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Non-blanchable erythema for predicting pressure ulcer development: a systematic review with an individual participant data meta-analysis

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Conflict of interest

The authors declare that they have no competing interests.

What's already known about this topic?

- Pressure ulcer reduction is a high priority for healthcare systems. Regularly inspecting skin to identify skin abnormalities is one key practice of preventing ulceration.
- Non-blanchable erythema – the discolouration of the skin that does not turn white when pressed – is one of clinically important skin abnormalities.
- Empirical evidence synthesised using conventional meta-analysis is uncertain regarding the value of non-blanchable erythema for predicting open pressure ulcer incidence partly because the conventional technique has weakness in terms of pooling prognosis effects of different multivariable analyses across studies.

What does this study add?

- The prognostic factor review – using individual-level data analysis to overcome the limitation of conventional meta-analysis technique – for the first time adds confirmatory and moderate-certainty evidence on the association of non-blanchable erythema with pressure ulcer incidence to current evidence base.
- People with non-blanchable erythema are more likely to develop new pressure ulcers of Stage 2 or severe within 28 days than people without non-blanchable erythema regardless of their age, baseline pressure ulcer risk or received support surfaces.

Non-blanchable erythema for predicting pressure ulcer development: a systematic review with an individual participant data meta-analysis

Abstract

Background: Empirical evidence is uncertain regarding the value of non-blanchable erythema in predicting Stage 2 (or more severe) pressure ulcer incidence. We aimed to investigate whether non-blanchable erythema is an independent prognostic factor for pressure ulcer incidence using individual patient data.

Methods: We performed an electronic database search in February 2017 to identify longitudinal studies that considered non-blanchable erythema for predicting pressure ulcer risk in any population. We collected individual participant data for the included studies, and assessed risk of bias of these studies using the Quality In Prognosis Studies tool. We analysed individual participant data in STATA using mixed-effects logistic regression for investigating the association of our interest. The certainty of evidence from individual participant data analysis was assessed using the Grades of Recommendation Assessment, Development and Evaluation.

Results: Of the thirteen included studies (68,077 participants), we had access to individual participant data from four ($n = 3,223$) and 11.88% of participants ($383/3,223$) developed new pressure ulcers of Stage 2 or above within 28 days. Mixed-effects logistic regression showed that participants with non-blanchable erythema had higher odds of developing new pressure ulcers of Stage 2 or above within 28 days of follow-up than those without non-blanchable erythema (multivariable association: $n = 2,684$; OR 2.72, 95% CI 2.02 to 3.69; tau-squared = 0; *moderate-certainty evidence*).

Conclusions: The first prognostic factor review with individual-level data analysis in pressure ulcers suggests people with non-blanchable erythema are more likely to develop new pressure ulcers of Stage 2 or above within 28 days than people without non-blanchable erythema. It is important to identify non-blanchable erythema in practice and intervene appropriately to prevent pressure ulceration.

Registration: PROSPERO (CRD42017081151)

Keywords

Pressure ulcer, non-blanchable erythema, prognostic factor review, individual participant data analysis

Introduction

Pressure ulcers (also known as pressure injuries, and decubitus ulcers) are localised injuries to skin and underlying tissue,¹ primarily caused by pressure or shear on the skin. Pressure ulcers are prevalent in approximately 3.1 per 10,000 people in the general United Kingdom (UK) population,² and in between 470 and 3,210 per 10,000 hospitalised patients in the UK, United States, and Canada.³

Non-blanchable erythema (i.e. Stage 1 ulcer) is intact skin with intractable redness in a localised area, and is conventionally regarded as an early sign of pressure ulceration.¹ From a pathophysiological perspective, the superficial damage of non-blanchable erythema—if continuously exposed to pressure and/or shearing forces—may deteriorate until the occurrence of open (Stage 2 or worse) pressure ulcers that affect underlying tissues.⁴

Non-blanchable erythema is reversible,¹ thus not all individuals with non-blanchable erythema will necessarily develop an open pressure ulcer. Conversely since some pressure ulceration starts with abnormalities of the deep tissue rather than superficial skin⁴ not all ulcers will be preceded by non-blanchable erythema. Empirical evidence is uncertain on the association of non-blanchable erythema with pressure ulcer incidence.⁵ In this review, we aimed to investigate whether non-blanchable erythema is an independent prognostic factor for pressure ulcer incidence using individual participant data analysis.

Methods

This review, prospectively registered with PROSPERO (CRD42017081151), follows the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) reporting guidance.⁶

Eligibility criteria

Eligible studies were prospective and retrospective longitudinal studies that applied multivariable analysis to evaluate the independent effects of multiple factors on pressure ulcer incidence in any population.⁷ Because multiple prognostic factors may be associated with pressure ulcer incidence,⁸ we excluded studies that considered non-blanchable erythema as the sole prognostic factor (univariable analysis).

Search strategy

Using comprehensive search strategies that combined terms for pressure ulcer⁹ with published prognosis study search filters,¹⁰⁻¹³ we searched Ovid MEDLINE and EBSCO CINAHL Plus in 14th February 2017 without any restriction. We also searched ProQuest for relevant doctoral theses and screened the reference lists of eight relevant systematic reviews,^{8,14-20} as well as of potentially eligible studies.

Study selection

The titles and abstracts of all citations were screened by two reviewers independently. One reviewer then inspected the full texts of all potentially eligible studies and a second reviewer independently judged the eligibility of 10% of the potentially eligible studies (random sample). Disagreements were resolved by discussion between two reviewers and involvement of a third reviewer if necessary.

