteria: cognitively impaired patients (any stage) aged 65 and older | Doloplus-2 scale | 100. Narrative overview: see evidence report | • Language restriction: English, French, German, Dutch/Flemish or a Scandinavian language<br>• Review process in duplicate |
| Siok 2012 | - Design: systematic review<br>- Funding: not reported; CoI: none<br>- Search date: 1990-2010<br>- Databases: CINAHL, Medline, Scopus, PsycINFO, ScienceDirect, Wiley-Interscience, Mosby's Nursing Consult, Web of Science, ProQuest<br>- Study designs: all<br>- N included studies: 23 | 74. Eligibility criteria: cognitively impaired elderly people older than 65 years in aged care, acute care or nursing home settings were included | Behavioural-observation methods in pain assessment | 101. 10 tools assessed<br>102. Narrative overview: see evidence report | • English literature only<br>• Review process in duplicate |

Primaire studies: RCT

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Fry 2018 | - Design: cluster RCT (ACTRN 12613000997752)<br>- Funding: the Emergency Care Institute and the Agency for Clinical Innovation | 75. Eligibility criteria: patients aged 65 years or more with cognitive impairment and a clinically suspected acute long bone fracture<br>76. Exclusion criteria: patients were excluded if they met any of the following | Across all sites, the bedside nurse screened patients for cognitive impairment using the SIS prior to a routine pain assessment | 103. Time to first dose of analgesia: adjusted HR 0.97 (95%CI 0.80-1.17, p=0.74)<br>104. Proportion of patients administered pain medication within 60 min: 28% vs. 32%, p=0.19 | Level of evidence: high risk of bias<br>• The lead investigator with an independent witness randomised sites to the intervention or control using |

| Study ID | Methods | Patient characteristics | Intervention | Results | Critical appraisal of study quality |
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| | (ACI/D12/1275) New South Wales; CoI: none<br>- Setting: 8 metropolitan EDs, Sydney, Australia<br>- Sample size: N=602<br>- Duration: Mar 2013 – Jun 2015 | criteria: a) Australasian Triage Scale category 1 (resuscitation case); b) polytrauma; c) systolic BP <90mm Hg and d) non-English-speaking patient with no interpreter available<br>77. *A priori* patient characteristics:<br>a. Median age: 86 vs. 83y, p=0.002<br>b. Female: 71% vs. 74%<br>c. Triage score ATS 4: 43% vs. 25%, p=0.001 | Intervention: pain assessment with PAINAD (N=323)<br><br>Control: pain assessment according to usual care (N=279) | | a balanced computer coin toss randomisation process<br>• Staff at intervention sites were not blinded<br>• Some baseline characteristics were significantly different |
| Lukas 2019 | - Design: cross-over RCT (DRKS00000525, U1111-1116-6820)<br>- Funding: Robert Bosch Foundation; CoI: two authors with lectures remuneration<br>- Setting: 3 geriatric hospitals, Germany<br>- Sample size: N=45<br>- Duration: Sep 2010 – June 2013 | 78. Eligibility criteria: patients with Alzheimer or vascular dementia and probable pain<br>79. Exclusion criteria: other forms of dementia or other diseases causing communication impairments (such as stroke or Parkinson disease)<br>80. *A priori* patient characteristics:<br>a. Mean age: 83.3 vs. 86.0y<br>b. Female: 76.2% vs. 79.2% | Oxycodone 10 mg (N=21) vs. placebo (N=24)<br><br>Pain assessment with:<br>PAINAD-G<br>BISAD<br>CNPI<br>Algoplus | 105. Correlations between the observational tools differed at the 3 measurement points. For example, correlation between PAINAD-G and BISAD ranged from p=0.609 at t1 to 0.805 at t3<br>106. Mostly, correlations increased over time, but not exclusively. Moderate to high correlations between the 4 pain assessment tools ranged from p=0.414 to 0.805 (p=0.01)<br>107. The highest correlation was seen between PAINAD-G and BISAD, followed by PAINAD-G and CNPI | Level of evidence: high risk of bias<br><br>• 2-factorial design: factor 1=analgesic intervention, factor 2=measurement points<br>• Randomisation was performed by an institute of biometrics (computer-generated list)<br>• No wash-out |

Primaire studies: observationele studies

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Ammaturo 2017 | - Design: quasi-experimental study<br>- Funding: grant from the Saskatchewan Health Research Foundation; CoI: one author is one of the developers of PACSLAC-II<br>- Setting: virtual setting<br>- Sample size: N=130 assessors | 81. Assessors: community-dwelling laypersons with no health care training (N=65) and LTC nurses (N=65)<br>82. *A priori* characteristics:<br>a. Mean age: 58.72y for laypeople and 51.17y for LTC staff<br>83. Patients: simulated | PAINAD<br>PACSLAC-II | 108. Internal consistency:<br>a. PACSLAC-II:<br>i. Cronbach's a 0.69<br>ii. Split-half: Spearman-Brown coefficient 0.72<br>b. PAINAD<br>i. Cronbach's a 0.61<br>ii. Split-half: Spearman-Brown coefficient 0.65<br>109. Inter-rater agreement:<br>a. PACSLAC-II: ICC 0.94<br>b. PAINAD: ICC 0.96<br>110. Concurrent validity: laypeople Pearson's r 0.12-0.60; LTC staff Pearson's r 0.24-0.40 | • 7 pain videos were presented depicting patients with dementia (portrayed by actors) displaying pain behaviours or during a calm relaxed state (no pain) |

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Atee 2017a | - Design: prospective observational study<br>- Funding: Alzheimer's Australia Dementia Research Foundation (AADRF); CoI: all authors are shareholders in EPAT Technologies Ltd<br>- Setting: two accredited residential aged care facilities, Australia<br>- Sample size: N=37 patients<br>- Duration: 10 weeks, Jan – Apr 2017 | 84. Assessors: two independent raters (ePAT by investigator, APS by nurse)<br>85. Patients: 65+; living in the facility for at least 3 months; diagnosed with dementia by a geriatrician; moderate-to-severe dementia based on a PAS-Cog score of >10; medical history or presenting complaint(s) that involved painful conditions<br>86. *A priori* characteristics:<br>a. Mean age: 85.5y<br>b. Female: 58.8% | ePAT<br>Abbey Pain Scale | 111. Internal consistency:<br>a. Cronbach's alpha:<br>i. Overall: 0.950<br>ii. Movement: 0.797<br>iii. Rest: 0.766<br>112. Inter-rater agreement:<br>a. Weighted kappa: overall 0.857 (95%CI 0.819-0.895), rest 0.840, movement 0.772<br>b. ICC: overall 0.904 (95%CI 0.885-0.921), rest 0.902 (0.872-0.925), movement 0.879 (0.843-0.908)<br>113. Concurrent validity: Pearson's r overall 0.911, rest 0.896, movement 0.904<br>114. Predictive validity:<br>a. ePAT: pain scores were significantly higher ($p < 0.0001$) with movement (mean: 11.44 ± 3.54; median: 11; mode: 13) than at rest (mean: 8.33 ± 3.34; median: 9; mode: 10)<br>b. APS: significantly higher pain scores ($p < 0.0001$) following movement (mean: 6.96 ± 3.85; median: 7; mode: 8) than at rest (mean: 4.34 ± 3.14; median: 4; mode: 1) | • Unclear selection bias<br>• 3 dropouts<br>• 400 paired pain assessments |
| Atee 2017b | - Design: prospective observational study<br>- Funding: Alzheimer's Australia; CoI: some authors are shareholders in EPAT Technologies Ltd<br>- Setting: three metropolitan aged care homes, Australia<br>- Sample size: N=40<br>- Duration: 13 weeks in each home; Mar 2015 – Apr 2016 | 87. Assessors: two independent raters (ePAT mostly by investigator, APS by nurse or carer)<br>88. Patients: (1) age greater than 60y, (2) living in a designated dementia unit of the ACH, (3) had a diagnosis of dementia, (4) their cognitive score based on the Mini-Mental State Examination (MMSE): < 19 or Psychogeriatric Assessment Scale–Cognitive Impairment Scale (PAS-CIS): > 10, and (5) possessed a documented history of a chronic pain condition such as osteoarthritis or currently suffer from acute (e.g., urinary tract infection), recurrent (e.g., gout) or incidental pain (e.g., pressure sores)<br>89. *A priori* characteristics:<br>c. Mean age: 79.9y | ePAT<br>Abbey Pain Scale | 115. Internal consistency:<br>a. Cronbach's alpha:<br>i. Overall: 0.925<br>116. Inter-rater agreement:<br>a. Weighted kappa: overall 0.74 (95%CI 0.69-0.80), rest 0.71, movement 0.78<br>117. Concurrent validity: Pearson's r overall 0.822 (95%CI 0.857-0.903), rest 0.880 (0.845-0.907), movement 0.894 (0.855-0.922) | • Unclear selection bias<br>• 353 paired pain assessments |

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | | d. Female: 70% | | | |
| Atee 2018 | - Design: observational study (part of a larger clinical trial, Australian New Zealand Clinical Trials Registry Number ACTRN12616001003460)<br>- Funding: Alzheimer's Australia; CoI: some authors are shareholders in EPAT Technologies Ltd<br>- Setting: accredited dementia-specific residential aged care facility, Australia<br>- Sample size: N=10<br>- Duration: 2 weeks | 90. Assessors: 11 aged care staff working in the facility; paired ratings (randomly)<br>91. *A priori* characteristics:<br>a. Mean age: 45.3y<br>b. Female: 81.8%<br>92. Patients: residents with moderate- to-severe dementia as indicated by Dementia Severity Rating Scale (DSRS) scores 〉18, documented behavioural problems, history of painful conditions<br>93. *A priori* characteristics:<br>c. Mean age: 74.4y<br>d. Female: 50% | ePAT | 118. Inter-rater agreement:<br>a. Kappa:<br>i. Broad pain categories: rest 1.0, movement 0.59 (0.27-0.91)<br>ii. Raw total pain scores: rest 0.72 (0.58-0.86), movement 0.69 (0.50-0.87)<br>b. Lin's concordance correlation coefficient: 0.92 (0.85-0.96) | • Unclear selection bias |
| Bonin-Guillaume 2016 | - Design: cross-sectional study<br>- Funding: Fondation de France and Laboratoires Grünenthal France; CoI: none<br>- Setting: 5 geriatric settings, France<br>- Sample size: N=176 | 94. Assessors: self-rating (NRS), local doctors and/or nursing staff<br>95. Patients: French-speaking in- and outpatients ≥65 years old, regardless of their medical conditions; hospitalized in acute care or rehabilitation settings or consulting at an outpatient geriatric clinic; with or without pain, with or without depression and with or without mild-or-moderate dementia<br>96. *A priori* characteristics:<br>c. Mean age: 82.3y | NRS<br>Algoplus (French)<br>Doloplus<br>PACSLAC | 119. Concurrent validity:<br>a. vs. NRS:<br>i. Dementia (N=30): Spearman's correlation coefficient 0.91<br>ii. Dementia & depression (N=26): Spearman's correlation coefficient 0.78<br>b. vs. Doloplus:<br>i. Dementia (N=37): Spearman's correlation coefficient 0.87<br>ii. Dementia & depression (N=31): Spearman's correlation coefficient 0.86<br>c. vs. PACSLAC: no data for dementia separately<br>120. Predictive validity: mean Algoplus scores decreased significantly after treatment (Wilcoxon signed-rank tests; before vs. after means, respectively): for 17 dementia patients: 3.5 +/- 1.2 versus 1.1 +/- 1.2 (Δ=-2.4 +/- 1.5; $p < 0.001$); 20 with dementia & depression: 3.5 +/- 1.1 versus 1.0 +/- 0.9 (Δ=-2.5 +/- 1.2; $p < 0.001$) | • Five exclusions |

