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# Systematic review of factors associated with energy expenditure in the critically ill

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SUMMARY

*Background and aims:* Indirect calorimetry is the reference standard for energy expenditure measurement. Predictive formulae that replace it are inaccurate. Our aim was to review the patient and clinical factors associated with energy expenditure in critically ill patients.

*Methods:* We conducted a systematic review of the literature. Eligible studies were those reporting an evaluation of factors and energy expenditure. Energy expenditure and factor associations with p-values were extracted from each study, and each factor was classified as either significantly, indeterminantly, or not associated with energy expenditure. Regression coefficients were summarized as measures of central tendency and spread. Metanalysis was performed on correlations.

*Results:* The search strategy yielded 8521 unique articles, 307 underwent full text review, and 103 articles were included. Most studies were in adults. There were 95 factors with 352 evaluations. Minute volume, weight, age, % body surface area burn, sedation, post burn day, and caloric intake were significantly associated with energy expenditure. Heart rate, fraction of inspired oxygen, respiratory rate, respiratory disease diagnosis, positive end expiratory pressure, intensive care unit days, C- reactive protein, and size were not associated with energy expenditure. Multiple factors (n = 37) were identified with an unclear relationship with energy expenditure and require further evaluation.

*Conclusions:* An important interval step in the development of accurate formulae for energy expenditure estimation is a better understanding of relationships between patient and clinical factors and energy expenditure. The review highlights the limitations of currently available data, and identifies important factors that are not included in current prediction formulae of the critically ill.

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## 1. Introduction

Underfeeding and overfeeding of critically ill patients has been associated with adverse effects leading to significant morbidity and mortality and arises as a consequence of inaccurate estimation of energy needs in the critically ill [1–8].

Indirect calorimetry is the standard for energy expenditure (EE) measurement [9], however due to its limited availability, most intensive care units (ICU) continue to utilize predictive formulae for EE estimation [9–11]. EE is utilized at the bedside to guide the caloric prescription of critically ill neonates, children, and adults. In the lack of access to indirect calorimetry, predictive equations have been used as a surrogate although they have been demonstrated to be inaccurate in adults [12–14] and children [9,12,15–19]. This inaccuracy could be related to the poor representation of potentially important clinical factors and metabolism altering treatments in EE predictive equations of critically ill children, neonates, and adults [20–23]. Errors in energy estimation and caloric prescription in adults and children can have profound impact on intensive care and post ICU outcomes [2,4,6,7,24]. Accurate clinical prediction

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**Abbreviations**

| | |
|---|---|
| EE | energy expenditure |
| ICU | intensive care unit |
| IQR | interquartile range |
| SD | standard deviation |
| BSA | body surface area |
| ISS | injury severity score |
| GCS | Glasgow coma scale |
| PRISM | pediatric risk of mortality score |
| CRP | C- reactive protein |
| WBC | white blood cell |
| $FiO_2$ | fraction of inspired oxygen |
| PEEP | positive end expiratory pressure |
| APACHE | acute physiologic assessment and chronic health evaluation score |
| SAPS | simplified acute physiology score |
| $CO_2$ | carbon dioxide |
| $O_2$ | oxygen |

formulae should be based on robust understanding of factors influencing EE. The objective of this review was to summarize the factors that have an effect on EE in critically ill patients.

## 2. Methods

A systematic review of the literature was performed following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria for conducting and reporting systematic reviews [25]. Methods and eligibility criteria were prespecified and the protocol was registered on PROSPERO (registration number CRD42016046650).

### 2.1. Search strategy

A librarian conducted literature search was performed of articles published from 1946 until January 2, 2018 in the English language. The following databases were searched: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science. Initial keywords that were used included: Indirect calorimetry, calorimeter, energy or basal metabolism, EE, and oxygen consumption. The full set of search terms is available in the supplement (Supplemental Table 1).

### 2.2. Selection criteria

Eligible studies were included if they were peer-reviewed, published in an English language journal, and reported an evaluation of relationship between eligible clinical factors and the measurement of EE performed by indirect calorimetry (including Douglas bag) or doubly labelled water in patients with critical illness. Critical illness was defined as any illness requiring an admission to an intensive care unit. Eligible factors were measured at time of EE measurement and an association was reported with EE. Studies were excluded if they included non-critically ill patients whose results could not be separated from the critically ill, if EE was estimated using a formula, and where clinical factors were not described at the time the measurement was done. Case studies, narrative reviews, editorials, letters, commentaries, guidelines, or grey literature were excluded.

### 2.3. Study identification and confirmation of eligibility

Titles and abstracts were reviewed to determine study eligibility and need for full text review by two authors: HM and MJSA. In cases of disagreement, the abstract was reviewed by a third author CP and decision made on inclusion. Full texts were obtained, reviewed, and it was determined if they should be included or excluded. Data was extracted by one author: HM.

### 2.4. Risk of bias assessment

In the absence of a tool to assess risk of bias in included studies we included whether studies reported calibration of indirect calorimetry and a report of steady state as a reflection of the reliability of the measured EE. This descriptive step was added post-hoc after the registration of the study protocol.

### 2.5. Data management and analysis

Data abstracted from studies included: publication year, age groups studied as reported by authors and if not reported then classified as neonates if age <1 month, child 1 month−18 years, and adult >18 years, method and name of machine used for EE measurement, calibration description, whether steady state was described and achieved, EE units utilized, number of patients, number of measurements, patient diagnoses, types of respiratory support, and study design. Study design was categorized into prospective observational, prospective interventional, retrospective observational, and retrospective interventional study. Method for EE measurement was categorized into indirect calorimetry and doubly labelled water. If a calibration method was described then this was categorized as present, if not it was absent. Steady state was categorized as either described and achieved, described and not achieved, not described and not achieved. If the number of measurements of EE was not explicitly reported, it was assumed that the number of patients and measurements were equal.