Data collection

We requested anonymised individual participant data for all eligible studies via e-mail with corresponding authors. Individual participant data at baseline were requested for the factors that (1) were reported to have possible associations with pressure ulcer incidence in literature; (2) can be easily obtainable in practice; (3) and can fit the conceptual frameworks of pressure ulcer development.²¹⁻²³ See Appendix file 1 for the list of these factors.

Received data were combined into a single data set; where necessary, data were cleaned following suggestions of Schmid.²⁴ For example, we imputed data for “the use of support surfaces” factor: if the use of support surfaces was described in study reports (e.g., an example case: all participants used

higher-specification foam mattress or gel mattress), all individuals were imputed to have used the named support surfaces. We also extracted study-level data from included papers using a pre-specified data extraction form as we reported in the paper related to this review.⁵

Risk of bias assessment

We undertook risk of bias assessment using the adapted Quality In Prognosis Studies (QUIPS) tool (see Appendix file 2 Table S1).²⁵ Each risk of bias domain was judged as low, unclear or high risk of bias by one reviewer.²⁵ A second reviewer checked all assessments independently. Any discrepancy between two reviewers was resolved by discussion and a third reviewer was involved where necessary.

Data synthesis

Methods for individual participant data analysis

We described the characteristics of participants using appropriate descriptive statistics (mean and standard deviation (SD), or number and percentage) and did exploratory tests (t test, ANOVA and chi-squared test) where necessary (1) to evaluate whether the data of each variable, where reported, were distributed similarly between the studies with individual-level data and those with aggregate data; and (2) to evaluate if potential clinical heterogeneity existed in individual participant data analysis through comparing the data distribution for each variable between the studies with individual-level data.

Using one-stage individual participant data meta-analysis, we performed the following mixed-effects models where random intercepts were assumed to account for clustering: (1) including non-blanchable erythema only in a univariable random coefficients logistic regression to evaluate the univariable association; (2) including non-blanchable erythema and other factors (those with more than 80% of data across studies²⁶ but not correlated with others²⁷) to perform a multivariable random coefficients logistic regression.²⁸ All factors selected above were included in the multivariable model without any elimination.²⁹ Of the included factors, non-blanchable erythema was assumed to have random-effects across studies, whilst other factors were assumed to have fixed-effects; continuous

factors were transformed via restricted cubic splines to consider the potential non-linear relationships between them and pressure ulcer incidence.²⁷ We used an unstructured covariance matrix in the modelling.³⁰

We performed the main analysis based on complete cases. In the case of missing data, we applied multiple imputation using chained equations (MICE)–with ten imputations in a sensitivity analysis.³¹

As for missing data at the study level, i.e., where a study did not collect data on specific factors, we pooled only studies with available data on specific factors because available imputation methods are still under development and not widely applied.^{32,33}

All analyses were conducted using STATA (Version 14.0, StataCorp, College Station, Texas). Odds ratios (ORs) and 95% confidence intervals (CIs) were presented for the pooled results. A significance level of (two-sided p -value) 0.05 was used. For continuous factors that were transformed with restricted cubic spline, we present the post-estimation results for some selected values of each factor and display the non-linear relationships graphically. The Grades of Recommendation Assessment, Development and Evaluation (GRADE) was used to assess the certainty of evidence from the individual participant data meta-analysis.³⁴

We performed pre-planned additional analyses (see Appendix file 3): (1) analyses to investigate the interaction effects of three potential confounders (age,³⁵ baseline pressure ulcer risk,^{36,37} and the use of support surfaces²²) in multivariable model; (2) one sensitivity analysis to explore the impact of follow-up duration and another to explore the impact of missing data. We also assessed publication bias.

Methods for aggregate data meta-analysis

We used generic inverse variance meta-analysis with a random-effects model to pool the aggregate data (ORs and variances) across studies. We then compared aggregate data analysis with individual participant data analysis to examine the consistency of both analysis results.

Results

Characteristics of included studies

Of 6,908 records identified through literature search, we included 13 studies (associated with 16 publications) in this review³⁸⁻⁵³ (see Fig. 1).

See Appendix file 4: Table 2 for the characteristics of these studies. Of the thirteen included studies, ten were conducted in hospital settings and three were in nursing homes/long-term facilities.⁴⁴⁻⁴⁶ The thirteen studies involved 68,077 participants. Individual-level data for 64,757 participants from eight studies were unavailable (for reasons provided in Fig. 1); Of these eight studies with data unavailable, three (involving a majority of participants included in this review, $n = 59,214$) applied American population healthcare data registries as data sources⁴³⁻⁴⁶ where data were not collected specifically for any research and were not expected to be available due to legitimate issue. The authors of five studies ($n = 3,320$) agreed to share their individual participant datasets, of which four ($n = 3,223$) could be used in the subsequent analyses in this review^{40,41,47-49,51,52} because one data set was not transferred.³⁸

Table 1 shows the characteristics of participants in each study and across the four studies. The mean (SD) age of 3,223 participants was 75.35 (11.94) years, which did not differ significantly from the mean age of participants in the unavailable studies (73.96, SD 12.79) (t test p-value = 0.23). Of the 3,223 participants, 62.27% were female (2,007), which was higher than the proportion of females (31.21%) in the studies without available individual participant data (chi-squared test p-value < 0.001).