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | | | | 121. Threshold testing:<br>a. Score threshold of 2<br>i. Dementia: sensitivity 95%, specificity 96%<br>ii. Dementia & depression: sensitivity 96%, specificity 71%<br>b. Score threshold of 3<br>i. Dementia: sensitivity 80%, specificity 100%<br>ii. Dementia & depression: sensitivity 83%, specificity 95% | |
| Chan 2014 | - Design: observational study<br>- Funding: grant from the Saskatchewan Health Research Foundation, Saskatoon, Saskatchewan; CoI: none<br>- Setting: long-term care facilities, Canada<br>- Sample size: N=124 | 97. Assessors: 26 LTC-staff<br>98. *A priori* characteristics:<br>c. Mean age: 47.6y<br>d. Female: 25/26<br>99. Patients: LTC residents dementia undergoing painful procedures as part of routine care<br>100. *A priori* characteristics:<br>e. Mean age: 83.94y<br>f. Female: 71% | PACSLAC<br>PACSLAC-II | 122. Internal consistency:<br>a. Cronbach's alpha:<br>i. Influenza vaccination: 0.77<br>ii. Movement: 0.74<br>b. Cohen's kappa: 0.63<br>123. Concurrent validity: Pearson's r<br>a. PACSLAC: swabbing 0.66, vaccination 0.89, movement 0.81<br>b. CNPI: swabbing 0.56, vaccination 0.78, movement 0.68<br>c. NOPPAIN: swabbing 0.73, vaccination 0.82, movement 0.81<br>d. PADE: swabbing 0.65, vaccination 0.77, movement 0.80<br>e. PAINAD: swabbing 0.68, vaccination 0.86, movement 0.79<br>124. Discriminative validity: PACSLAC-II differentiated between control and pain segments, for the vaccination condition, $F_{2,92}$=80.92, p<0.001, partial $\eta^2$=0.64; and for the movement-exacerbated pain condition $F_{1,105}$=118.02, p<0.001, partial $\eta^2$=0.53 | • Use of video-taped pain expressions<br>• Unclear selection bias |
| Erin Browne 2019 | - Design: observational study<br>- Funding: AGE WELL Network of Centres of Excellence and the Canadian Institutes of Health Research; CoI: not reported<br>- Setting: partly LTC facility, partly community, Canada<br>- Sample size: N=102 | 101. Assessors: trained and untrained observers<br>102. Patients: adults (65+) with and without dementia<br>103. Exclusion: known acute pain problems such as fractures<br>104. *A priori* characteristics:<br>a. Mean age: 78.84y | FACS<br>PACSLAC-II | 125. Inter-rater agreement:<br>a. PACSLAC-II: Kappa=0.66-0.92<br>b. FACS: Pearson's r=0.92-0.99 | • Video-recording using cameras capturing different observational angles (e.g. front vs. profile view) both during a physiotherapy examination designed to identify painful areas and during a baseline period |

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Ersek 2019 | - Design: observational study<br>- Funding: grant from the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development Service (1I01HX000507); CoI: not reported<br>- Setting: four Veterans Affairs community living centers (nursing homes) and 12 community nursing homes in Alabama, Pennsylvania, and New Jersey, US<br>- Sample size: N=190<br>- Duration: Nov 2013 – Aug 2016 | 105. Assessors: research staff for PIMD, LTC staff for other measures<br>106. Patients: long-term care residents who 1) were age 50 years or older, 2) had a documented dementia diagnosis, and 3) were moderately to severely cognitively impaired, as defined by a score of <10 on the Brief Inventory of Mental Status<br>107. *A priori* characteristics:<br>c. Mean age: 84y<br>d. Female: 49.5% | PIMD<br>MOBID | 126. Internal consistency:<br>a. Cronbach's alpha:<br>i. Movement: 0.72<br>ii. Rest: 0.18<br>127. Inter-rater agreement:<br>a. ICC: rest 0.70, movement 0.82<br>128. Concurrent validity: Pearson's r<br>a. Expert clinician pain intensity ratings:<br>i. Moving: 0.49-0.75<br>ii. Rest: -0.03 – 0.14<br>b. MOBID:<br>i. Moving: 0.59<br>ii. Rest: 0.24 | • Unclear selection bias |
| Haghi 2019 | - Design: observational study<br>- Funding: supported by the University of Social Welfare and Rehabilitation Sciences, Tehran, Iran; CoI: none<br>- Setting: two nursing homes, Iran<br>- Sample size: N=138<br>- Duration: Nov 2016 – Aug 2017 | 108. Assessors: unclear<br>109. Patients: adults age ≥60, the MMSE score ≤21 for literate older adults or Clinical Dementia Rating (CDR) score ≥1 for the illiterate, Persian language speaking, and presence of a clinically painful event for more than 3 months according to medical records<br>110. *A priori* characteristics:<br>c. Mean age: 74.5y<br>d. Female: 53.6% | PACSLAC-II (Persian) | 129. Internal consistency: Cronbach's alpha<br>a. Facial expression (0.82), verbalisation (0.72), and body movement (0.84) sub-scales<br>130. Inter-rater agreement: ICC 0.76<br>131. Concurrent validity: Spearman's rank order correlation<br>a. Brief Pain Inventory: 0.43 | • Unclear selection bias |
| Husebo 2014 | - Design: analysis based on data from RCT<br>- Funding: Norwegian Research Council (Sponsor's Protocol Code: 189439) and the University of Bergen (09/1568); CoI: none<br>- Setting: 18 Norwegian nursing homes<br>- Sample size: N=352 | 111. Assessors: patients' primary caregivers (N=53)<br>112. Patients: patients with moderate to severe dementia and significant behavioural disturbances; score of ≤19 on MMSE scale; independent of painful diagnoses, presumed pain or ongoing pain treatment | MOBID-2 | 132. Test-retest reliability:<br>a. Separate items: baseline-2w ICC 0.731-0.857, 2w-4w ICC 0.729-0.889<br>b. Total score: baseline-2w ICC 0.805, 2w-4w ICC 0.852<br>133. Responsiveness:<br>a. Mean improvement: intervention group 1.7, control group 0.3, p<0.001 | • 163 patients were included in the test-retest reliability analysis, 203 patients in the responsiveness analysis |

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
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| | - Duration: Oct 2009 – Jun 2010 | | | | |
| Jordan 2011 | - Design: observational study<br>- Funding: North-umbria Healthcare NHS Foundation Trust; CoI: none<br>- Setting: 1 NHS continuing care unit & 3 nursing homes, UK<br>- Sample size: N=79 | 113. Assessors: researcher or nurse<br>114. Patients: nursing home residents with advanced dementia (clinical dementia rating of 3)<br>115. *A priori* characteristics:<br>b. Mean age: 82y<br>c. Female: 72% | PAINAD | 134. Diagnostic accuracy: sensitivity 92%, specificity 61%<br>135. Responsiveness:<br>a. Improvement after pain intervention: baseline mean score 5 (SD 2.63), after 1 month 3.23 (SD 2.52), p=0.008 | • 79/131 residents meeting inclusion criteria were included |
| Likar 2015 | - Design: observational study<br>- Funding: not reported; CoI: none<br>- Setting: single centre, geriatric ward, Austria<br>- Sample size: N=127 | 116. Assessors: trained physicians and nurses<br>117. Patients: patients aged 65+, incapable of communicating, with dementia (mild cognitive impairment, Alzheimer, Lewy-Body)<br>118. *A priori* characteristics:<br>b. Mean age: 81.8y<br>c. Female: 69.3% | Doloshort (German version) | 136. Inter-rater agreement: r 0.946-0.964<br>137. Intra-rater agreement: r 0.949-0.970 | • Unclear selection bias |
| Lukas 2013 | - Design: prospective observational study<br>- Funding: first author is partially funded by a Forschungskolleg Geriatrie grant from the Robert Bosch Foundation, Stuttgart, Germany and Mundipharma GmbH, Limburg, Germany; CoI: none<br>- Setting: geriatric hospital, Germany<br>- Sample size: N=178<br>- Duration: Jun-Dec 2009 | 119. Assessors: researchers<br>120. Patients: patients older than 65 years of age, signs of multimorbidity and geriatric syndromes, inpatient at the AGAPLESION, indications of pain and/ or have been prescribed analgesics<br>121. *A priori* characteristics:<br>a. Mean age: 82.4y<br>b. Female: 74.7% | PAINAD-G | 138. Inter-rater agreement: Cohen's kappa 0.742 (95%CI 0.546-0.938)<br>139. Test-retest reliability: Cohen's kappa 0.553 (0.285-0.821)<br>140. Concurrent validity: Spearman's r<br>a. Self-report scales:<br>i. Rest: 0.093-0.335<br>ii. Movement: 0.382-0.435 | • No separate data for patients with dementia |