EE and factor associations were extracted. Some factors evaluated in different formats were joined into one factor. Size represented a combination of weight for age z scores, weight for height z scores, ideal body weight in kg, or a classification of small or appropriate for gestational age. Anthropometrics were midarm fat area or midarm muscle area. Cardiac output represented direct or indirect measures of cardiac output expressed in liter/min or liters/min/$m^2$. % open burn represents a quantification of burn size after the initial % body surface area burn quantification and therapy instituted. Nutritional support represented protein intake or comparison of enteral vs parenteral nutrition, or continuous versus intermittent feeds, whereas caloric intake was total energy intake. For each factor-EE reported association, the type of association, point estimates with confidence intervals, and p-value were abstracted as available. In cases of multivariate regression equations, factors included in the final equation were assumed to have a p-value < 0.05 if no explicit p-value was reported. If more than one association was reported for a single factor in a study, one association was selected based on the following hierarchy: regression coefficient with adjustment for cofactors, regression coefficient with no adjustment, correlation, and last, all other types of associations for example: comparison of EE means between groups, or F-value. Factors were separated into broad domains and factors evaluated twice or more were presented with the number of unique evaluations and the total number of measurements used in evaluations. The relationship with EE was categorized as positive association if >75% of measurements contributed to evaluations

with significant p-values, negative association if <25% of measurements contributed to evaluations with significant p-values, and indeterminate association if 25–75% of measurements contributed to evaluations with significant p-values. This classification was then reevaluated based on sample size and physiologic rationale.

Associations with EE reported as effect sizes were summarized. The percentage of significant measurements of regression coefficients and correlations evaluated more than twice was reported. For factor-EE associations reported as regression coefficients, no metanalysis was performed due to lack of reporting of standard errors of regression coefficients. Regression coefficients were summarized as medians (IQR) and means (SD) for each factor per patient age group. A metaanalysis were performed for all correlations reported more than twice in the entire patient population, and in the age group subpopulations. The meta-analysis was done regardless of extent of heterogeneity, using random effects model and software by Suurmond and colleagues [26]. All other analyses were performed using SAS Studio Software Version 9.3.7.1, SAS Institute Inc., Cary, NC, USA.

## 3. Results

The search strategy yielded 8521 unique articles, 307 underwent full text review, and 103 articles were included. PRISMA flowchart for the selection of studies is shown in Fig. 1 [27], and a detailed description of included studies is presented in Supplemental Table 2.

The median (Q1, Q3) publication year was 1999 (1994, 2008) with 42 (41%) of studies being published between 1991 and 2000. The study design was prospective observational in 70 (68%) studies, prospective interventional in 25 (24%) studies, and retrospective in 7 (7%) studies, other in 1 (1%) (Table 1). Studies included a median (Q1, Q3) of 25 (16, 46) patients, with a minimum of 5 patients and maximum of 204 patients. The population evaluated was adults in 61 (59%), children in 20 (19%), and neonates in 19 (19%) studies. Patients were receiving invasive ventilation in 56 (55%) studies and not ventilated in 20 (19%). Indirect calorimetry was used to measure EE in 101 (98%) studies and doubly labelled water in 2 (2%). The Deltatrac indirect calorimeter was used in 43 (44%) studies, the Sensormedics in 7 (7%), not reported in 10 (10%) studies. Calibration was described in 55 (53%) studies and not reported in 48 (47%). In studies utilizing indirect calorimetry, steady state was described and achieved in 29 (29%) studies, not described but achieved in 8 (8%), and not described or reported as achieved in 64 (63%) studies. The units utilized to express EE were kcal/day in 47 (46%) studies and kcal/kg/day in 29 (28%) studies. Standardization to size was reported in 16 of 61 adult studies [22,28–49], 13 (65%) of 20 pediatric studies [23,50–61], and all of the neonatal and mixed population studies [62–84] (Table 1).

### 3.1. Eligible factors studied

The 103 articles studied 97 factors with 435 non-unique evaluations, 27 evaluations of 2 factors had no reported p-value and 56 evaluations were reported in duplicate format within the same study. Therefore, 95 factors with 352 unique evaluations were available. Of those, 77 factors with 204 evaluations were regression coefficients or correlations (Fig. 2). Factors were grouped into 10 categories: size, diagnosis and pathology, nutritional intake, vital signs, ventilatory parameters, laboratory, clinical scores, time data, medications, and other (Table 2). Of the 95 factors, there were 54 factors with two or more unique evaluations. The median (Q1, Q3) number of measurements for those factors was 453 (155, 780).

There were 16 factors with a positive association: weight, age, anthropometrics, blood pressure, cardiac output, % body surface area (BSA) burn, multiorgan failure, caloric intake, sedation,

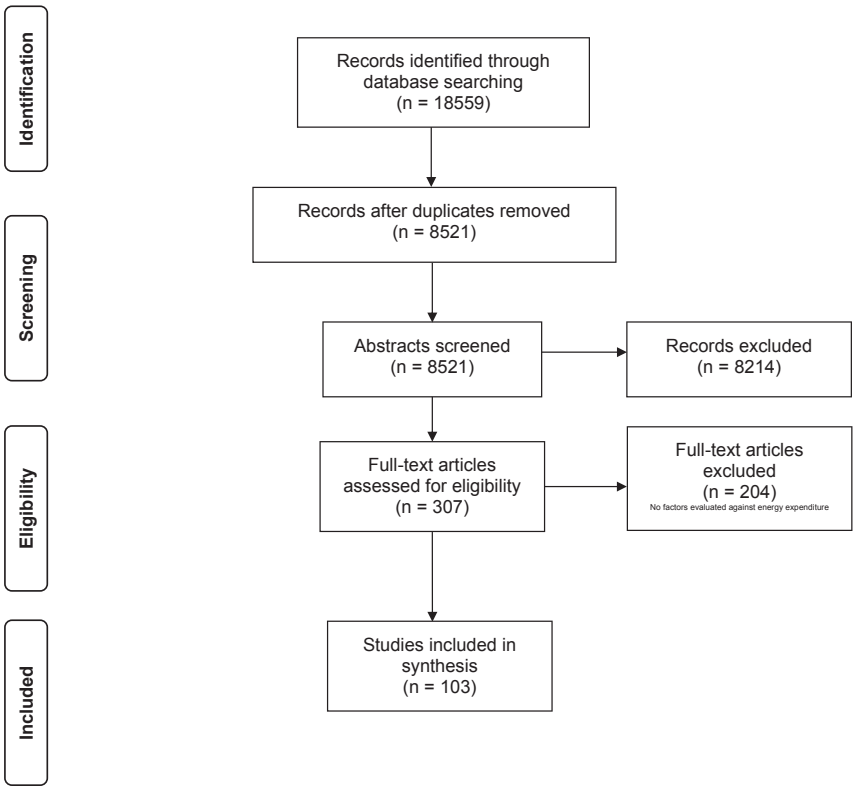


**Fig. 1.** PRISMA flow chart for study selection. This chart depicts the study selection process as described by the PRISMA work-group.