Table 1: The characteristics of participants within and across the included studies

At baseline, 22.12% of participants (713/3,223) had non-blanchable erythema; among 98.45% of participants (3,173/3,223) with baseline Braden scores, 87.61% (2,780/3,173) were judged at risk of developing pressure ulcers with a Braden score ≤ 18 as the criterion of being 'at risk'. The incidence of new pressure ulcers of Stage 2 or above within 28 days of follow-up was 11.88% (383/3,223). The stage of ulcers was specified in 51.13% of participants (192/383) with incident ulcers; 97.39%

(187/192) were Stage 2 ulcers and 2.60% (5/192) were Stage 3. When participants with incident ulcers beyond 28 days were counted, 12.47% (417/3,223) developed a new pressure ulcer of Stage 2 or above at any time.

Risk of bias assessment

The four studies with individual participant data were judged as low risk of bias for all domains^{40,41,47,48} or as unclear risk of bias for one domain.^{49,51,52} See Figure 2 for all risk of bias assessments.

Individual participant data analyses

For the univariable association, mixed-effects logistic regression involving non-blanchable erythema alone showed that participants with non-blanchable erythema had 3.52 times the odds of developing new pressure ulcers of Stage 2 or above within 28 days compared with those without non-blanchable erythema (random coefficients model: n = 3,223; OR 3.52, 95% CI 2.72 to 4.56; tau-squared = 0; see Table 2). This evidence is *low-certainty*, downgraded twice for strongly suspected publication bias, but upgraded once for a moderate effect size. This means that if we assume 77 people per 1,000 without non-blanchable erythema develop new pressure ulcers of Stage 2 or above within 28 days, 227 people per 1,000 (95% CI 185 to 275) with non-blanchable erythema might be expected to develop new ulcers.

Table 2: Results of univariable and multivariable multilevel analyses using complete cases and imputed data

In the multivariable model including non-blanchable erythema, and nine additional variables, participants with non-blanchable erythema had 2.72 times the odds of developing a new pressure ulcer of Stage 2 or above within 28 days compared with those without non-blanchable erythema (random coefficients model: n = 2,684; OR 2.72, 95% CI 2.02 to 3.69; tau-squared = 0; see Table 2). This evidence is *moderate-certainty*, downgraded twice for strongly suspected publication bias and upgraded once for a moderate effect size and once for plausible confounding. This suggests that if we assume 73 people per 1,000 without non-blanchable erythema develop new pressure ulcers of Stage 2

or above within 28 days, 176 people per 1,000 (95% CI 137 to 225) *with* non-blanchable erythema will probably develop new ulcers.

Estimation of effect modifications (interactions)

None of the three pre-planned interactions showed statistically significant results, meaning that participants with non-blanchable erythema had higher pressure ulcer risk than those without non-blanchable erythema regardless of their age, Braden scores or received support surfaces (see Appendix files 8-10: Figs S4 to S6).

Sensitivity analyses

Appendix file 11 Table S3 suggested that ignoring the missing data (539/3,223) might result in bias. The analysis with ten multivariable imputations of missing data was conducted, suggesting a significant multivariable association of non-blanchable erythema and pressure ulcer incidence (n = 3,183; OR 2.70, 95% CI 2.08 to 3.52). Another sensitivity analysis using data on pressure ulcers of Stage 2 or above at any time also showed a significant association of non-blanchable erythema and pressure ulcer incidence (n = 2,684; OR 2.77, 95% CI 2.05 to 3.75).

Publication bias

The literature search was comprehensive. We did not produce a funnel plot to for excluding the possibility of publication bias because only four data sets (the small volume of individual participant data: 4.73%, 3,223/68,077) were included in the analysis.

Aggregate data meta-analyses compared with individual participant data analyses

For univariable association, meta-analysis using aggregate data from three studies without individual participant data^{38,39,50} suggested that non-blanchable erythema was associated with increased odds of pressure ulcer incidence (random-effects model: n = 4,485; OR = 5.12, 95% CI 3.21 to 8.17; $I^2 = 67.6\%$).

For multivariable association, meta-analysis with aggregate data from six studies without individual participant data^{42,44-46,50,53} showed that participants with non-blanchable erythema had 2.23 times higher the odds of developing new pressure ulcers than those without non-blanchable erythema

(random-effects model: $n = 62,718$; OR 2.23, 95% CI 2.02 to 2.46; $I^2 = 75.7\%$). Both above meta-analyses are consistent with the corresponding individual participant data analyses.

Discussion

Main findings

We have conducted this review with meta-analysis of individual participant data ($n = 3,223$) to summarise the evidence on the prognostic value of non-blanchable erythema for predicting pressure ulcer development. *Moderate-certainty* evidence from multivariable analysis suggests that 103 more people with non-blanchable erythema (95% CI 64 to 152 more) per 1,000 will probably develop new pressure ulcers of Stage 2 or above within 28 days than those without non-blanchable erythema. Non-blanchable erythema will be predictive for pressure ulcer incidence without any distinction between older and younger participants, between lower and higher Braden scores and between active air mattress use and reactive mattress use. Given the characteristics of participants whose data were available for analysis, evidence in this review is expected to be applicable for older—particularly female—inpatients.