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Massaro 2014 | - Design: observational study<br>- Funding: not reported; CoI: not reported<br>- Setting: Department of Pediatrics of the Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, and the Institute of Physiatrics and Rehabilitation Gervasutta, Udine, Italy<br>- Sample size: N=40<br>- Duration: Jan 2010 – Sep 2013 | 122. Assessors: two external observers and the child's caregiver<br>123. Patients: children, aged 3–18, who were not capable of any verbal communication due to cognitive impairment<br>124. *A priori* characteristics:<br>b. Median age: 9.1y<br>c. Female: 47.5% | NCCPC-PV<br>DESS<br>CHEOPS | 141. Inter-rater agreement: ICC<br>a. NCCPC-PV: 0.43-0.69<br>b. DESS: 0.67-0.78<br>c. CHEOPS: 0.54-0.72<br>142. Concurrent validity:<br>a. Spearman's r<br>i. DESS & NCCPC-PV: 0.76<br>ii. CHEOPS & NCCPC-PV: 0.66<br>iii. CHEOPS & DESS: 0.67<br>b. Cohen's kappa<br>i. DESS & NCCPC-PV: 0.61<br>ii. CHEOPS & NCCPC-PV: 0.58<br>iii. CHEOPS & DESS: 0.51 | • Unclear selection bias<br>• Consecutive children |
| McGuire 2011 | - Design: observational study<br>- Funding: Project 2 was funded in part by the Oncology Nursing Foundation Small Grants Program. Project 3 was funded in part by the University of Pennsylvania School of Nursing National Institute of Nursing Research (NINR)-funded P30 Center for Advancing Care in Serious Illness; CoI: none<br>- Setting: project 2: inpatient units of two hospices in the south-eastern United States; project 3: single inpatient hospice located in the north-eastern United States<br>- Sample size: N=35 for project 2, N=23 for project 3 | 125. Assessors: pairs of trained study and hospice nurses<br>126. Patients: project 2: (1) known to have cancer-related pain, (2) having an exacerbation of previously controlled pain or development of a new pain according to family members and/or hospice nurses; project 3: not only cancer<br>127. *A priori* characteristics:<br>c. Mean age: 60.6-67.5y<br>d. Female: 61-55% | MOPAT | 143. Internal consistency using Cronbach's coefficient was 0.85 and 0.78 for the Behavioral and Physiological Subscales, respectively<br>144. Sensitivity to change after pain-relieving intervention: mean scores for the Behavioral and Physiological Subscales were 6.67 and 2.23 pre, and 2.55 and 0.86 post ($p<0.001$) | • Description of 4 projects in the construction of the MOPAT-instrument<br>• 52% was cognitively impaired |

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Mosele 2012 | - Design: prospective observational study<br>- Funding: not reported; CoI: none<br>- Setting: acute geriatric section of the Department of Medicine at Padua University, Italy<br>- Sample size: N=§00<br>- Duration: Jan 2010 – Feb 2011 | 128. Assessors: trained physician<br>129. Patients: elderly subjects, including cases with different degrees of cognitive impairment<br>130. Exclusion: patients unable to communicate their experience of pain by means of self-assessment scales [uncommunicative patients or those with a MMSE score ≤5], delirium, acute psychiatric symptoms, end-of-life care, and severe sensory impairment<br>131. *A priori* characteristics:<br>a. Mean age: 83.2y<br>b. Female: 73.2%<br>c. Cognitive decline: 52% | PAINAD (Italian version) | 145. Internal consistency:<br>a. Dementia: Cronbach's alpha 0.90<br>146. Concurrent validity: compared with NRS, Kendall's tau 0.73<br>a. MMSE 18-24: 0.77<br>b. MMSE <18: 0.77<br>147. Inter-rater agreement: Cohen's kappa 0.74<br>a. MMSE 18-24: 0.76<br>b. MMSE <18: 0.77 | • Consecutive patients<br>• 100/700 excluded |
| Sheu 2011 | - Design: observational study<br>- Funding: grants from the Social Sciences and Humanities Research<br>- Council of Canada and Vancouver Coastal Health, Ottawa,<br>- Canada; CoI: none<br>- Setting: single centre, Canada<br>- Sample size: N=60 | 132. Assessors: 5 trained coders<br>133. Patients: elderly inpatients with clinically significant pain in the hip or back, aged 65 years or older<br>134. *A priori* characteristics:<br>c. Mean age: 84y<br>d. Female: 81.7% | FACS<br>Doloplus-2<br>Mahoney Pain Scale<br>Abbey Pain Scale<br>NOPPAIN<br>PACSLAC<br>PAINAD | 148. Inter-rater reliability: Cohen's kappa<br>a. Doloplus-2: -0.20 to 0.68<br>b. Mahoney Pain Scale: 0.06-0.59<br>c. Abbey Pain Scale: -0.20 to 0.52<br>d. NOPPAIN: 0.23<br>e. PACSLAC: 0.02; Pearson's r: 0.00-0.74<br>f. PAINAD: -0.10 to 0.54<br>149. Concurrent validity with FACS: Pearson's r<br>a. Doloplus-2: -0.134 to 0.161<br>b. Mahoney Pain Scale: 0.450-0.593<br>c. Abbey Pain Scale:0.259-0.674<br>d. NOPPAIN: 0.346-0.700<br>e. PACSLAC: 0.094-0.755<br>f. PAINAD: 0.412-0.582 | • Assessments of videotaped facial expressions of 30 randomly selected patients (out of the 60 included)<br>• 3 levels of pain presented<br>• Facial expression components of each instrument are validated against FACS |
| The 2016 | - Design: observational study<br>- Funding: not reported; CoI: not reported<br>- Setting: nursing home, Brasil<br>- Sample size: N=50 | 135. Assessors: 2 researchers<br>136. Patients: elderly (60+) with dementia, residing in a nursing home and with limited communication ability, exposed to potentially painful situations<br>137. *A priori* characteristics:<br>g. Mean age: 87.8y<br>h. Female: 78% | PACSLAC (Brazilian version) | 150. Internal consistency: Cronbach's alpha 0.646 for facial expressions, 0.619 for body activities/movements, 0.618 for social/personality/mood, 0.247 for others subscale; total score 0.827<br>151. Inter-rater reliability: ICC 0.852, kappa 0.381<br>152. Test-retest reliability: ICC 0.643, kappa 0.215<br>153. Concurrent validity with VAS: Pearson's r 0.643 | • Unclear selection bias |

| Study ID | Methods | Patient characteristics | Instrument(s) | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Ware 2015 | - Design: observational study<br>- Funding: not reported; CoI: not reported<br>- Setting: three acute care hospitals in the southeastern United States<br>- Sample size: N=75 | 138. Assessors: unclear<br>139. Patients: patients 65 years and older who agreed to participate and were able to follow and comprehend instructions<br>140. *A priori* characteristics:<br>a. Age: 65-92y<br>b. Female: 49.3% | Revised Iowa Pain Thermometer | 154. Test-retest reliability: Spearman rank correlation: 0.80 (0.79 for original instrument)<br>155. Convergent validity: Spearman rank correlation between IPT-R and IPT=0.87-0.95 for cognitively impaired group; IPT-R and NRS: 0.91-0.94 for cognitively impaired | • Unclear selection bias |
| Zhou 2011 | - Design: observational study<br>- Funding: partially supported by Prince of Songkla University, Thailand; CoI: none<br>- Setting: university-affiliated hospital, China<br>- Sample size: N=200 | 141. Patients: age over 20 years, admission for scheduled operation, not more than a mild CI level for elderly aged ≥60 years according to the Chinese Mini-Mental State Examination (score ≥17 if illiterate, ≥20 for people with primary school educational level, ≥24 for people with secondary school educational level or above)<br>142. *A priori* characteristics:<br>a. Mean age: 55.56y<br>b. Female: 46% | VDS<br>FPS<br>CAS<br>BS-21<br>NRS | 156. Convergent validity with VDS (60+ with mild CI):<br>a. FPS: r=0.84<br>b. CAS: r=0.82<br>c. BS-21: r=0.83<br>157. Test-retest reliability (60+ with mild CI):<br>a. VDS: r=0.84<br>b. FPS: r=0.80<br>c. CAS: r=0.76<br>d. BS-21: r=0.77 | • Chinese study<br>• Unclear selection bias |
| Zwakhalen 2012 | - Design: observational study<br>- Funding: not reported; CoI: none<br>- Setting: single urban nursing home, the Netherlands<br>- Sample size: N=61<br>- Duration: Jan-Jun 2008 | 143. Assessors: 2 observers, a physician-researcher and a nursing staff member familiar with the patient<br>144. Patients: nursing home patients with dementia<br>145. *A priori* characteristics:<br>e. Mean age: 81y<br>f. Female: 70% | PAINAD (Dutch version?) | 158. Cut-off score 1: sensitivity 100%, specificity 48%<br>159. Cut-off score 2: sensitivity 93%, specificity 77% | • Also literature search reported (2003 – Oct 2010): 27 publications found<br>• Also secondary data analysis of Zwakhalen 2006 |

Abbreviations: 95%CI: 95% confidence interval; ADD: Assessment of Discomfort in Dementia; APS: Abbey Pain Scale; BISAD: Observation Instrument for Assessing Pain in Elderly With Dementia; BS-21: Numeric Box-21 Scale; CAS: Colored Analogue Scale; CHEOPS: Children's Hospital of Eastern Ontario Pain Scale; CI: cognitive impairment; CNPI: Checklist of Nonverbal Pain Indicators; CoI: conflict of interest; CPAT: Certified Nursing Assistant Pain Assessment Tool; CSDD: Cornell Scale for Depression in Dementia; DESS: Echelle Douleur Enfant San Salvador; DS-DAT: Discomfort Scale - Dementia of Alzheimer Type; ED: emergency department; ePAT: Electronic Pain Assessment Tool; EPCA-2: Elderly Pain Caring Assessment; FACS: Facial Action Coding System; FPS: Faces Pain Scale; HR: hazard ratio; ICC: intra-class coefficient; INRS: Individualized Numeric Rating Scale; LTC: long-term care; MMSE: mini-mental state examination; MOBID: Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale; MOPAT: Multidimensional Objective Pain Assessment Tool; NOPPAIN: Non-communicative Patient's Pain Assessment Instrument; NCCPC-PV: Non- Communicating Child's Pain Checklist – Postoperative Version; NRS: numeric rating scale; PACSLAC: Pain Assessment Checklist for Seniors with Limited Ability to Communicate; PADE: Pain Assessment for Dementing Elderly; PAINAD: Pain Assessment in Advanced Dementia Scale; PAINE: Pain Assessment in Noncommunicative Elderly Persons; PATCOA:

Pain Assessment Tool in Confused Older Adults; PPI: Present Pain Intensity; PPP: Pediatric Pain Profile; REPOS: Rotterdam Elderly Pain Observation Scale; r-FLACC: revised Face, Leg, Activity, Cry and Consolability scale; VAS: visual analogue scale; VDS: Verbal Descriptor Scale.