**Table 1**
Summary description of included studies.

| Study Characteristics | Number of Studies (%) | Number of Measurements (%) |
|---|---|---|
| Study Design | | |
| Prospective Observational | 70 (68) | 6222 (78) |
| Prospective Interventional | 25 (24) | 582 (7) |
| Retrospective Observational | 7 (7) | 1051 (13) |
| Retrospective Interventional | 1 (1) | 84 (2) |
| Publication Years | | |
| 1979–1990 | 15 (15) | 1337 (17) |
| 1991–2000 | 42 (41) | 2072 (26) |
| 2001–2010 | 28 (27) | 2579 (32) |
| 2011–2017 | 18 (17) | 1951 (25) |
| Age Groups | | |
| Adults | 61 (59) | 5277 (66) |
| Children | 20 (19) | 1973 (25) |
| Neonates | 19 (19) | 635 (8) |
| Adults and Children | 1 (1) | 16 (0.5) |
| Children and Neonates | 2 (2) | 38 (0.5) |
| Type of Respiratory Support | | |
| Invasive Ventilation | 56 (55) | 5184 (65) |
| Not Ventilated | 20 (19) | 1449 (18) |
| Non-Invasive Ventilation | 1 (1) | 18 (0) |
| Mixed | 20 (19) | 995 (13) |
| Not reported | 6 (6) | 293 (4) |
| Energy Expenditure Measurement Method | | |
| Indirect Calorimetry | 101 (98) | 7908 (99) |
| Deltatrac | 43 (43) | 2779 (35) |
| Sensormedics | 7 (7) | 513 (6) |
| Metabolic Gas Monitor | 6 (6) | 400 (5) |
| Other | 33 (32) | 3264 (41) |
| Not reported | 10 (10) | 282 (4) |
| Douglas Bag | 2 (2) | 670 (9) |
| Double Labelled Water | 2 (2) | 31 (1) |
| Calibration Described | | |
| Yes | 55 (54) | 4737 (60) |
| No | 48 (46) | 3202 (40) |
| Steady State[a] | | |
| Achieved and Described | 29 (29) | 3827 (48) |
| Achieved and Not Described | 8 (8) | 402 (5) |
| Not reported | 64 (63) | 3679 (47) |
| Energy Expenditure Units | | |
| kcal/day | 47 (46) | 4409 (56) |
| kcal/kg/day | 29 (28) | 2060 (26) |
| kcal/$m^2$/day | 7 (7) | 659 (8) |
| kJ/kg/day | 7 (7) | 125 (1) |
| Other | 13 (12) | 686 (9) |

Summary of study characteristics including design, publication year, age group, type of respiratory support, energy expenditure method used, calibration description, steady state description, and energy expenditure units. Total number of studies was 103 except for steady state.
[a] Steady state description included studies utilizing indirect calorimetry (n = 101).

stimulants, urinary urea nitrogen, minute volume, postburn day, room temperature, and activity level. There were 17 factors with a negative association and 21 with an indeterminate association (Table 2). Factors with positive association varied by population (Supplemental Table 3). In adults, these factors were weight, age, sex, temperature, cardiac output, surgery, % BSA burn, caloric intake, edation, neuromuscular blockade, urinary urea nitrogen, minute volume, and post burn day. In children, factors with positive association were weight, age, anthropometrics, % BSA burn, respiratory disease, and multiorgan failure. While in neonates, age, heart rate, sepsis, caloric intake, nutritional support, and stimulants had a positive association with EE (Supplemental Table 3).

### 3.2. Effect size description

There were 77 factors with 204 evaluations comprised of 89 correlations (r) of 53 factors, and 115 regression coefficients (beta) of 46 factors (Fig. 2). Significant associations were reported in 49 (55%) correlations and 83 (72%) regression coefficients. There were 28 factors with three or more effect size relationships with EE reported (Table 3). Factors with more than 75% significant effect size associations were weight, age, size, heart rate, blood pressure, % BSA burn, caloric intake, sedation, and minute volume. Size, sedation, % BSA burn, and minute volume effect sizes were all significant (Supplemental Table 4). The summary of regression coefficients of different factor - EE relationships in different patient populations are summarized in Table 4. Sex had the largest magnitude of effect on EE: −302.9 ± 424.7 followed by minute volume: 245.2 ± 373.3 kcal/day per 1 L/minute. The regression coefficients suggest that a change in temperature of 2 °C results in 154 kcal/day change in EE, and an increase in heart rate of 20 beats/min results in an increase of EE by 324 kcal/day (Table 5).

The correlation metaanalysis for all patients is presented in Fig. 3. The majority of correlations were reported in adults, except for weight. In adults, the metanalysis showed a moderate correlation with heart rate 0.48 (0.04, 0.77), sedation 0.39 (0.11, 0.61), and temperature 0.46 (0.40, 0.53), and weak correlation with age 0.13 (−1.00, 1.00), caloric intake 0.23 (−0.61, 0.83), APACHE score 0.06 (−0.41, 0.50). In children, metanalysis was performed on weight and showed a strong correlation [r = 0.86 (−1.00, 1.00)] with significant heterogeneity. In the metanalysis performed on all patients and in subpopulations, only two factors had low heterogeneity:

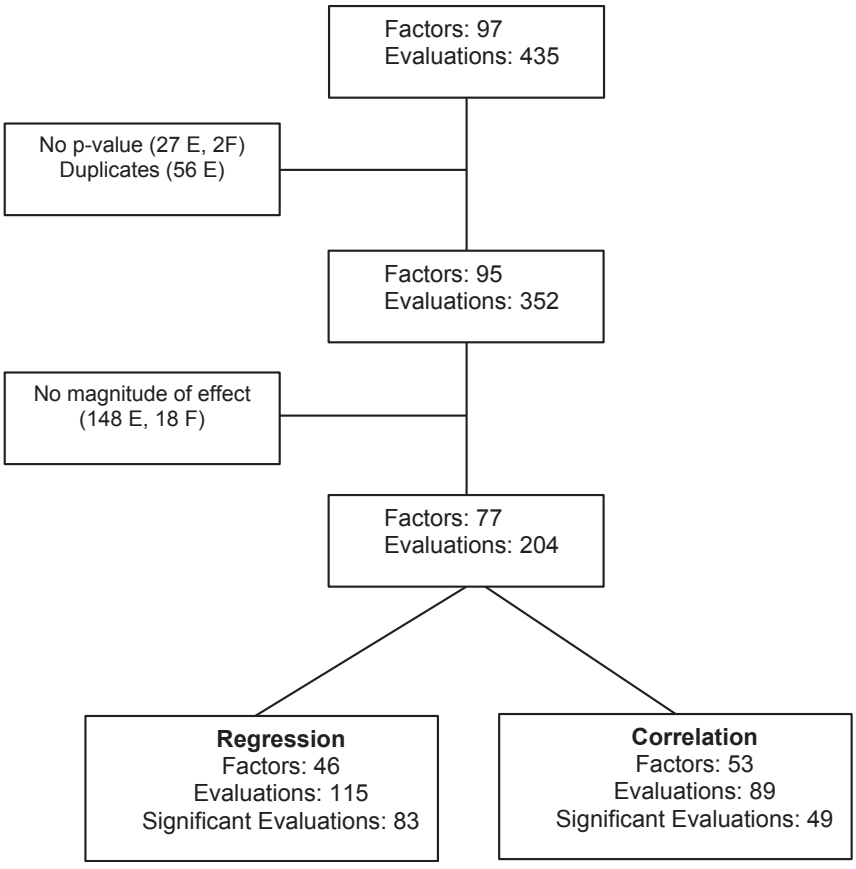


**Fig. 2.** Number of Factors and Evaluations. The total number of factors evaluated with energy expenditure was 95 with 352 evaluations. 46 factors were evaluated with regression methods and 72% of those evaluations being significant. 53 factors were evaluated by correlation and 55% of those being significant.

**Table 2**
Evaluations and measurements of factors evaluated twice or more.

| Factors and factor domains | Number of evaluations | Number of significant evaluations (%) | Number of measurements | Number of measurements in significant evaluations (%) |
|---|---|---|---|---|
| Size | | | | |
| Weight[a] | 19 | 17 (89) | 1588 | 1540 (97) |
| Age[a] | 17 | 15 (88) | 1743 | 1518 (87) |
| Sex[c] | 7 | 5 (71) | 589 | 378 (64) |
| Height[c] | 7 | 4 (57) | 758 | 292 (39) |
| Size[b,d] | 5 | 4 (80) | 739 | 174 (24) |
| Body surface area[c] | 3 | 2 (67) | 788 | 223 (28) |
| Anthropometrics[a,e] | 2 | 2 (100) | 154 | 154 (100) |
| Vital signs | | | | |
| Temperature[c] | 28 | 19 (68) | 4285 | 2888 (67) |
| Heart rate[b] | 14 | 10 (71) | 1458 | 294 (20) |
| Respiratory rate[b] | 3 | 2 (67) | 1253 | 121 (10) |
| Blood pressure[a] | 3 | 1 (33) | 134 | 112 (84) |
| Cardiac output[a,f] | 2 | 1 (50) | 127 | 111 (87) |
| Clinical scores | | | | |
| APACHE[c] | 8 | 4 (50) | 593 | 217 (37) |
| SAPS[c] | 5 | 1 (20) | 515 | 155 (30) |
| ISS[b] | 4 | 1 (25) | 283 | 52 (18) |
| GCS[b] | 4 | 0 (0) | 171 | 0 (0) |
| PRISM[b] | 3 | 0 (0) | 141 | 0 (0) |
| Diagnosis and pathology | | | | |
| Surgery[c] | 9 | 6 (67) | 441 | 306 (69) |
| % Body surface area burn[a] | 9 | 9 (100) | 1251 | 1251 (100) |
| Sepsis[c] | 7 | 5 (71) | 134 | 96 (72) |
| Cardiopulmonary bypass[c] | 5 | 3 (60) | 465 | 243 (52) |
| Respiratory disease[b] | 3 | 2 (67) | 1171 | 39 (3) |
| Liver failure[c] | 3 | 2 (67) | 98 | 28 (29) |
| % Open burn[b,g] | 2 | 0 (0) | 571 | 0 (0) |
| Head injury[c] | 2 | 1 (50) | 43 | 23 (53) |
| Multiorgan failure[a] | 2 | 2 (100) | 252 | 252 (100) |
| Renal failure[b] | 2 | 1 (50) | 92 | 22 (24) |

(*continued on next page*)

**Table 2** (*continued*)

| Factors and factor domains | Number of evaluations | Number of significant evaluations (%) | Number of measurements | Number of measurements in significant evaluations (%) |
|---|---|---|---|---|
| Nutritional intake | | | | |
| Caloric intake[a] | 10 | 8 (80) | 633 | 503 (79) |
| Nutritional support[c] | 8 | 3 (38) | 554 | 209 (38) |
| Glucose infusion[c] | 2 | 1 (50) | 135 | 24 (18) |
| Medications | | | | |
| Sedation[a] | 17 | 13 (76) | 1118 | 989 (88) |
| Neuromuscular blockade[c] | 9 | 5 (56) | 1111 | 784 (71) |
| Inotropes and vasopressors[c] | 7 | 2 (29) | 612 | 188 (31) |
| Stimulants[a] | 4 | 3 (75) | 61 | 48 (79) |
| Growth hormone injection[c] | 2 | 0 (0) | 210 | 105 (50) |
| Steroids[c] | 2 | 1 (50) | 222 | 111 (50) |
| Laboratory measurements | | | | |
| C-reactive protein[b] | 6 | 3 (50) | 759 | 63 (8) |
| Cytokines[c] | 5 | 3 (60) | 555 | 333 (60) |
| T3 level[c] | 3 | 2 (67) | 315 | 210 (67) |
| Cortisol level[b] | 3 | 1 (33) | 240 | 30 (14) |
| Glucagon level[c] | 3 | 1 (33) | 315 | 105 (33) |
| Growth hormone level[c] | 2 | 0 (0) | 210 | 105 (50) |
| Insulin level[b] | 2 | 0 (0) | 210 | 0 (0) |
| Urinary urea nitrogen[a] | 2 | 2 (100) | 153 | 153 (100) |
| White blood cell count[b] | 2 | 1 (50) | 321 | 20 (6) |
| Ventilatory parameters | | | | |
| Minute volume[a] | 7 | 5 (71) | 1595 | 1575 (99) |
| Fraction of inspired oxygen[b] | 4 | 2 (50) | 1457 | 310 (21) |
| Peep[b] | 2 | 0 (0) | 1147 | 0 (0) |
| Ventilatory mode[c] | 2 | 1 (50) | 110 | 40 (36) |
| Time | | | | |
| Intensive care unit days[b] | 4 | 1 (25) | 541 | 100 (18) |
| Post burn day[a] | 4 | 3 (75) | 888 | 747 (84) |
| Measurement time[b] | 2 | 0 (0) | 33 | 0 (0) |
| Other | | | | |
| Room temperature[a] | 5 | 3 (60) | 46 | 40 (87) |
| Activity level[a] | 4 | 2 (50) | 159 | 128 (81) |

Factors that were evaluated more than twice are depicted in the table. The number of evaluations represents the number of studies where the factor was evaluated. The number of measurements represents the sum of measurements done in each of the evaluations. Temperature was the most frequently measured factor (n = 4285) and measurement time the least measured factor (n = 33).