Comparison with previous reviews

We could not identify any previous systematic review quantifying the prognostic association of non-blanchable erythema and pressure ulcer incidence, except for a systematic review we have published.⁵ Our previous review pooled study-level data to investigate the prognostic associations of 15 skin status descriptors (including non-blanchable erythema) and pressure ulcer incidence. For non-blanchable erythema, meta-analysis of multivariable data from nine studies suggested substantial heterogeneity ($I^2 = 72.1\%$) that was not explained by sub-group analyses of study-level characteristics. Mainly due to, for example, the use of different sets of covariates across multivariable analyses of included studies, such a heterogeneity cannot be tackled via, for example, sub-group analysis technique related to aggregate data meta-analysis.⁵ The previous review concluded with low-certainty evidence on the association of our interest, leaving considerable uncertainty. Our new study using individual participant data analysis adds important confirmatory evidence: firstly, evidence

from individual participant data is more certain than evidence from aggregate data, which may be because individual participant data analysis (adjusting for the same set of covariates across studies) has a lower heterogeneity ($\tau^2 = 0$) than the aggregate data analysis. Secondly, non-significant findings of all interaction effects confirm the prognostic value of non-blanchable erythema for pressure ulcer development in different patient populations.

Strengths and limitations of this review and analysis

The first strength of this review is the application of individual participant data analysis to help overcome the issues of heterogeneity and incomplete reporting of multivariable results that occurred in the aggregate data meta-analysis.^{5,54} Using individual participant data allows us to use a consistent set of factors for adjustment of the prognostic effect and to examine non-linear relationships and interactions between factors.⁵⁴ The second strength is the application of optimal evidence synthesis methods, e.g., a comprehensive literature search, the use of the QUIPS tool for risk of bias assessment.

The individual participant data analysis has some limitations. Firstly, it is difficult to know all factors that are associated with pressure ulcer incidence, thus it is unclear if we have factor selection bias in this work. To minimise the risk of such selection bias, we considered existing research evidence on specific prognostic factors of pressure ulcer incidence,⁸ the availability of factors in clinical practice, and the conceptual frameworks of pressure ulceration²¹⁻²³ to determine the factors on which we requested data. Additionally we have to acknowledge that challenges exist in defining and retrieving potentially eligible types of studies for this review. Longitudinal studies should have been eligible regardless of univariate or multivariable analyses applied. However, given multiple factors are regarded to be contributory for pressure ulcer development, we reasonably required that eligible studies include multiple variables (including non-blanchable erythema). Studies using multivariable analysis can be prone to meet this requirement and have established approaches to retrieve them. If studies with univariate analysis were considered too, it can be expected the review and analysis could be extremely unmanageable and it is difficult to retrieve such studies. In order to avoid further bias, the eligibility of studies with multivariable analysis was pre-specified in our registered protocol.

Secondly, due to reasons beyond our control, only a small portion of individual participant data were obtained in this analysis which might lead to biased prognostic results.⁵⁵ One solution to tackle this problem is deriving aggregate data using individual participant data and then simply pooling them and aggregate data extracted from the studies without individual participant data available.⁵⁵ This strategy was not followed because it has to synthesise both derived and extracted aggregate data using two-stage approach. As a result, it shares the same issue of heterogeneity as the previous aggregate data meta-analysis,⁵ and disables the advantage of one-stage individual participant data analysis in terms of investigating heterogeneity.⁵⁴ To improve this situation, we planned to re-construct individual-level data from aggregate level data where possible using the method suggested by Riley and Steyerberg.⁵⁶ For example, if a study reported a contingency table that grouped the numbers of cases with or without non-blanchable erythema by pressure ulcer incidence, individual-level data can be re-constructed. However, this was not performed due to the incomplete reporting of aggregate data. Nonetheless, we applied two approaches to assess whether the results of individual participant data analysis based on part of eligible participants are trustworthy. (1) We checked the agreement regarding the characteristics between 3,223 participants and all 68,077 eligible participants; and exploratory analysis suggests participants with available data are generally representative for all participants. (2) We avoided ignoring the eight studies in which individual participant data are unavailable through assessing whether the results of the individual participant data analysis and the aggregate data meta-analysis of the eight studies are consistent. The consistency we found means that the unavailability of some data might not be a serious concern in this review. However, the potential for bias was acknowledged by our downgrading of the certainty of evidence due to possible publication bias.

Thirdly, ideally we would have implemented a single model to simultaneously address the issues of continuous and missing data under the framework of mixed-effects modelling using STATA. Morris et al.⁵⁷ proposed a possible single model approach that employs a multiple fractional polynomial technique to handle continuous data and multiple imputation technique for missing data, but it does not support mixed-effects modelling. In this review, we used two stages to address the above issues:

employing a restricted cubic spline method to identify non-linear terms of a continuous factor, and then, using MICE to impute missing data. The strategy was used in deriving the QRISK tool,⁵⁸ and was considered as a practical alternative. In terms of addressing missing data at the study level, we decided to use complete case analysis in this review, that is, analysing only studies with full individual participant data on all variables (termed fully adjusted method) because other existing techniques are regarded inappropriate in the case of this review. One simple technique includes all studies in analysis but removes those variables without individual participant data available (termed partially adjusted method). As a result, variables of interest may lose part of the data, thus producing imprecise estimates. A technique, as the combination of fully and partially adjusted methods, has only been evaluated with two-stage analysis approach.³³ A multiple imputation method includes all studies and adjusts for all variables. This method seems to be appropriate, however, it has only been evaluated for systematically imputing missing data for continuous variables.³²

Implications for current practice and future research

Strong confirmatory evidence we produced in this review suggests that once erythema occurs in practice, care practitioners should confirm whether it is non-blanchable or blanchable. Once non-blanchable erythema is identified, people are probably at higher risk of developing new pressure ulcers and appropriate preventive measures should be provided in time to deter the progression towards a more severe pressure ulcer.⁵⁹ As well as being of clinical importance, findings from this review highlight that non-blanchable erythema should be considered as an important prognostic factor in future prognostic models for pressure ulcer prediction.⁶⁰ However, this evidence is based on clinical studies with high degrees of standardisation. Correctly identifying non-blanchable erythema in clinical practice is still a major challenge, for example, with low reliability as numerous studies suggest^{61,62}. Future research can assess the reliability of potential methods (e.g., use of transparent disk, or finger test approach) used for measuring non-blanchable erythema.