**Onderzoeksvraag 3: Welke complicerende factoren gedurende de palliatieve fase op het gebied van de lichamelijke, psychische, sociale en existentiële aspecten worden beschreven bij mensen met een verstandelijke beperking of dementie en hoe beïnvloeden die de kwaliteit van bestaan en de mate van tevredenheid van mensen met een verstandelijke beperking en hun naasten in de palliatieve fase?**

Primaire studies

| Study ID | Methods | Patient characteristics | Complicating factors | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Appelhof 2017 | - Design: cross-sectional study (NTR5018)<br>- Funding: Netherlands Organization for Health Research and Development; Archipel Care Group, the Florence Care Group, Dutch Alzheimer Society; CoI: none<br>- Setting: multicenter study of 13 special care units in nursing homes<br>- Sample size: N=207<br>- Duration: not reported | 146. Eligibility criteria: residents with a dementia diagnosis with a symptom onset before the age of 65 (young-onset dementia)<br>147. Exclusion criteria: lack of informed consent, dementia caused by human immunodeficiency virus, traumatic brain injury, Down syndrome, Korsakov syndrome, or Huntington disease<br>148. *A priori* patient characteristics:<br>a. Mean age: 64y<br>b. Male: 51.2%<br>c. Dementia severity:<br>Mild=16.9%<br>Moderate=21.7%<br>Severe=61.4% | 149. Physical: -<br>150. Psychological: neuropsychiatric symptoms, dementia severity, psychotropic drug use<br>151. Social: -<br>152. Existential: - | Quality of life: QUALIDEM questionnaire<br>160. Patients:<br>a. Significant predictors of lower QoL<br>i. Dementia severity: overall p=0.005; mild p=0.004; moderate p=0.026<br>ii. Psychotropic drug use: p=0.011<br>iii. NPI factors: agitation p=0.000, depression p=0.001, apathy p=0.000<br>b. Significant differences between dementia subtypes in QoL subscales:<br>i. Residents with fronto-temporal dementia (FTD) scored higher on the "Care relationship" subscale than residents with vascular/mixed dementia (mean 16.02 vs. 13.26, p=0.012)<br>ii. The scores on the subscale "Negative affect" were lower in residents with Alzheimer Disease (AD) compared to residents with FTD (mean 5.75 vs. 7.02, p=0.007)<br>iii. Residents with FTD scored higher on the subscale "Positive self-image" compared to residents with vascular/mixed dementia (mean 8.49 vs. 7.45, p=0.012)<br>iv. The score on the subscale "Feeling at home" was higher in residents with FTD than in residents with vascular/mixed dementia (mean 10.04 vs. 8.67, p=0.014)<br>v. Residents with FTD scored lower on the subscale "Social relations" than residents with AD (mean 9.77 vs. 11.71, p=0.005) and with vascular/mixed dementia (mean 9.77 vs. 12.16, p=0.007)<br>161. Carers / family: not reported<br><br>Satisfaction:<br>162. Patients: not reported<br>163. Carers / family: not reported | • Baseline data from larger multicentre study<br>• Unclear selection process<br>• Unclear blinding<br>• Not all patients seem to be included in the analysis |

| Study ID | Methods | Patient characteristics | Complicating factors | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Arneson 2019 | - Design: cross-sectional study<br>- Funding: National Institutes of Health's National Institute on Aging; CoI: none<br>- Setting: 7 assisted living communities, Atlanta, USA<br>- Sample size: N=67<br>- Duration: 5 years; inclusion Nov 2015 – Sep 2018 | 153. Eligibility criteria: residents with cognitive impairment with at least one of the following criteria: at least 85 years, multiple chronic medical conditions, diagnosed with a life-limiting illness, enrolled in hospice<br>154. *A priori* patient characteristics:<br>a. Mean age: 86y<br>b. Male: 36%<br>c. Cognitive impairment: mild=40%, moderate=39%, severe=21% | 155. Physical: fatigue, pain, functional limitation<br>156. Psychological: cognitive Impairment, psychological distress<br>157. Social: race<br>158. Existential: - | Quality of life: QoL-AD<br>164. Patients:<br>a. Bivariate correlation with QoL: cognitive impairment r=0.065, p=0.6; psychological distress: r=-0.43, p<0.001; fatigue: r=-0.4, p=0.001; functional limitation: r=-0.33, p=0.05; pain: r=-0.21, p=0.09, race: r=0.22, p=0.077<br>b. Regression analysis: psychological distress p=0.032, fatigue p=0.048, race p=0.063<br>165. Carers / family: not reported<br><br>Satisfaction:<br>166. Patients: not reported<br>167. Carers / family: not reported | • Unclear selection process<br>• Unclear blinding<br>• 23% drop-outs |
| Bolt 2019 | - Design: observational study<br>- Funding: Netherlands Organisation for Scientific Research; ZonMw the Netherlands Organisation for Health Research and Development; the VU University Medical Center; CoI: none<br>- Setting: 34 nursing homes, Netherlands<br>- Sample size: N=252 reports<br>- Duration: 2007-2010 | 159. Eligibility criteria: family caregivers where their relative resided on psychogeriatric ward in a participating nursing home, their relative was diagnosed with dementia by a physician, and they were able to understand and write Dutch or English<br>160. *A priori* participants' characteristics:<br>a. Male: 39%<br>b. Relation with residents: son or daughter: 61%; partner or spouse: 20%; cousin: 6%; brother or sister: 2.4%<br>161. *A priori* residents' characteristics:<br>a. Male: 34%<br>b. Type of dementia: Alzheimer 41%, vascular 27%, Alzheimer and vascular 17%, Lewy body 6% | 162. Physical: -<br>163. Psychological: -<br>164. Social: -<br>165. Existential: dying peacefully | Quality of life:<br>168. Patients: not reported<br>169. Carers / family: not reported<br><br>Satisfaction:<br>170. Patients: not reported<br>171. Carers / family: associations with dying peacefully, adjusted coefficients (95%CI)<br>a. Satisfaction with care (EOLD-SWC): 0.08 (0.05-0.11)<br>b. Satisfaction with decisions (DSI): 0.16 (0.07-0.24)<br>c. Satisfaction with the decision-making process (DSI): 0.04 (0.01-0.07)<br>d. Any unpleasant experiences: -0.73 (-1.37 to -0.09)<br>e. Neglect: -0.66 (-1.22 to -0.09)<br>f. Lack of respectful treatment: -0.65 (-1.47 to 0.16) | • Secondary data analysis of family caregiver data collected in the observational Dutch End of Life in Dementia (DEOLD) study<br>• Unclear selection process<br>• Unclear blinding |
| Cordner 2010 | - Design: cross-sectional study<br>- Funding: National institute of Neurological Disorders and Stroke; CoI: 3 authors declared CoIs with DEMeasure or | 166. Eligibility criteria: residents with diagnosis of dementia, receiving hospice or palliative care or met hospice criteria for dementia patients<br>167. *A priori* patient characteristics:<br>a. Mean age: 81.6y | 168. Physical: demographic factors, pain, medication, receiving hospice/palliative care | Quality of life: ADRQL<br>172. Patients:<br>a. Significant predictors of QoL:<br>i. SIRS: 95%CI 0.966-1.65, p<0.001<br>ii. Use of pain medication: 95%CI 3.3-19.6, p=0.006<br>iii. Behavioural problems: 95%CI -11.6 to -1.3, p=0.014 | • Possible selection bias<br>• Unclear blinding<br>• Not all patients included in analysis |

| Study ID | Methods | Patient characteristics | Complicating factors | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | relation to Janssen Pharmaceutica<br>- Setting: 3 nursing homes, USA<br>- Sample size: N=125<br>- Duration: Dec 2000 - Aug 2004 | b. Male: 46% | 169. Psychological: severity of neuropsychiatric symptoms, behavioural problems<br>170. Social: education<br>171. Existential: - | 173. Carers / family: not reported<br><br>Satisfaction:<br>174. Patients: not reported<br>175. Carers / family: not reported | |
| Ernecoff 2019 | - Design: secondary analysis of RCT<br>- Funding: NIH; CoI: none<br>- Setting: 22 nursing homes, USA<br>- Sample size: N=241 dyads<br>- Duration: 9 months | 172. Eligibility criteria: residents of age 65 years or older, with 5-7 on Global Deterioration Scale, having survived 9 months follow-up together with their family decision makers<br>173. *A priori* patient characteristics:<br>a. Age: 86.2y<br>b. Male: 17%<br>c. Dementia stage: moderate 26%, moderately-severe 51%, severe 23%<br>174. *A priori* decision maker characteristics:<br>a. Age: 63 years<br>b. Male: 35%<br>c. Relationship: Spouse 14%, Son/son in-law 27% daughter/daughter in law 51%, others 7% | 175. Physical: demographic factors<br>176. Psychological: dementia stage, severity of illness<br>177. Social: -<br>178. Existential: - | Quality of life: ADRQL<br>176. Patients: QoL at baseline and at 9 months<br>a. Significant predictors at 9 months:<br>i. Age: coefficient -0.4, SE 0.1; p=0.004<br>ii. Hospice enrolment: coefficient -6.0, SE 2.5; p=0.019<br>iii. Decision at baseline of a primary goal of comfort: coefficient 4.2, SE 1.8; p=0.022<br>177. Carers / family: not reported<br><br>Satisfaction:<br>178. Patients: not reported<br>179. Carers / family: not reported | • Secondary analysis<br>• Selection bias<br>• Unclear blinding |
| Hendriks 2014 | - Design: observational study<br>- Funding: The Netherlands organisation of Scientific Research and ZonMw and a grant from SBOH; CoI: none<br>- Setting: 34 long-term care facilities, the Netherlands<br>- Sample size: N=330<br>- Duration: 2007-2011 | 179. Eligibility criteria: residents diagnosed with dementia at any stage and family representative<br>180. *A priori* patient characteristics:<br>a. Age: 85y<br>b. Male: 33%<br>c. Advanced Dementia: 43% | 181. Physical: pain, shortness of breath, agitation<br>182. Psychological: -<br>183. Social: -<br>184. Existential: - | Quality of life: QUALID<br>180. Patients:<br>a. Predictors of QoL: adjusted coefficient<br>i. Pain: 4.0 (95%CI 2.1-6.0)<br>ii. Shortness of breath: 0.7 (95%CI -1.2 to 2.6)<br>iii. Agitation: 6.1 (95%CI 4.2-8.1)<br>181. Carers / family: not reported<br><br>Satisfaction:<br>182. Patients: not reported<br>183. Carers / family: not reported | • Secondary data analysis of family caregiver data collected in the observational Dutch End of Life in Dementia (DEOLD) study<br>• Unclear selection process<br>• Unclear blinding |