APACHE: Acute physiology and chronic health evaluation, SAPS: Simplified acute physiology score, GCS: Glasgow Coma Scale, ISS: Injury Severity Score, PRISM: Pediatric risk of mortality, T3: Tri-iodothyronine, PEEP: Positive end expiratory pressure.

[a] Factors significantly associated with energy expenditure.

[b] Factors not associated with energy expenditure.

[c] Factors with indeterminate association with energy expenditure.

[d] Size represented a combination of weight for age z scores, weight for height z scores, ideal body weight in kg, or a classification of small or appropriate for gestational age.

[e] Anthropometrics were midarm fat area or midarm muscle area.

[f] Cardiac output represented direct or indirect measures of cardiac output expressed in liter/min or liters/min/$m^2$.

[g] % open burn represents a quantification of burn size after the intial % BSA burn quantification and therapy instituted.

temperature and sedation. All factor-EE correlations are presented in Supplemental Table 5. A summary of all significant correlations and regression coefficients is presented in Table 6.

## 4. Discussion

Our review identified 103 studies including 95 factors evaluated for associations with EE in 4388 critically ill patients with 7939 measurements. Most studies and measurements were in adult patients (59%) and performed by the current reference standard for EE measurement: indirect calorimetry [9,20]. There are five main findings.

First, this systematic review provides some explanation for the inaccuracies of EE predictive equations in critically ill patients [19–23,85]. The majority of equations focus on factors representing body size, age, sex, and disease categories. Body size is clearly associated with EE as represented by weight [22,23,31–33,55,57,60,69,86–94] but not necessarily when represented as standardized z-scores, body mass index, BSA or height in the studies reviewed. This could be related to the presence of multiple factors representing size in the evaluations resulting in the dilution of some of the factors' effect on EE, or the interactions between those factors resulting from their exclusion in models predicting EE. Future studies of EE should consider each of those factors separately and then evaluate the co-interaction between those. Age is shown to be associated with EE, and this relationship could be related to its representation of body size, therefore, age and body size should be assessed for collinearity in predictive models for EE [22,23,30,32,57,60,69,76,84,86,88,90–93,95]. Sex and EE have an indeterminate association and inclusion of more dynamic factors might be prudent [22,43,57,87,88,90,93].The relationship between EE and diagnoses is indeterminate at best. Some diseases are associated with EE, however this systematic review points out multiple other factors that could represent the physiologic state at different times of illness and could be more useful in predicting energy expenditure. For instance, minute volume – the product of respiratory rate and tidal volume - was most frequently evaluated (n = 1575 measurements) and consistently associated with energy expenditure with a large effect size in

**Table 3**
Effect size evaluations and measurements of factors evaluated more than twice.

| Factor categories and factors | Effect size evaluations (n) | Effect size measurement number and % significant [n (%)] | Regression coefficient evaluations (n) | Number of regression coefficient measurements [n (%significant)] | Correlation evaluations (n) | Number of correlation measurements [n (%significant)] |
|---|---|---|---|---|---|---|
| Size | | | | | | |
| *Weight* | 18 | 1558 (97) | 12 | 1215 (99) | 6 | 343 (89) |
| *Age* | 16 | 1555 (86) | 10 | 1200 (87) | 6 | 355 (80) |
| Sex | 4 | 386 (45) | 3 | 286 (61) | 1 | 100 (0) |
| Height | 7 | 758 (39) | 5 | 613 (24) | 2 | 145 (100) |
| Size | 3 | 142 (100) | 1 | 100 (100) | 2 | 42 (100) |
| Vital signs | | | | | | |
| Temperature | 19 | 3026 (75) | 9 | 2449 (72) | 10 | 577 (85) |
| Heart rate | 12 | 1440 (20) | 5 | 109 (91) | 7 | 1331 (14) |
| Respiratory rate | 3 | 1244 (10) | 2 | 121 (100) | 1 | 1132 (0) |
| Blood pressure | 3 | 134 (84) | 1 | 10 (0) | 2 | 124 (90) |
| Clinical scores | | | | | | |
| APACHE | 7 | 520 (28) | 1 | 70 (100) | 6 | 450 (16) |
| SAPS | 5 | 515 (30) | 1 | 155 (100) | 4 | 360 (0) |
| ISS | 4 | 283 (18) | | | 4 | 283 (18) |
| GCS | 4 | 171 (0) | | | 4 | 171 (0) |
| Diagnosis and pathology | | | | | | |
| Surgery | 3 | 308 (64) | 3 | 308 (64) | | |
| *% Body surface area burn* | 8 | 1062 (100) | 6 | 891 (100) | 2 | 171 (100) |
| Cardiopulmonary bypass | 4 | 444 (50) | 4 | 444 (50) | | |
| Nutritional intake | | | | | | |
| *Caloric intake* | 10 | 633 (79) | 3 | 221 (100) | 7 | 412 (68) |
| Nutritional support | 4 | 347 (57) | 2 | 232 (52) | 2 | 115 (67) |
| Medications | | | | | | |
| Sedation | 3 | 479 (100) | | | 3 | 479 (100) |
| Neuromuscular blockade | 4 | 250 (72) | 3 | 184 (62) | 1 | 66 (100) |
| Inotropes and vasopressors | 4 | 451 (42) | 3 | 374 (30) | 1 | 77 (100) |
| Laboratory measurements | | | | | | |
| C-reactive protein | 4 | 735 (5) | 2 | 670 (0) | 2 | 65 (60) |
| Cytokines | 5 | 555 (60) | 5 | 555 (60) | | |
| Cortisol level | 3 | 240 (13) | 2 | 210 (0) | 1 | 30 (100) |
| Ventilatory parameters | | | | | | |
| *Minute volume* | 4 | 1555 (100) | 4 | 1555 (100) | 1 | |
| Fraction of inspired oxygen | 3 | 1442 (21) | 2 | 310 (100) | | 1132 (0) |
| Time | | | | | | |
| Intensive care unit days | 4 | 541 (18) | 3 | 481 (21) | 1 | 60 (0) |
| Post burn day | 4 | 1029 (73) | 3 | 888 (84) | 1 | 141 (0) |