The evidence in this review is largely applicable for predicting Stage 2 pressure ulcers because only a small proportion of participants in the studies included here (2.60%, 5/192) developed Stage 3 ulcers. Given that Stage 3 and 4 ulcers may have different pathophysiological pathways from Stage 2 ulcers,⁴

future research should investigate whether non-blanchable erythema is predictive for ulcers of Stage 3 or above.

Conclusions

There is moderate-certainty evidence that people with non-blanchable erythema have more than twice the odds of developing new pressure ulcers of Stage 2 or above within 28 days than people without non-blanchable erythema regardless of their age, baseline pressure ulcer risk (Braden scores) or received support surfaces. This review offers empirical evidence to favour the *React to Red Skin* campaign – a campaign aiming to educate people in the community with simple knowledge about erythema for pressure ulcer prevention.⁶³

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Supporting Information

Appendix file 1: The list of factors that individual-level data were requested

Appendix file 2: Table S1. The adapted Quality In Prognosis Studies (QUIPS) tool

Appendix file 3: Methods of additional analyses

Appendix file 4: Table S2. Characteristics of included studies

Appendix file 5: Figure S1. The scatter plots of the estimated odds ratios with 95% confidence intervals for age in years showing a non-linear relationship

Appendix file 6: Figure S2. The scatter plot of the estimated odds ratios with 95% confidence intervals for BMI in kg/m² showing a non-linear relationship

Appendix file 7: Figure S3. The scatter plot of the estimated odds ratios with 95% confidence intervals for Braden scores showing a non-linear relationship

Appendix file 8: Figure S4. Interaction plot of non-blanchable erythema and the ten categories of age

Appendix file 9: Figure S5. Interaction plot of non-blanchable erythema and the ten categories of Braden scores

Appendix file 10: Figure S6. Interaction plot of non-blanchable erythema and mattress types

Appendix file 11: Table S3. Comparisons of data on the included variables in the model between complete cases and cases with any missing values

Figure legends

Figure 1: Flow chart of study selection

Figure 2: Risk of bias assessment

Table legends

Table 1: The characteristics of participants within and across the included studies

Factors *	Demarre et al. ^{47,48} (n = 610)	Molon and Estrella ⁴⁹ (n = 40)	Nixon et al. ^{40,41} (n = 1,971)	Smith et al. ^{51,52} (n = 602)	Overall (n = 3,223)
Number of participants with incident pressure ulcers within 28 days – no. (%)	35 (5.74%)	7 (17.50%)	192 (9.74%)	149 (24.75%)	383 (11.88%)
Number of participants with incident pressure ulcers at any time – no. (%)	35 (5.74%)	8 (20.00%)	207 (10.50%)	152 (25.25%)	402 (12.47%)
Non-blanchable erythema – no. (%)	94 (15.41%)	4 (10.00%)	325 (16.49%)	290 (48.17%)	713 (22.12%)
Age (years) – mean (SD)	76.33 (14.00)	38.93 (16.38)	75.19 (9.46)	77.34 (12.73)	75.36 (11.94)
Missing	0	0	0	0	0
Sex – no. (%)					
Male	241 (39.51%)	31 (77.50%)	711 (36.07%)	233 (38.70%)	1,216 (37.73%)
Female	369 (60.49%)	9 (22.50%)	1,260 (63.93%)	369 (61.30%)	2,007 (62.27%)

Missing	0	0	0	0	
Weight (kg) – mean (SD)	65.81 (15.28)	59.52 (11.01)	70.52 (16.21)	73.88 (27.92)	70.08 (19.05)
Missing	0	0	185 (9.39%)	15 (2.49%)	200 (6.21%)
Weight loss – no. (%)					
No	214 (35.08%)	NA	1,785 (90.56%)	454 (75.41%)	2,453 (76.11%)
Yes	183 (30.00%)	NA	170 (8.63%)	147 (24.42%)	500 (15.51%)
Missing	213 (34.92%)	40	16 (0.81%)	1 (0.17%)	270 (8.38%)
Height (cm) – mean (SD)	165.77 (9.54)	164.2 (6.78)	165.26 (9.20)	166.23 (10.60)	165.52 (9.52)
Missing	0		45 (2.28%)	15 (2.49%)	60 (1.86%)
Body mass index (kg/cm ²) – mean (SD)	23.83 (4.65)	22.09 (3.98)	25.76 (5.22)	26.71 (9.50)	25.50 (6.25)
Missing	0	0	210 (10.65%)	24 (3.99%)	234 (7.26%)
Other skin problems (yes/no) – no. (%)					
Yes	39 (6.39%)	10 (25.00%)	229 (11.62%)	127 (21.09%)	405 (12.57%)
No	571 (93.61%)	30 (75.00%)	1,742 (88.38%)	474 (78.74%)	2,817 (87.40%)
Missing	0	0	0	1 (0.17%)	1 (0.03%)