| Study ID | Methods | Patient characteristics | Complicating factors | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| Liu 2012 | - Design: retrospective study<br>- Funding: no funding received; CoI: none<br>- Setting: managed care organisation, USA<br>- Sample size: N=131<br>- Duration: Oct 2008 - Apr 2009 | 185. Eligibility criteria: family members or health care proxies of residents with a diagnosed dementia having died between October 2008 and April 2009<br>186. Exclusion: resident received hospice services<br>187. *A priori* patient characteristics:<br>a. Age: 65y<br>b. Male: 29%<br>c. Relationship to resident: Spouse 4%, adult children 65%, other 31% | 188. Physical: resident comfort<br>189. Psychological: -<br>190. Social: communication, satisfaction with nurse practitioners<br>191. Existential: - | Quality of life:<br>184. Patients: not reported<br>185. Carers / family: not reported<br><br>Satisfaction:<br>186. Patients: not reported<br>187. Carers / family:<br>a. Pearson's correlations demonstrated that overall satisfaction was significantly associated with (a) NP–family communication (r=0.68), (b) resident comfort (r=0.65), (c) satisfaction with NP care (r=0.66)<br>b. These three predictor variables were entered into a simultaneous multiple regression model. Results indicated that the linear combination of the predictors accounts for 56.6% of the overall satisfaction with all three predictors demonstrating statistically significant unique effects, $F(3, 127)=55.26$, $p < 0.001$, with NP–family communication (β=0.33), resident comfort (β=0.27), and satisfaction with NP care (β=0.25) | • Survey was mailed to 239 family members, response rate of 55%<br>• Unclear blinding<br>• Unclear loss-to-follow-up |
| Nakanishi 2017 | - Design: cross-sectional study<br>- Funding: JSPS KAKENHI; CoI: noneI<br>- Setting: 334 home- or community-based agencies, Japan<br>- Sample size: N=2197 and 4502 questionnaires<br>- Duration: 4 week period, May 2016 | 192. Eligibility criteria: professional caregivers agencies; exclusion if they had less than 5 caregivers or started after April 2015; participants were asked to rate patients diagnosed with dementia and older than 65 years<br>193. *A priori* patient characteristics:<br>a. Age: 84.4y<br>b. Male: 26.8% | 194. Physical: physical restraints, impairment of ADL, comorbid disease (vascular, hypertension, diabetes)<br>195. Psychological: dementia type, cognitive impairment, antipsychotic medication use<br>196. Social: care setting<br>197. Existential: - | Quality of life: Japanese Quality of Life Instrument for Older Adults Experiencing Dementia (QLDJ)<br>188. Patients: significant factors, coefficient (95%CI)<br>a. Interaction with surroundings:<br>i. Age 0.15 (0.06 to 0.24)<br>ii. Male -7.39 (-8.9 to -5.9)<br>iii. Attitude: 25-75$^{th}$ percentile 3.1 (1.18 to 5.0), >75$^{th}$ percentile 5.18 (2.96 to 7.4)<br>iv. Alzheimer 4.15 (2.49-5.82), vascular 4.02 (1.49 to 6.55)<br>v. Cognitive impairment -2.8 (-3.21 to -2.39)<br>vi. Impairment of ADL -3.2 (-3.67 to -2.73<br>vii. Use of antipsychotic medication -4.1 (-5.7 to -2.4)<br>b. Self-expression:<br>i. Knowledge 2.9 (0.97 to 4.9)<br>ii. Attitude 25-75$^{th}$ percentile 2.25 (0.4-4.1), > 75$^{th}$ percentile 4.26 (2.2-6.4)<br>iii. Age 0.15 (0.06-0.23)<br>iv. Male -3.78 (-5.2 to -2.5)<br>v. Alzheimer -2.35 (-3.9 to -0.8) | • Response rate: 25.6%<br>• Of the 4052 questionnaires, 449 were excluded because of incomplete information<br>• The final sample for analysis consisted of 3603 questionnaires completed by 2116 caregivers from 329 agencies<br>• Selection bias<br>• Unclear blinding |

| Study ID | Methods | Patient characteristics | Complicating factors | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | | | | vi. Cognitive impairment -4.27 (-4.6 to -3.9)<br>vii. Impairment of ADL -5.42 (-5.9 to -5.0)<br>viii. Hypertension 1.37 (0.14-2.6)<br>ix. Use of antipsychotic medication -2.71 (-4.2 to -1.2)<br>c. Exhibiting minimum negative behaviour:<br>i. Knowledge 25-75$^{th}$ percentile 2.45 (0.58-4.32)<br>ii. Age 0.12 (0.04-0.21)<br>iii. Male -2.05 (-3.4 to -0.76)<br>iv. Vascular Dementia 2.33 (-0.08 to 4.58)<br>v. Impairment of ADL -0.59 (-1.01 to -0.17)<br>vi. Use of antipsychotic medication -10.94 (-12.4 to -9.5)<br>189. Carers / family: not reported<br><br>Satisfaction:<br>190. Patients: not reported<br>191. Carers / family: not reported | |
| Sternberg 2014 | - Design: retrospective cohort study<br>- Funding: Helen Bader Foundation; CoI: none<br>- Setting: provider organisation, Israel<br>- Sample size: N=117<br>- Duration: 2012 | 198. Eligibility criteria: older people with advanced dementia living in the community with primarily responsible caregivers<br>199. *A priori* patient characteristics:<br>a. Male: 45%<br>b. Age: <85y 34%, 85-94y 49%, 95+ 17y<br>200. *A priori* caregiver characteristics:<br>a. Male: 29%<br>b. Age<55: 24%, >=75: 19%<br>c. Relationship: spouse74%, child 22% | 201. Physical: demographic variables, number of comorbidities, problems swallowing, weight loss, falls, number of medications, use of antipsychotics, and method of feeding<br>202. Psychological: depression<br>203. Social: education<br>204. Existential: - | Quality of life: not reported -> surrogate=SM-EOLD and CAD-EOLD<br>192. Patients:<br>a. Factors for SM-EOLD: (adjusted for age and sex)<br>i. Less comorbidities: B=-1.43 (p<0.001)<br>ii. Longer duration of dementia: B=0.676 (p=0.004)<br>iii. Higher education of caregiver: B=4.535 (p=0.03)<br>iv. Depression of caregiver: B=-6.087 (p=0.003)<br>b. Factors for CAD-EOLD: no multivariate analysis<br>i. Demographic characteristics were not significantly associated with CAD-EOLD<br>ii. Significant association of CAD-EOLD (p<0.005) found with problems of swallowing and eating<br>193. Carers / family: not reported<br><br>Satisfaction:<br>194. Patients: not reported<br>195. Carers / family: not reported | • Possible selection bias<br>• Unclear blinding |
| van Dam 2019 | - Design: secondary analysis of multicenter, cluster-RCT | 205. Eligibility criteria: long-term care facility residents 65 | 208. Physical: paracetamol use | Quality of life: QUALIDEM-6D<br>196. Patients: | • Unclear blinding |

| Study ID | Methods | Patient characteristics | Complicating factors | Results | Critical appraisal of study quality |
|---|---|---|---|---|---|
| | - Funding: G.C. Rieber Foundation and the Norwegian Government; CoI: none<br>- Setting: long-term care facilities, Norway<br>- Sample size: N=407<br>- Duration: Aug 2014 - Dec 2015; follow-up 9 months | years or older with moderate to advanced dementia<br>206. Exclusion criteria: less than 6 months life expectancy or having schizophrenia<br>207. *A priori* patient characteristics:<br>a. Age: 87y<br>b. Male: 28% | 209. Psychological: -<br>210. Social: -<br>211. Existential: - | a. No significant association between QoL / QoL-subdomains and paracetamol use:<br>i. QUALIDEM-6D: b=-1.18 (p=0.39), Care relationship: b=-1.76 (p=0.46), Positive effect: b=-0.67 (p=0.80), Negative affect: b=-2.42 (p=0.37), Restless tense behaviour: b=-3.64 (p=0.22), Social relationship: b=0.87 (p=0.75), Social isolation: b=0.96 (p=0.67)<br>197. Carers / family: not reported<br><br>Satisfaction:<br>198. Patients: not reported<br>199. Carers / family: not reported | |

Abbreviations: 95%CI: 95% confidence interval; ADL: activities of daily living; CoI: conflict of interest; NPI: Neuropsychiatric Inventory; QoL: quality of life; RCT: randomized controlled trial; SE: standard error.

**Onderzoeksvraag 4: Welke wetenschappelijke kennis is beschikbaar over gemiddelde leeftijd en oorzaak van overlijden bij syndromen 22q11, Down, Rett, Prader-Willi, Angelman, fragiele X, tubereuze sclerose, Williams, Cornelia de Lange, Noonan, foetaal alcoholsyndroom, NF type I, CHARGE?**

22q11 deletion syndrome

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| Cancrini 2014 | - Design: retrospective and prospective multicenter cohort study<br>- Funding: European Commission (CELL-PID HEALTH- F5-2010-261387), Italian Ministry of Health (Ricerca corrente); CoI: none<br>- Setting: 16 Italian centers from 10 of the 20 Italian regions<br>- Sample size: N=228<br>- Duration: 2006 – 2012; median follow-up=43 months | 212. Eligibility criteria: patients with 22q11 deletion syndrome<br>213. *A priori* patient characteristics:<br>a. Male: 49.1%<br>b. Median age at diagnosis: 4 months (range 0 – 36y 10mo)<br>c. Mean age at diagnosis: 24 months<br>d. Cardiac defects: 55%<br>e. Neonatal hypocalcemia: 20%<br>f. Infections: 12%<br>g. Autoimmune manifestations: 2%<br>h. ORL manifestations: 5%<br>i. Neuropsychological manifestations: 12%<br>j. Typical features: 17% | Age of death:<br>200. Survival probability=0.92 (SE 0.02) at 15y after diagnosis<br><br>Cause of death: Deaths: N=13<br>201. Cardiovascular complications: N=11; 10 within 2nd year of life, 1 at 4y of age<br>202. Severe autoimmune anemia and thrombocytopenia/ N=1<br>203. Cardiac insufficiency secondary to cardiac hypertrophy during growth hormone treatment: N=1; at age of 10y | • Consecutive cases in representative part of Italy<br>• No confounding factors taken into account<br>• Not all data available for all patients |
| Repetto 2014 | - Design: retrospective cohort study<br>- Funding: FONDECYT-Chile grants #1100131 and 1130392; CoI: none<br>- Setting: genetic services in tertiary care centres, Chile<br>- Sample size: N=419<br>- Duration: 1998 - 2013 | 214. Eligibility criteria: patients with postnatal diagnosis of 22q11 deletion syndrome<br>215. *A priori* patient characteristics:<br>a. Male 47.2%<br>b. Median age: 12y (range 0-52y)<br>c. Cardiac defects: 63.7% | Age of death:<br>204. Median age at death: 3.4 months<br>d. Only 2 patients died after age of 2y: septic shock (9.9y) and pulmonary fibrosis / chronic respiratory insufficiency (32.4y)<br><br>Cause of death: Deaths: N=59 (14.1%)<br>205. Cardiac causes: single cause 45.8%, in combination 32.2%<br>206. Infectious / immunodeficiency: single cause 11.9%, in combination 11.8%<br>207. Respiratory: single cause 3.4%, in combination 15.2%<br>208. Univariate analysis: mortality<br>e. Presence of cardiac anomaly: OR 5.27 (95%CI 2.06-13.99; p<0.0001)<br>f. Hypocalcemia: OR 4.27 (95%CI 1.67-11.15; p=0.001)<br>g. Airway malacia: OR 13.375 (95%CI 1.19-110.514; p=0.043) | • Of 430 known patients with postnatal diagnosis, 419 consented to participate<br>• Living or deceased status in Dec 2013<br>• Not all data available for all patients<br>• No multivariate analysis |
| Van 2019 | - Design: prospective case-control study<br>- Funding: supported by CIHR (MOP-313331 and MOP-111238) and the Clinican-Scientist Program | 216. Eligibility criteria: adults (17+) with 22q11 deletion syndrome<br>217. *A priori* patient characteristics: | Age of death:<br>209.<br>210. Median: 46.4y (range 18.1-68.6)<br>211. Major CHD: median age 37.3y<br>212. No major CHD: median age 50.7y | • Patients were recruited through specialty clinic, referrals and/or active screening<br>• Multivariate analysis |