Factors evaluation by regression or correlation three times or more are summarized in this table. Temperature was the most commonly measured factor. Weight, age, temperature, % body surface area burn, caloric intake, and minute volume were consistently associated with EE in more than 500 measurements of effect size (in *italics*). Heart rate and ICU days were consistently not associated with EE in more than 500 measurements of effect size. The remaining factors were of an indeterminate effect size relationship with EE. APACHE: Acute physiology and chronic health evaluation, SAPS: Simplified acute physiology score, GCS: Glasgow Coma Scale, ISS: Injury Severity Score.

regression equations [90–92,95–97]. Minute volume maintains a stable carbon dioxide ($CO_2$) and acid base balance in an organism. Therefore, physiologic changes that affect acid base homeostasis will be associated with a change in minute volume. $CO_2$ production is a part of the Weir equation and this relationship between minute volume and EE is expected [Resting energy expenditure (kcal/d) = 1.44 (3.9*oxygen consumption + 1.1*carbon dioxide production)]. Sedation – an intervention that can decrease $O_2$ consumption [98] and hence EE is associated with EE and deserves further consideration for inclusion in EE predictive equations [36,40,45,47,50,90,99–104]. Caloric intake – a factor not included in any predictive equation of EE, was significantly associated with EE in this review [40,69,74,76,90,105–107]. This relationship is based on physiologic phenomena, where the rate of metabolic heat production represented as $VO_2$ and $VCO_2$ is dependent on the substrate available for the metabolic processes to occur [108]. Therefore, a change in the extrinsic intake of one of the substrates affects the measured EE. In certain patient populations, as burns, the % of the initial BSA burn [33,37,38,86,106,107,109,110] and the post burn day [37,107,109,110] were associated with energy expenditure, however, the % open burn wound after therapy is initiated is not useful as a predictive factors of EE. This relationship could be explained by the underlying inflammatory and hormonal process that is triggered by the initial burn insult and its evolution across ICU days [111].

Second, this study identified groups of factors that were significant in different patient populations. Factors representing size, inflammatory state, and caloric intake were positively associated with EE in studies of adults, children, and neonates. Representations of these factors should be included in additional studies of EE in critically ill patients to determine the specific factor within these categories that are associated with EE, the optimal factor representation, and the types of interactions between these different factors and how it affects the relationship with EE.

Third, this review highlights the need for more rigorous evaluations of some factors to better determine their relationship with EE. A change in temperature is expected to increase metabolic demand

**Table 4**
Summary statistics for significant regression coefficients evaluated twice or more.

| Factor – Age group | Energy expenditure units | Number of evaluations | Mean ± SD | Median (Q1, Q3) |
|---|---|---|---|---|
| Sex – Adult | kcal/day | 2 | −302.9 ± 424.7 | −302.9 (−603.2, −2.6) |
| Minute Volume (L/Min) – Adult | kcal/day | 4 | 245.2 ± 373.3 | 72.7 (41.7, 448.8) |
| Temperature (Celsius) – Adult | kcal/day | 5 | 76.8 ± 45.4 | 93.8 (71.4, 104.2) |
| Heart Rate – Adult | kcal/day | 2 | 16.2 ± 5.8 | 16.2 (12.0, 23.3) |
| Weight (kg) – Adult | kcal/day | 5 | 10.6 ± 10.4 | 7.7 (5.5, 12.5) |
| Age (years) – Adult | kcal/day | 3 | −8.8 ± 5.6 | −6.3 (−15.1, −4.8) |
| Post Burn Day – Adult | kcal/day | 3 | −7.7 ± 3.0 | −8.1 (−10.5, −4.5) |
| % BSA Burn – Adult | kcal/day | 4 | 7.6 ± 3.2 | 7.6 (4.8, 10.3) |
| Caloric intake (kcal/day) – Adult | kcal/day | 2 | 0.2 ± 0.02 | 0.2 (0.2, 0.3) |
| Weight (kg) – Child | kcal/day | 3 | 38.3 ± 29.3 | 37.4 (9.5, 68) |
| Weight (kg) – Child | kcal/kg/day | 2 | 24.0 ± 34.5 | 24.0 (−0.3, 48.4) |
| % BSA Burn – Child | kcal/day | 2 | 6.6 ± 3.8 | 6.6 (3.9, 9.3) |
| Cytokines – Child | kcal/kg/day | 3 | 2.4 ± 1.1 | 1.8 (1.7, 3.6) |
| Cardiopulmonary bypass – Child | kcal/kg/day | 2 | −0.23 ± 0.16 | −0.23 (−0.34, −0.12) |

Factor – EE evaluations reported as regression coefficients represented as measures of central tendency and spread. In adults, minute volume (L/min) and sex had the largest magnitude of effect on EE (kcal/day), followed by temperature. In children, weight had the largest magnitude of effect.
SD: Standard deviation; BSA: Body surface area.

**Table 5**
Effect of factor changes on energy expenditure.

| Δ Factor | Adults - Δ EE (kcal/day) |
|---|---|
| Weight = 10 kg | 106 |
| % BSA Burn = 10 | 726 |
| Temperature = 2 °C | 154 |
| Minute Ventilation = 0.5 L/min | 122 |
| Heart Rate = 20 beats/min | 324 |

The change in EE in adults as it relates to the change in factors represented as regression coefficients. Δ: Delta; BSA: Body Surface Area.

with an increase in heart rate and $O_2$ consumption, but was associated with EE in 67% of the measurements. Potential explanations are the comparisons between groups of patients rather than its inclusion as a co-factor in multivariate evaluations hence diluting its effect [22,23,34,40–42,47,54,61,88,90–93,95,106,107,109,112–120]. Neuromuscular blockade was inconsistently associated with EE in 1111 measurements [23,40,44,50,57,61,90,93,103]. In 23% of those measurements, neuromuscular blockade was evaluated in an effect size format, with 72% of those evaluations being significant. Although the number of measurements of this factor were high, the overall low