Current pressure ulcers at Stage 2 or above – no. (%)					
Yes	0	0	113 (5.73%)	164 (27.24%)	277 (8.59%)
No	610 (100%)	40 (100%)	1,858 (94.27%)	438 (72.76%)	2,946 (91.41%)
Missing	0	0	0	0	0
Braden mobility – no. (%)					
Completely immobile	87 (14.26%)	1 (2.50%)	362 (18.37%)	21 (3.49%)	471 (14.61%)
Very limited	421 (69.02%)	7 (17.50%)	1,342 (68.09%)	262 (43.52%)	2,032 (63.05%)
Slightly limited	87 (14.26%)	26 (65.00%)	102 (5.17%)	231 (38.37%)	446 (13.84%)
No limitations	1 (0.16%)	6 (15.00%)	114 (5.78%)	88 (14.62%)	209 (6.48%)
Missing	14 (2.30%)	0	51 (2.59%)	0	65 (2.02%)
Braden activity – no. (%)					
Bedfast	165 (27.05%)	31 (77.50%)	1,558 (79.05%)	104 (17.28%)	1,858 (57.65%)
Chairfast	366 (60.00%)	6 (15.00%)	211 (10.70%)	313 (51.99%)	896 (27.80%)
Walks occasionally	65 (10.66%)	3 (7.50%)	51 (2.59%)	157 (26.08%)	276 (8.56%)
Walks frequently	1 (0.16%)	0	101 (5.12%)	28 (4.65%)	130 (4.03%)
Missing	13 (2.13%)	0	50 (2.54%)	0	63 (1.95%)

Braden friction – no. (%)					
Problem	248 (40.66%)	1 (2.50%)	1,176 (59.66%)	101 (16.78%)	1,526 (47.35%)
Potential problem	326 (53.44%)	10 (25.00%)	559 (28.36%)	413 (68.60%)	1,308 (40.58%)
No apparent problem	21 (3.44%)	29 (72.50%)	186 (9.44%)	88 (14.62%)	324 (10.05%)
Missing	15 (2.46%)	0	50 (2.54%)	0	65 (2.02%)
Braden total score – mean (SD)	13.30 (2.30)	17.78 (2.50)	13.63 (3.14)	17.17 (2.30)	14.29 (3.20)
Missing	0	0	50 (2.54%)	0	50 (1.55%)
Support surface use – no. (%)					
Standard mattress	0	40 (100%)	0	36 (5.98%)	76 (2.36%)
Reactive mattress	0	0	0	273 (45.35%)	273 (8.47%)
Active air mattress	610 (100%)	0	1,971 (100%)	292 (48.50%)	2,873 (89.14%)
Hybrid mattress	0	0	0	0	0
Missing	0	0	0	1 (0.17%)	1 (0.03%)
Diabetes – no. (%)					
Yes	135 (22.13%)	NR	190 (9.64%)	153 (25.41%)	478 (14.83%)
No	475 (77.87%)	NR	1,770 (89.80%)	448 (74.42%)	2,693 (83.56%)
Missing	0	40 (100%)	11 (0.56%)	1 (0.17%)	52 (1.61%)

Peripheral vascular disease – no. (%)					
Yes	76 (12.46%)	NR	NR	NR	76 (2.36%)
No	534 (87.54%)	NR	NR	NR	534 (16.57%)
Missing	0	40 (100%)	1,971 (100%)	602 (100%)	2,613 (81.07%)
If any surgery is underwent recently – no. (%)					
Yes	NR	23 (57.50%)	NR	NR	23 (0.71%)
No	NR	17 (42.50%)	NR	NR	17 (0.53%)
Missing	610 (100%)	0	1,971 (100%)	602 (100%)	3,183 (98.76%)

Notes: * Among the factors we requested, only factors with any available individual participant data are summarised in this table. Across the four studies, there were data for over 80% of participants on: non-blanchable erythema, age, body mass index, other skin problems, current pressure ulcer of Stage 2 or above, Braden scores, support surface use, weight loss, and diabetes. Skin problem is incontinence-associated dermatitis in Demarré et al.^{47,48}, dry skin in Molon and Estrella⁴⁹ and chronic wounds or others in Nixon et al.^{40,41} and Smith et al.^{51,52} Molon and Estrella⁴⁹ did not collect data on weight loss, diabetes, or mattresses, but the authors claimed that all participants used standard hospital mattress.

Table 2: Results of univariable and multivariable multilevel analyses using complete cases and imputed data *

Factors	Univariable analysis of complete cases – OR (95% CI)	Multivariable analysis of complete cases– OR (95% CI)	Multivariable analysis of imputed data (ten imputations) – OR (95% CI)	Multivariable analysis of the secondary outcome data – OR (95% CI)
Total number of sample	3,223	2,684	3,183 **	2,684
The primary outcome: number of participants with new pressure ulcers within 28 days – no. (%)	383 (11.88%)	315 (11.74%)	376 (11.81%)	Not applicable
The secondary outcome: number of participants with new pressure ulcers at any time – no. (%)	Not applicable	Not applicable	Not applicable	329 (12.26%)
Non-blanchable erythema				
No (Reference)	1	1	1	1
Yes	3.52 (95% CI 2.72 to 4.56) <i>Low-certainty evidence</i>	2.72 (95% CI 2.02 to 3.69) <i>Moderate-certainty evidence</i>	2.70 (95% CI 2.08 to 3.52)	2.77 (95% CI 2.05 to 3.75)
Other skin problems				
No (reference)		1	1	1