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| | at the University of Toronto; CoI: none<br>- Setting: specialty clinic for adults with 22q11 deletion syndrome, Canada<br>- Sample size: N=309 patients, N=1014 unaffected parents and siblings<br>- Duration: median follow-up 5.3y | a. Male: 47.9%<br>b. Major CHD: 36.2%<br>c. Median age at diagnosis: 17y | Cause of death: Deaths: N=31 (10%)<br>213. Causes: cardiovascular 71%, cancer 9.7%, stroke 6.5%, pneumonia 6.5%, septic shock 3.2%, suicide 3.2%<br>214. Risk factors for all-cause mortality:<br>d. Major CHD: HR 4.77 (95%CI 2.05-11.1; p=0.0003)<br>e. Later age at laboratory diagnosis: HR 0.94 (95%CI 0.90-0.98; p=0.0032)<br>f. Intellectual disability: HR 2.48 (95%CI 0.89-6.93; p=0.08) | |

## CHARGE Syndrome

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| Bergman 2010 | - Design: prospective cohort study<br>- Funding: Netherlands Organization for Health Research, Canadian Pediatric Surveillance Program and grants from CHARGE Canada and CHARGE USA; CoI: not reported<br>- Setting: outpatient clinic, The Netherlands<br>- Sample size: N=48 + 4 additional<br>- Duration: 2005-2009 | 218. Eligibility criteria: patients with CHARGE syndrome who survived the neonatal period (28d or older)<br>219. *A priori* patient characteristics:<br>a. Male: 56.25%<br>b. Mean age at first admission to clinic: 11y 8mo | Age of death:<br>215. 3 patients of the cohort died: 11,5mo, 8y and 22y<br>216. Actuarial post-neonatal survival at 1y of age: 98%; at 10y of age: 95%; at 25y of age: 76%<br><br>Cause of death:<br>217. Fatal choking on food: N=1<br>218. Respiratory aspiration or cardiac arrest: N=5<br>219. Hypoxic encephalopathy: N=1<br>220. Univariate analysis death <10y: congenital heart defect p=0.022, feeding difficulties p=0.002, breathing + feeding difficulties + GERD p=0.029 | • Possible selection bias<br>• No autopsies performed<br>• Follow-up duration unclear<br>• Not all patients included in univariate analysis |

## Cornelia de Lange Syndrome

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| Schrier 2011 | - Design: retrospective study<br>- Funding: NIH grants NIH/NICHD PO1HD052860 (IDK), NIH/NICHD R21HD050538 (IDK), NIH/NICHD K08HD055488 (MAD), T32GM008638 (SAS), CHOP Institutional Development Funds (IDK); CoI: not reported<br>- Setting: single University centre, US<br>- Sample size: N=426<br>- Duration: 1966-2007 | 220. Eligibility criteria: patients with Cornelia de Lange Syndrome and a known date of death | Age of death:<br>221. Patients who survived neonatal period: 12y 9mo<br>222. Patients who survived age 1y: 16y 2mo<br>223. Patients who survived age 18y: 28y 2mo<br><br>Cause of death:<br>224. Deaths in the first 28 days: N=30<br>a. Congenital diaphragmatic hernia: >33%<br>b. CHD: 5/30 (17%)<br>c. Respiratory: 4/30 (13%)<br>225. 29d-1y: N=51<br>d. Respiratory: 18/51 (35%)<br>e. CV: 14/51 (27%) | • Not all data available for all patients<br>• Follow-up duration unknown |

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| | | | f. GI: 9/51 (18%)<br>g. Sepsis: 2/51 (4%)<br>h. CNS: 2/51 (4%)<br>226. 1-18y: N=117<br>i. Respiratory: 38/117 (32%)<br>j. GI: 22/117 (18.8%)<br>k. CV: 12/117 (10.2%)<br>l. Accidents: 12/117 (10.2%)<br>m. CNS: 11/117 (9%)<br>n. Sepsis: 7/117 (6%)<br>o. Renal: 3/117 (2.5%)<br>227. >18y: N=97<br>p. Respiratory: 31/97 (32%)<br>q. GI: 25/97 (26%)<br>r. CNS: 10/97 (10%)<br>s. Accidents: 9/97 (9%)<br>t. CV: 7/97 (7%)<br>u. Sepsis: 4/97 (4%)<br>v. Renal: 1/97 (1%) | |

Down syndrome

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| O'Leary 2018 | - Design: systematic review (CRD42015020161)<br>- Funding: Scottish Learning Disabilities Observatory; CoI: not reported<br>- Databases: CINAHL, MEDLINE, PsycINFO, Web of Science and EMBASE<br>- Search date: Oct 2016<br>- Included studies: N=34 | 221. Eligibility criteria: studies that reported deaths or mortality rates of people with Down syndrome; minimum of 50% of participants with intellectual disabilities | 228. Narratively reported | • Selection process by one reviewer, 5% checked by second reviewer<br>• Quality appraisal with Critical Appraisal Skills Programme by two reviewers<br>• Data extraction: not clear if done by two reviewers<br>• Language restricted to English |
| Holz 2019 | - Design: retrospective study<br>- Funding: not reported; CoI: none<br>- Setting: two forensic labs, Germany<br>- Sample size: N=23<br>- Duration: 1998-2017 | 222. Eligibility criteria: forensic autopsy cases with DS<br>223. *A priori* patient characteristics:<br>a. Male: 26.1% | Age of death: range 23d – 61y<br>229. Mean: 21.6y<br>230. Median: 14.8y<br><br>Cause of death:<br>231. Infection: N=13 (mainly pneumonia)<br>232. Accident: N=6<br>233. Medical malpractice: N=1<br>234. Other: N=3 | • Very specific population |
| Hosking 2016 | - Design: retrospective study<br>- Funding: Health Services and Delivery Research Programme of the NIHR (project number 12/64/154); CoI: not reported | 224. Eligibility criteria: people with intellectual disability<br>225. *A priori* patient characteristics:<br>a. Mean age: 39.1y | Age of death:<br>235. Not reported<br><br>Cause of death: | • Population-based study |

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| | - Setting: 343 English primary care practices<br>- Sample size: N=16666, of which 1793 with DS<br>- Duration: 2009-2013 | | 236. Intellectual disability was strong predictor of mortality in people with DS: HR 9.21 (95%CI 7.22-11.76)<br>237. Respiratory disease: 20.3%-42.4% | |
| Miodrag 2013 | - Design: retrospective study<br>- Funding: not reported; CoI: none<br>- Setting: state of Tennessee, US<br>- Sample size: N=2046<br>- Duration: 1997-2008 | 226. Eligibility criteria: individuals with DS between ages of 1 and 29 years at either their deaths or their last recorded hospitalization<br>227. *A priori* patient characteristics:<br>a. Not reported | Age of death:<br>238. Individuals with DS who died were, on average, 17.24y<br><br>Cause of death: N=85<br>239. Cardiac-related conditions: 33%<br>240. Respiratory-pulmonary conditions: 15.3%<br>241. Accidents: 7.1%<br>242. Cancer: 5.9%<br>243. Brain-related causes: 4.7%<br>244. Infections: 3.5%<br>245. Kidney and intestinal-related problems: 2.4% each<br>246. Obesity and diabetes: 1.2% each<br>247. DS was listed as the cause of death for 21.2%<br>248. Another 2.4% of deaths were caused by other diseases, including sleep apnoea and infantile cerebral palsy | • Participants were excluded if they did not have complete data |
| Nahar 2013 | - Design: prospective study<br>- Funding: none; CoI: none<br>- Setting: tertiary care center, India<br>- Sample size: N=543<br>- Duration: 2010 | 228. Eligibility criteria: children with DS counselled at the Center of Medical Genetics, Sir Ganga Ram Hospital from 2005 through 2009<br>229. *A priori* patient characteristics:<br>a. Male: 64.8% | Age of death:<br>249. 0-5y: N=66<br>250. 5-10y: N=3<br>251. 10+: N=2<br><br>Cause of death: N=71<br>252. Congenital heart disease: N=35<br>253. The other causes of death included leukemia (N=3), pneumonia (N=4) and miscellaneous causes | • Not all causes of death are (clearly) reported |
| Ng 2017 | - Design: retrospective study<br>- Funding: Forte (2006-1512), the Swedish Research Council for Health, Working Life and Welfare (2014-4753 & 2013-2056); CoI: none<br>- Setting: Sweden<br>- Sample size: N=942 with DS that died<br>- Duration: 2002-2015; mean follow-up 9.4y | 230. Eligibility criteria: individuals, 55+, with intellectual disability<br>231. *A priori* patient characteristics:<br>a. Men: 51.6% | Age of death:<br>254. Mean: 63.5y<br><br>Cause of death:<br>255. Diseases of the respiratory system: 37.1%<br>256. Diseases of the circulatory system: 25.9%<br>257. Mental and behavioural disorders: 10.7%<br>258. Diseases of the nervous system: 7.8%<br>259. Infectious and parasitic diseases: 4.3%<br>260. Diseases of the digestive system: 2.1%<br>261. Neoplasms: 2% | • Population-based study based on ICD-10 codes |
| Oppewal 2018 | - Design: prospective study<br>- Funding: ZonMw (no. 57000003 and no. 314030302); CoI: not reported | 232. Eligibility criteria: cliënts aged 50 years and over receiving care from one of the participating organizations | Age of death:<br>262. Not reported for DS<br><br>Cause of death: N=54<br>263. Respiratory failure: 73.3% | • 1050 of 2322 cliënts participated<br>• During the follow-up period 13 cliënts with DS deregistered |