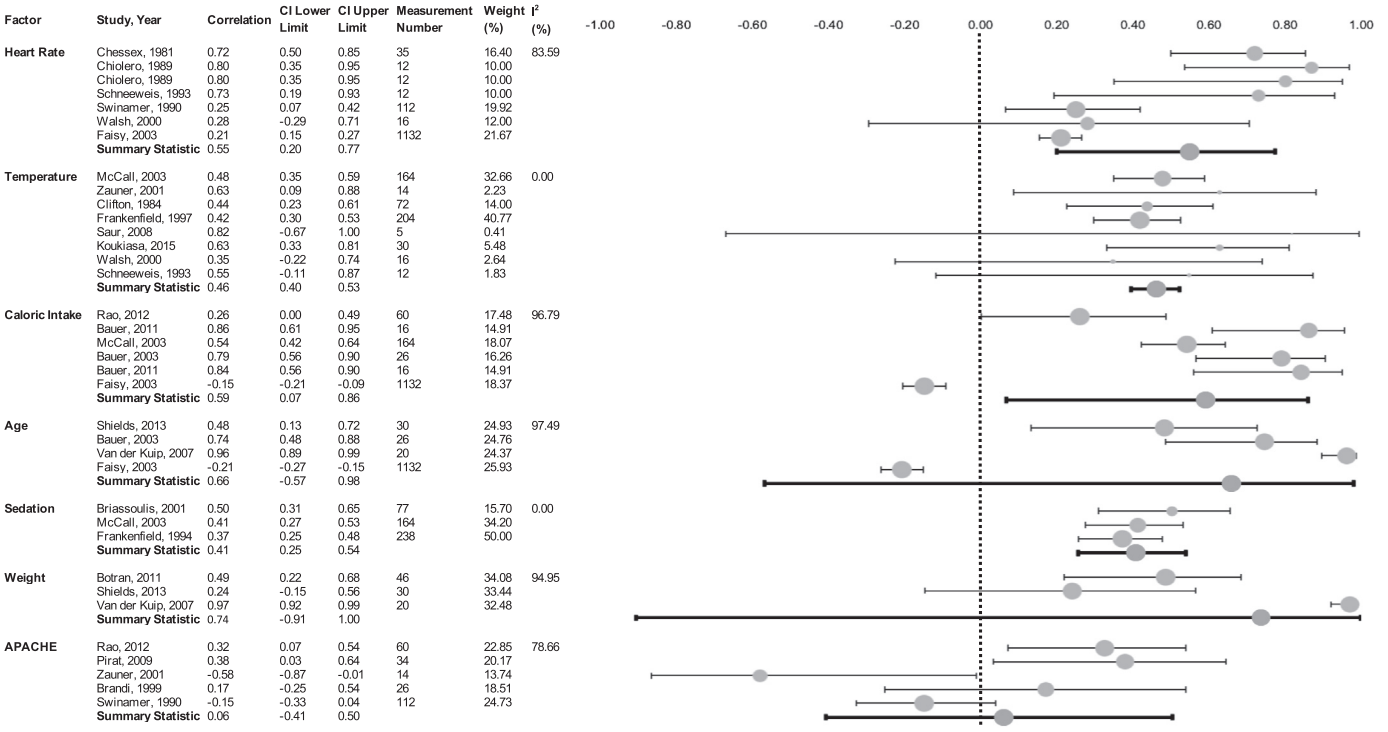


**Fig. 3.** Meta-analysis of correlations reported more than twice per factor. Weight and age had a strong correlation with EE with an r of 0.74 and 0.66 respectively. Heart rate (r = 0.55), temperature (r = 0.46), caloric intake (r = 0.59), sedation (r = 0.41) were moderately associated with energy expenditure. APACHE score (r = 0.06) had a very weak correlation with energy expenditure. All factors except weight and temperature had considerable heterogeneity in the metaanalysis. APACHE: Advanced physiology and chronic health evaluation.

**Table 6**
Significant regression coefficients and correlations per factor.

| Factor | Study, Year | Regression coefficient | Correlation | Factor description |
|---|---|---|---|---|
| % BSA burn | Giantin, 1995 | 5.16 | | |
| | Cunningham, 1989 | 10.1 | | |
| | Allard, 1988 | 10.5 | | |
| | Khorram, 1999 | 4.5 | | |
| | Mayes, 1996 | 9.3 | | |
| | Mayes, 1996 | 3.9 | | |
| | Milner, 1994 | | 0.587 | |
| | Shields, 2013 | | 0.67 | |
| Adrenaline Level | Matthews, 1995 | 0.71 | | log adrenaline |
| Age | De Marie, 1999 | 1.3 | | Days |
| | Osuka, 2013 | −4.83 | | Years |
| | White, 2000 | 20 | | Months |
| | Floh, 2015 | −0.004 | | Days |
| | Swinamer, 1990 | −6.3 | | Years |
| | Meyer, 2012 | 1.22 | | Years |
| | El Khatib, 1996 | 75.7 | | Years |
| | Goes, 2017 | −15.13 | | Years |
| | Shields, 2013 | | 0.48 | Years |
| | Bauer, 2003 | | 0.743 | Days |
| | Vanderkuip, 2007 | | 0.96 | Years |
| Anthropometrics | Briassoulis, 2000 | | 0.63 | Midarm muscle area |
| | Briassoulis, 2000 | | 0.52 | Midarm fat area |
| APACHE | Brown, 1993 | 31.92 | | |
| | Rao, 2012 | | 0.324 | |
| | Zauner, 2001 | | −0.58 | |
| Blood pressure | Swinamer, 1990 | | 0.28 | |
| Body mass index | Zauner, 2006 | | −0.48 | |
| BSA | Floh, 2015 | −11.6 | | |
| | Swinamer, 1990 | 941 | | |
| C-reactive protein | Hickmann, 2014 | | 0.41 | |
| Caloric intake | De Marie, 1999 | 0.4 | | kcal/kg/day |
| | Giantin, 1995 | 0.26 | | kcal/day |
| | Allard, 1988 | 0.23 | | kcal/day |
| | Rao, 2012 | | 0.259 | kcal/day from Lipids |
| | Bauer, 2011 | | 0.86 | In small for gestational age neonates |
| | Bauer, 2011 | | 0.844 | In appropriate for gestational age neonates |
| | McCall, 2003 | | 0.54 | kcal/kg/day |
| | Bauer, 2003 | | 0.789 | kJ/kg/day |
| Cardiac output | Floh, 2015 | 13.7 | | log cardiac output in L/min/m2 |
| Cardiopulmonary bypass | Floh, 2015 | −0.12 | | Time in hr after cardiopulmonary bypass |
| | Floh, 2015 | −0.34 | | Time in min of hypothermic circulatory arrest |
| CNS disease | Meyer, 2012 | 33 | | |
| Cortisol level | Koukiasa, 2015 | | 0.62 | |
| Cytokines | Floh, 2015 | 3.6 | | log IL8 |
| | Floh, 2015 | 1.76 | | log IL6 |
| | Floh, 2015 | 1.7 | | log IL10 |
| Extracellular water volume | Faisy, 2003 | | 0.32 | Height$^2$/body impedance at 5 kHZ |
| FiO2 | de Meer, 1997 | −56.6 | | |
| | Goes, 2017 | 14.2 | | |
| Glucagon Level | Matthews, 1995 | 0.04 | | |
| Growth Hormone Level | Matthews, 1995 | 4.9 | | |
| Head Injury | White, 2000 | 0 | | |
| Heart rate | de Meer, 1997 | 0.64 | | |
| | Jones, 1995 | 0.39 | | |
| | Giantin, 1995 | 20.3 | | |
| | Giantin, 1995 | 12.03 | | |
| | Chessex, 1981 | | 0.72 | |
| | Chiolero, 1989 | | 0.87 | 10% HR reduction with propranolol |
| | Chiolero, 1989 | | 0.8 | Prior to propranolol |
| | Schneeweiss, 1993 | | 0.73 | |
| | Swinamer, 1990 | | 0.25 | |
| Height | El Khatib, 1996 | 13.9 | | cm |
| | Faisy, 2003 | 13.9 | | cm |
| | Shields, 2013 | | 0.39 | Inches |
| ICU days | White, 2000 | 122 | | Days |
| Injury Severity Score | Swinamer, 1990 | | 0.17 | |
| Inotropes & Pressors | Floh, 2015 | 0.009 | | |
| | Briassoulis, 2000 | | 0.45 | |
| Minute Volume | Osuka, 2013 | 93.6 | | In liters/minute |
| | Swinamer, 1990 | 803.9 | | In liters/minute |
| | Faisy, 2003 | 31.62 | | In liters/minute |
| | Goes, 2017 | 51.78 | | In liters/minute |
| Multiorgan failure | Meyer, 2012 | 226 | | |