Yes		2.21 (95% CI 1.63 to 2.99)	2.00 (95% CI 1.51 to 2.66)	2.41 (95% CI 1.79 to 3.24)
Current pressure ulcers at Stage 2 or above				
No (reference)		1	1	1
Yes		1.70 (95% CI 1.19 to 2.42)	1.50 (95% CI 1.07 to 2.09)	1.62 (95% CI 1.14 to 2.30)
Support surface use				
Standard mattress (reference)		1	1	1
Reactive mattress		1.41 (95% CI 0.55 to 3.63)	1.50 (95% CI 0.60 to 3.77)	1.18 (95% CI 0.47 to 2.93)
Active air mattress		0.86 (95% CI 0.33 to 2.24)	0.95 (95% CI 0.37 to 2.43)	0.71 (95% CI 0.28 to 1.81)
Weight loss				
No (reference)		1	1	1
Yes		0.86 (95% CI 0.60 to 1.24)	0.90 (95% CI 0.65 to 1.26)	0.87 (95% CI 0.61 to 1.24)
Diabetes				
No (reference)		1	1	1
Yes		1.53 (95% CI 1.11 to 2.12)	1.53 (95% CI 1.13 to 2.07)	1.55 (95% CI 1.12 to 2.13)
Age (years) [¶]			Not estimable	
Age 50 (reference)		1		1

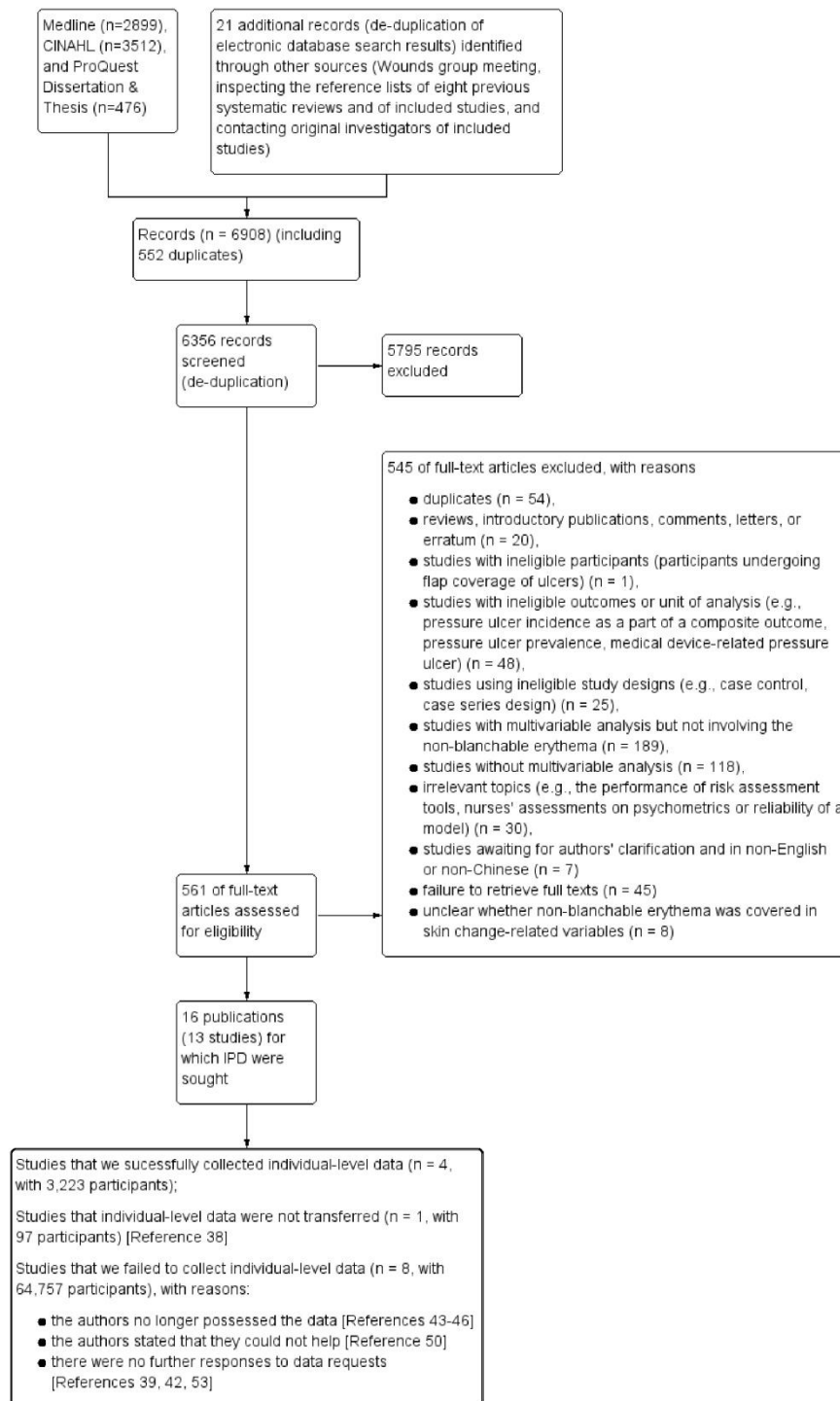
Age 55		1.01 (95% CI 0.80 to 1.28)		1.01 (95% CI 0.80 to 1.27)
Age 60		1.03 (95% CI 0.65 to 1.63)		1.02 (95% CI 0.65 to 1.61)
Age 65		1.10 (95% CI 0.60 to 2.04)		1.09 (95% CI 0.59 to 2.01)
Age 70		1.32 (95% CI 0.69 to 2.53)		1.30 (95% CI 0.69 to 2.48)
Age 75		1.75 (95% CI 0.92 to 3.32)		1.73 (95% CI 0.92 to 3.27)
Age 80		2.12 (95% CI 1.15 to 3.89)		2.15 (95% CI 1.17 to 3.94)
Age 85		2.25 (95% CI 1.20 to 4.22)		2.31 (95% CI 1.24 to 4.32)
Age 90		2.23 (95% CI 1.19 to 4.21)		2.24 (95% CI 1.20 to 4.21)
Age 95		2.19 (95% CI 1.04 to 4.58)		2.13 (95% CI 1.02 to 4.43)
Age 100		2.14 (95% CI 0.84 to 5.46)		2.01 (95% CI 0.80 to 5.10)
Body mass index (kg/cm ²) [¶]			Not estimable	
Body mass index 20 (reference)		1		1
Body mass index 22		0.98 (95% CI 0.86 to 1.11)		0.96 (95% CI 0.85 to 1.09)
Body mass index 24		0.92 (95% CI 0.67 to 1.26)		0.95 (95% CI 0.70 to 1.28)
Body mass index 26		0.86 (95% CI 0.59 to 1.26)		0.89 (95% CI 0.62 to 1.28)
Body mass index 28		0.82 (95% CI 0.59 to 1.15)		0.82 (95% CI 0.59 to 1.14)