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| | - Setting: 3 care organizations, the Netherlands<br>- Sample size: N=1050, of which 149 with DS<br>- Duration: Nov 2008 – Jul 2010, mortality data Mar 2015 | 233. *A priori* patient characteristics:<br>a. Not reported for DS | 264. Diseases of the digestive system: 4.4%<br>265. Infectious and bacterial diseases: 4.4%<br>266. Cardiovascular diseases: 2.2%<br>267. Dehydration / malnutrition: 2.2%<br>268. Other: 2.2%<br>269. Unknown 11.1% | |
| Patti 2010 | - Design: retrospective study<br>- Funding: not reported; CoI: not reported<br>- Setting: metropolitan diagnostic and research clinic, US<br>- Sample size: N=140, of which 61 with DS<br>- Duration: 12y | 234. Eligibility criteria: individuals with intellectual disability who were born prior to the year 1946 and were age 50 or older prior to death<br>235. *A priori* patient characteristics:<br>a. Mean age: 61.8y<br>b. Men: 59% | Age of death:<br>270. Mean: 61.4y<br><br>Cause of death: N=44<br>271. Not reported | • Unclear if selection bias and if loss-to-follow-up |
| Tenenbaum 2012 | - Design: retrospective study<br>- Funding: not reported; CoI: not reported<br>- Setting: university centre, Israel<br>- Sample size: N=120<br>- Duration: 1988-2007 | 236. Eligibility criteria: adults with DS, who were hospitalized at the Hadassah Medical Centers, during the years 1988–2007<br>237. *A priori* patient characteristics:<br>a. Age range: 18-73y<br>b. Men: 60.8%<br>c. Average age at hospitalization: 36.1y | Age of death:<br>272. Mean: 39.8y<br>273. Median: 44y<br><br>Cause of death: N=8<br>274. Respiratory failure due to aspiration pneumonia: N=3<br>275. Acute myelocytic leukemia: N=1<br>276. Urosepsis: N=1<br>277. Myocardial infarct: N=1<br>278. Acute gastroenteritis with acute renal failure: N=1<br>279. Accident: N=1 | • Unclear if selection bias |

## Fetal Alcohol Syndrome

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| Easton 2015 | - Design: retrospective study<br>- Funding: Public Health Agency of Canada (PHAC).; CoI: not reported<br>- Setting: general population, Canada<br>- Sample size: N=327<br>- Duration: 2011 | 238. Eligibility criteria: individuals with fetal alcohol syndrome that died<br>239. *A priori* patient characteristics:<br>a. Not reported | Age of death:<br>280. 0-19: 47 deaths (14.3%)<br>281. 20-29: 29 deaths (8.9%)<br>282. 30-44: 55 deaths (16.8%)<br>283. 45-59: 110 deaths (33.6%)<br>284. 60-69: 86 deaths (26.3%)<br><br>Cause of death:<br>285. Not reported | • Population-based study based on ICD-10 coded deaths |
| Thanh 2016 | - Design: retrospective study<br>- Funding: Alberta Health; CoI: not reported | 240. Eligibility criteria: people with fetal alcohol syndrome coded with ICD-9 code 760.71 in the practitioner claims database, and ICD-10 codes Q86.0 and P04.3 in | Age of death:<br>286. Average: 28y, SD 19<br>287. Median: 25y, IQR 18-40<br>288. Average life expectancy at birth: 34y (95%CI 31-37) | • Population-based study based on ICD-9 and ICD-10 coded deaths<br>• 15 cases with missing causes of death were excluded |

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| | - Setting: Alberta provincial databases of inpatients, outpatients, or practitioner claims<br>- Sample size: N=6052<br>- Duration: 2003-2012 | the inpatient and outpatient databases in any of the diagnostic code fields<br>241. *A priori* patient characteristics:<br>a. Not reported | Cause of death: N=113<br>289. External causes: 44%<br>b. Suicide: 15%<br>c. Accident: 14%<br>d. Poisoning by illegal drugs or alcohol: 7%<br>e. Other: 7%<br>290. Diseases of the nervous system: 8%<br>291. Diseases of the respiratory system: 8%<br>292. Diseases of the digestive system: 7%<br>293. Congenital malformations, deformations, and chromosomal abnormalities: 7%<br>294. Mental and behavioural disorders: 4%<br>295. Diseases of the circulatory system: 4%<br>296. Neoplasms: 3%<br>297. Certain conditions originating in the perinatal period: 3%<br>298. Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified: 3%<br>299. Certain infectious and parasitic diseases: 3%<br>300. Endocrine, nutritional, and metabolic diseases: 2%<br>301. Diseases of the genitourinary system: 2%<br>302. Diseases of the blood and blood-forming organs: 1% | |

## Fragile-X Syndrome

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| Arvio 2016 | - Design: prospective study<br>- Funding: Päijät-Häme Joint Municipal Authority; CoI: none<br>- Setting: outpatient setting, South Häme specialist care district, Finland<br>- Sample size: N=34<br>- Duration: 1994-2014 | 242. Eligibility criteria: all known FXS males living in the South Häme specialist care district<br>243. *A priori* patient characteristics:<br>a. 19 males (56%) lived with their parents, 5 (15%) in a care-home residence, and 10 (29%) in a nursing home<br>b. The mean IQ for seven males younger than 16 was 49 (34–75) and of those 21 older than 15, 26 (16–39) | Age of death:<br>303. Range: 32-77<br>304. Mean: 53y<br><br>Cause of death: N=10<br>305. Cardiac death: N=2<br>306. Neoplasm: N=2<br>307. Thromboembolism: N=2<br>308. Accident: N=1<br>309. Hip bone fracture, pneumonia: N=1<br>310. Status epilepticus: N=1<br>311. Unknown: N=1 | • Clinical evaluation twice at 10-year interval<br>• 3/37 not willing to participate |

Neurofibromatosis 1

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| Duong 2011 | - Design: retrospective study<br>- Funding: "Association Neurofibromatoses et Recklinghausen" and "Ligue française de lute contre les Neurofibromatoses"; CoI: none<br>- Setting: multicentre, France<br>- Sample size: N=1895<br>- Duration: 1980-2006; median follow-up 6.8y | 244. Eligibility criteria: patients meeting NIH criteria for NF1<br>245. *A priori* patient characteristics:<br>a. Median age at inclusion: 17.7y | Age of death:<br>312. Median age at death: 31.7y<br><br>Cause of death: N=67 (of 1226), 5.5%<br>313. MPNSTs: 60%<br>314. CNS tumours: 14%<br>315. Spinal cord compression by neurofibroma: 3%<br>316. Organ compression by neurofibroma: 9%<br>317. Pheochromocytoma: 3% | • Consecutive patients<br>• Vital status was known for 1226 patients (65%)<br>• Cause of death known for 58 patients |
| Evans 2011 | - Design: retrospective study<br>- Funding: NIHR Biomedical Research Centre at Central Manchester Foundation Trust; CoI: none<br>- Setting: genetic services, Manchester, UK<br>- Sample size: N=1186<br>- Duration: 1957-2009 | 246. Eligibility criteria: patients with confirmed or near-certain diagnosis of NF1<br>247. *A priori* patient characteristics:<br>a. Not reported | Age of death:<br>318. Mean: 43.55y<br>319. Median: 44.13y<br><br>Cause of death: N=131 (11%)<br>320. MPNSTs: 26%<br>321. Glioma: 11%<br>322. Other tumours: 21%<br>323. Cerebrovascular: 8%<br>324. Myocardial infarction: 7%<br>325. Respiratory: 8% | • Cause of death unknown for 1 patient |
| Masocco 2011 | - Design: retrospective study<br>- Funding: none; CoI: none<br>- Setting: Italy<br>- Sample size: N=632 deaths<br>- Duration: 1995-2006 | 248. Eligibility criteria: patients with NF1 that died<br>249. *A priori* patient characteristics:<br>a. Not reported | Age of death:<br>326. Mean: 55.5y<br><br>Cause of death: 531 deaths 1995-2003 and 2006<br>327. NF1: N=150<br>328. Other neoplasms: N=182<br>329. Diseases of circulatory system: N=101<br>330. Diseases of respiratory system: N=33<br>331. Diseases of digestive system: N=14<br>332. Diseases of nervous system: N=10 | • Population-based study based on ICD-9 and ICD-10 coded deaths |

Noonan Syndrome

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| Calcagni 2017 | - Design: retrospective study<br>- Funding: grants from Associazione Italiana Studio Malformazioni (n. 201403X003268) and Ministry of Health (Ricerca Corrente 2017) (n. 201702P003973); Fondazione Bambino Gesù (CUoRE), Ministry of Health (n. RF-2011-02349938) (Ricerca Corrente 2016 and 2017) and E-Rare (NSEuroNet); CoI: none | 250. Eligibility criteria: all patients with molecularly confirmed diagnosis of NS, NSML, CS or CFCS, followed up until July 2014<br>251. *A priori* patient characteristics:<br>a. Median age at last follow-up: 8.75 years<br>b. Females: 44.5%<br>c. Cardiac involvement: 80.1% | Age of death:<br>333. Range: 11 days – 28.6y<br><br>Cause of death: N=10, of which 7 with NS<br>334. Post-surgical low cardiac output: N=3<br>335. Leukaemia: N=2<br>336. Sudden death: N=1<br>337. Heart transplant rejection: N=1 | • Unclear selection bias<br>• Unclear loss-to-follow-up |

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| | - Setting: multicentric, 7 cardiac centres, Italy<br>- Sample size: N=371, of which 297 with Noonan Syndrome<br>- Duration: unclear | | | |