Body mass index 30		0.81 (95% CI 0.57 to 1.15)		0.78 (95% CI 0.55 to 1.10)
Body mass index 32		0.81 (95% CI 0.56 to 1.18)		0.77 (95% CI 0.54 to 1.11)
Body mass index 34		0.83 (95% CI 0.58 to 1.21)		0.79 (95% CI 0.54 to 1.14)
Braden total score [¶]			Not estimable	
Score 23 (reference)		1		1
Score 6		0.85 (95% CI 0.17 to 4.21)		1.12 (95% CI 0.24 to 5.24)
Score 7		1.14 (95% CI 0.29 to 4.49)		1.49 (95% CI 0.40 to 5.59)
Score 8		1.55 (95% CI 0.49 to 4.91)		1.98 (95% CI 0.64 to 6.11)
Score 9		2.09 (95% CI 0.78 to 5.60)		2.63 (95% CI 0.99 to 6.96)
Score 10		2.82 (95% CI 1.17 to 6.80)		3.49 (95% CI 1.45 to 8.42)
Score 11		3.69 (95% CI 1.57 to 8.68)		4.49 (95% CI 1.90 to 10.60)
Score 12		3.99 (95% CI 1.71 to 9.29)		4.71 (95% CI 2.01 to 11.04)
Score 13		3.20 (95% CI 1.45 to 7.07)		3.62 (95% CI 1.63 to 8.05)
Score 14		2.39 (95% CI 1.09 to 5.24)		2.62 (95% CI 1.19 to 5.79)
Score 15		2.11 (95% CI 0.94 to 4.75)		2.31 (95% CI 1.02 to 5.25)
Score 16		2.05 (95% CI 0.87 to 4.87)		2.29 (95% CI 0.96 to 5.47)
Score 17		1.97 (95% CI 0.82 to 4.74)		2.21 (95% CI 0.91 to 5.35)

Score 18		1.82 (95% CI 0.80 to 4.16)		2.03 (95% CI 0.89 to 4.67)
Score 19		1.65 (95% CI 0.81 to 3.35)		1.81 (95% CI 0.88 to 3.70)
Score 20		1.46 (95% CI 0.84 to 2.54)		1.57 (95% CI 0.90 to 2.74)
Score 21		1.29 (95% CI 0.89 to 1.87)		1.36 (95% CI 0.93 to 1.97)
Score 22		1.14 (95% CI 0.94 to 1.37)		1.16 (95% CI 0.97 to 1.40)

Notes: * degree of freedom for all multivariable analyses = 19; ** All 40 cases in Molon and Estrella⁴⁹ were not included after imputed data analysis because data on weight loss and diabetes were not collected;

¶ Continuous data of age, body mass index, and Braden total score were modelled using the restricted cubic spline method; their odds ratios in the table were for some selected values of these continuous data, which was only for the purpose of presenting potential non-linear relationship (see Appendix files 5-7: Figs S1 to S3 for the graphical presentations of the results). For the imputed data analysis (i.e., the analysis in the third column of the table), the odds ratios for the selected values of the three continuous factors cannot be calculated using the current STATA package though restricted cubic splines of the three factors can be done in the analysis.



	Study participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Follow-up duration
Allman 1995 [42]	+	+	?	?	?	+
Anthony 2000 [43]	+	?	+	-	?	+
Berlowitz 1996 [44]	+	+	-	?	?	+
Berlowitz 2001 [45]	+	+	?	?	?	+
Berlowitz 2001 [46]	?	+	?	?	?	+
Demarre 2015 [47, 48]	+	+	+	+	+	+
Molon and Estrella 2011 [49]	+	+	+	?	+	+
Nixon 2006 [40, 41]	+	+	+	+	+	+
Nixon 2007 [38]	?	?	+	?	?	?
Reed 2003 [50]	+	+	?	?	-	+
Smith 2017 [51, 52]	+	+	+	?	+	+
Vanderwee 2005 [53]	+	+	+	?	?	?
Vanderwee 2007 [39]	+	+	+	?	?	?