Prader-Willi syndrome

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| Alfaro 2019 | - Design: retrospective study<br>- Funding: none; CoI: none<br>- Setting: France<br>- Sample size: N=104<br>- Duration: 2004-2014 | 252. Eligibility criteria: patients with PWS who died<br>253. *A priori* patient characteristics:<br>a. Year of birth: 1951-2013<br>b. Male: 41% | Age of death:<br>338. Median: 30y (range 1 mo – 58y)<br><br>Cause of death:<br>339. Respiratory cause: N=55, 53%<br>340. Sudden death: N=18, 17%<br>341. Cardiovascular cause: N=15, 14%<br>342. Gastrointestinal cause: N=4, 4%<br>343. Severe infection: N=4, 4%<br>344. Other: N=3, 3%<br>345. Unknown: N=5 | • Population-based study based on ICD-coded deaths |
| Butler 2017<br>Manzardo 2018 | - Design: retrospective study<br>- Funding: National Institute of Child Health and Human Development (grant HD02528), unrestricted grant from Zafgen, Inc.; CoI: none<br>- Setting: US<br>- Sample size: N=486<br>- Duration: 1973-2015 | 254. Eligibility criteria: patients with PWS who died<br>255. *A priori* patient characteristics:<br>a. Male: 54% | Age of death:<br>346. Mean: 29.5 +/- 16y (range 2 mo – 67y)<br><br>Cause of death:<br>347. Respiratory failure: N=94, 31%<br>348. Cardiac: N=50, 16%<br>349. Gastrointestinal: N=30, 10%<br>350. Infection: N=29, 9%<br>351. Obesity: N=22, 7%<br>352. Pulmonary embolism: N=19, 7%<br>353. Choking: N=18, 6%<br>354. Accident: N=17, 6%<br>355. Renal failure: N=7, 2%<br>356. Neurologic: N=6, 2%<br>357. Cancer: N=4, 2%<br>358. Hypothermia: N=3, 1%<br>359. Drug reaction: N=3, 1% | • Patients recruited through PWSA (non-profit organisation): data collection started in 1999, with some changes since then<br>• Cause of death known for 312 patients (36%) |
| Hedgeman 2017 | - Design: retrospective study<br>- Funding: not reported; CoI: several authors had links with Zafgen Inc.<br>- Setting: Denmark<br>- Sample size: N=155<br>- Duration: 1995-2012 | 256. Eligibility criteria: patients diagnosed with PWS<br>257. *A priori* patient characteristics:<br>a. Male: 45.8%<br>b. Mean age: 18y (SD 17) | Age of death:<br>360. Peak RR of mortality was at ages 30–39 years, with an increased risk of 27.7 (95%CI 9.1-84.1)<br><br>Cause of death:<br>361. Not reported<br>362. Comorbid diabetes significantly increased risk of mortality (RR 26.9; 95%CI 10.0-72.6) as compared with the general population | • Population-based study based on ICD-10 codes |

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| Lionti 2012 | - Design: retrospective study<br>- Funding: Ultimate Challenge Auxiliary of the Royal Children's Hospital, the Victorian Government's Operational Infrastructure Support Program; CoI: not reported<br>- Setting: Children's hospital, Australia<br>- Sample size: N=163<br>- Duration: 1950-2010 | 258. Eligibility criteria: patients diagnosed with PWS<br>259. *A priori* patient characteristics:<br>a. Males: 55%<br>b. Age range: 3w – 60y, mean 19.8y | Age of death:<br>363. Two infants died at 1 month of age, four died between 5 and 15 years, four between 16 and 25 years and five after the age of 25<br>364. Mean: 20.3y<br><br>Cause of death: N=15<br>365. A genetic syndrome was the only recorded cause of death for five individuals, including both infants<br>366. Causes of death were known for three of the four children who died between 5 and 15 years. The listed causes were endocarditis, pulmonary thromboembolism and sepsis resulting from an infected trunk wound<br>367. In the four 16- to 25-year-olds, the two known causes of death were respiratory failure associated with scoliosis and obesity, and heart failure due to an acute myocardial infarction with co-morbid obesity and sleep apnoea<br>368. The five deaths in adults aged 26–40 were pulmonary embolism with type 1 diabetes, hypertensive heart disease with diabetes and obesity, pulmonary heart disease, chronic respiratory failure associated with obesity and one death caused by an acute pancreatitis in a person with sleep apnoea, primary pulmonary hypertension and congestive heart failure | • Hospital registry |
| Whittington 2015 | - Design: retrospective study<br>- Funding: Health Foundation and the National Institute for Health Research (NIHR) Collaborations in Leadership for Applied Health Research and Care (CLAHRC) for the East of England; CoI: none<br>- Setting: UK<br>- Sample size: N=62<br>- Duration: 1998-2009 | 260. Eligibility criteria: patients diagnosed with PWS<br>261. *A priori* patient characteristics:<br>a. Not reported | Age of death:<br>369. Narratively reported with few details on exact ages<br><br>Cause of death: N=7<br>370. Not reported | • 20 patients untraced |

## Rett syndrome

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| Freilinger 2010 | - Design: retrospective study<br>- Funding: not reported; CoI: not reported<br>- Setting: Australia<br>- Sample size: N=332<br>- Duration: 1976-2008 | 262. Eligibility criteria: patients with Rett syndrome<br>263. *A priori* patient characteristics:<br>a. Age at entry: 11 months to 24 years 7.2 months | Age of death:<br>371. Historical cohort: median 13y 4.8 mo, mean 15y 6mo<br>372. Australian cohort: mean 16y 7.2mo; median 16y 9.6mo | • Comparison with historical Austrian cohort (N=22)<br>• Population-based |

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| | | | Cause of death:<br>373. Historical cohort (N=19): 7 known; pneumonia in two; heart failure in two; and gastric ulcer, status epilepticus, and death in the context of a chronic disease in one each<br>374. Australian cohort (N=40): aspiration in 11 (27.5%), respiratory infection in 10 (25%), respiratory failure in three (7.5%), and related to seizures in three (7.5%); other reported single causes included haemorrhagic stroke, cardiogenic shock, feeding disorder, asphyxiation, and in the course of palliative care | |
| Kirby 2010 | - Design: retrospective study<br>- Funding: NIH grants (RR019478), MRRC grant (HD38985), funds from International Rett Syndrome Association and Civitan International Research Center; CoI: none<br>- Setting: US & Canada<br>- Sample size: N=1928<br>- Duration: unclear | 264. Eligibility criteria: patients with Rett syndrome<br>265. *A priori* patient characteristics:<br>a. Not reported | Age of death:<br>375. 1-5y: N=24 (8%)<br>376. 5-10y: N=45 (15%)<br>377. 10-20y: N=119 (40%)<br>378. 20-30y: N=62 (21%)<br>379. 30-40y: N=34 (12%)<br>380. 40-50y: N=8 (3%)<br>381. 50+: N=3 (1%)<br><br>Cause of death: N=305 (15.8%)<br>382. Not reported | • Recruitment through mailing of IRSA members (response rate 52%), consultation of two patient databases and the Canadian RTT database |
| Sarajllija 2015 | - Design: retrospective study<br>- Funding: grant from the Ministry of Science and Technology, Republic of Serbia (project no. 175087); CoI: none<br>- Setting: Serbia<br>- Sample size: N=102<br>- Duration: 1981-2012 | 266. Eligibility criteria: patients with Rett syndrome<br>267. *A priori* patient characteristics:<br>a. Mean age at diagnosis: 3.5y | Age of death:<br>383. Median: 13y (range 4-24)<br><br>Cause of death: N=19<br>384. Pneumonia: 57.9%<br>385. Chronic respiratory insufficiency: 2nd most common<br>386. Sudden death: N=3 | • Population-based |
| Tarquinio 2015 | - Design: retrospective study<br>- Funding: International Rett Syndrome Association and Civitan International Research Center, NIH grants (RR019478); CoI: none<br>- Setting: multicentre, US<br>- Sample size: N=1189<br>- Duration: 2006-2015; median follow-up 7y | 268. Eligibility criteria: patients with Rett syndrome<br>269. *A priori* patient characteristics:<br>a. Male: 4.2% | Age of death:<br>387. Range: 3.9 – 66.6y<br><br>Cause of death: N=51<br>388. Respiratory: N=9<br>389. Postoperative complications: N=5<br>390. Epilepsy: N=4<br>391. Infection: N=4<br>392. Other: N=2<br>393. Unknown: N=27 | • Diagnosis could not be verified in 14/1205 patients |

Tuberous sclerosis

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| Amin 2017 | - Design: retrospective study<br>- Funding: not reported; CoI: none | 270. Eligibility criteria: patients with a definite diagnosis of tuberous sclerosis complex | Age of death:<br>394. Median: 33y (IQR 26-46) | • Unclear selection bias |

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| | - Setting: specialist supra-regional clinic, UK<br>- Sample size: N=284<br>- Duration: 1981-2015; median follow-up 8y | 271. *A priori* patient characteristics:<br>a. Learning disabilities: 52% | Cause of death: N=18<br>395. Not attributable to TSC: N=2<br>396. Renal causes: N=8; chronic kidney failure N=3, haemorrhage from renal angiomyolipomas N=3, renal cell carcinoma N=2<br>397. Sudden unexplained death in epilepsy (SUDEP): N=4<br>398. Pulmonary lymphangioleiomyomatosis: N=2<br>399. Metastatic non-secreting neuroendocrine pancreatic tumour: N=1<br>400. Subependymal giant cell astrocytoma: N=1 | |

Williams syndrome

| Study ID | Methods | Patient characteristics | Results | Critical appraisal of study quality |
|---|---|---|---|---|
| Collins 2010 | - Design: retrospective study<br>- Funding: not reported; CoI: not reported<br>- Setting: Children's hospital, US<br>- Sample size: N=270<br>- Duration: 1980-2007; mean follow-up 8.9y | 272. Eligibility criteria: patients with the diagnosis of WS who were evaluated at the Children's Hospital of Philadelphia<br>273. *A priori* patient characteristics:<br>a. Female: 50.4%<br>b. Mean age at initial evaluation: 3.3y<br>c. Mean age at diagnosis: 4.9y<br>d. Cardiovascular abnormalities: 82% | Age of death:<br>401. Range: 145 days – 50y<br><br>Cause of death: N=8<br>402. Severe SVAS and PPS: N=2<br>403. Pulmonary hypertension: N=1<br>404. Sudden death: N=3<br>405. Peroperatively: N=1<br>406. Subdural hematoma due to fall: N=1 | • Unclear selection bias |

Abbreviations: 95%CI: 95% confidence interval; CHD: congenital heart disease; CNS: central nervous system; CoI: conflict of interest; CV: cardiovascular; DS: Down Syndrome; FXS: fragile-X syndrome; GERD: gastro-esofageal reflux disease; GI: gastrointestinal; HR: hazard ratio; ICD: International Classification of Diseases; IQR: interquartile range; MPNST: malignant peripheral nerve sheet tumour; NF1: neurofibromatosis 1; NS: Noona syndromeOR: odds ratio; ORL: oto-rhino-laryngeal; PPS: peripheral pulmonary stenosis; PWS: Prader-Willi syndrome; RR: relative risk; SD: standard deviation; SE: standard error; SVAS: supravalvar aortic stenosis.