(*continued on next page*)

**Table 6** (*continued*)

| Factor | Study, Year | Regression coefficient | Correlation | Factor description |
|---|---|---|---|---|
| Neuromuscular Blockade | Boulanger, 1994 | 274 | | |
| | Frankenfield, 1994 | | 0.56 | Received vs not |
| Nutritional support | Briassoulis, 2000 | | 0.48 | Protein intake |
| Oxygen saturation | Faisy, 2003 | | 0.24 | |
| Post burn day | Cunningham, 1989 | −8.1 | | |
| | Allard, 1988 | −4.5 | | |
| | Khorram, 1999 | −10.5 | | |
| Respiratory Disease | White, 2000 | −512 | | |
| Respiratory failure | Meyer, 2012 | 79 | | |
| Respiratory quotient | Floh, 2015 | −19.7 | | |
| Respiratory rate | de Meer, 1997 | 0.95 | | |
| | Swinamer, 1990 | 24.2 | | |
| Room temperature | Shields, 2013 | | 0.17 | Degrees Fahrenheit |
| SAPS | Drolz, 2014 | −0.06 | | |
| Sedation | Briassoulis, 2000 | | 0.5 | Sedation vs none |
| | McCall, 2003 | | 0.41 | Morphine dose pre measurement |
| | Frankenfield, 1994 | | 0.37 | Morphine equivalents mg/12hr |
| Sepsis | White, 2000 | −227 | | |
| Sepsis Score | Swinamer, 1990 | | 0.21 | |
| Sex | Hunter, 1988 | −603.2 | | |
| | Drolz, 2014 | −2.57 | | |
| Size | White, 2000 | 151 | | Weight-age z score |
| | de Wit, 2010 | | −0.521 | Weight-age z score |
| | de Wit, 2010 | | −0.584 | Weight-height z score |
| Steroids | Floh, 2015 | −6.7 | | Preoperative |
| Surgery | White, 2000 | 105 | | |
| | Meyer, 2012 | 0 | | |
| T3 Level | Matthews, 1995 | 0.84 | | |
| Temperature | Boulanger, 1994 | 71.4 | | |
| | White, 2000 | 279 | | |
| | Allard, 1988 | 114 | | |
| | Drolz, 2014 | 0.71 | | |
| | Swinamer, 1990 | 104.2 | | |
| | Faisy, 2003 | 93.78 | | |
| | McCall, 2003 | | 0.48 | Celsius |
| | Zauner, 2001 | | 0.63 | Celsius |
| | Clifton, 1984 | | 0.44 | Celsius |
| | Frankenfield, 1997 | | 0.42 | |
| | Saur, 2008 | | 0.82 | Celsius |
| | Koukiasa, 2015 | | 0.63 | |
| Urinary creatinine | Hunter, 1988 | −0.66 | | gr/24hr |
| Urinary urea nitrogen | Milner, 1994 | | 0.667 | |
| | Chiolero, 1989 | | 0.85 | gr/day |
| Ventilatory Index | Wahlig, 1994 | | 0.63 | |
| Weight | Hunter, 1988 | 27.3 | | kg |
| | White, 2000 | 31 | | kg |
| | Drolz, 2014 | −0.13 | | kg |
| | Zauner, 2006 | 12.49 | | kg |
| | Floh, 2015 | −0.33 | | kg |
| | Meyer, 2012 | 48.4 | | kg |
| | El Khatib, 1996 | 9.5 | | kg |
| | Faisy, 2003 | 7.73 | | kg |
| | Mayes, 1996 | 68 | | kg |
| | Mayes, 1996 | 37.4 | | kg |
| | Goes, 2017 | 5.50 | | kg |
| | Botran, 2011 | | 0.485 | kg |
| | Shields, 2013 | | 0.24 | kg |
| | Vanderkuip, 2007 | | 0.97 | kg |
| WBC count | Hunter, 1988 | 28.8 | | |

Summary of significant correlations and regression coefficients per factor. APACHE: Acute Physiologic Assessment and Chronic Health Evaluation; BSA: Body surface area; CPB: Cardiopulmonary bypass; $FiO_2$: fraction of inspired oxygen; ICU: Intensive care unit; IL: Interleukin; HR: heart rate; SAPS: simplified acute physiology score; SNAP: score for neonatal acute physiology; T3: Triiodothyronine; WBC: White blood cell.

number of effect size evaluations points out to the lack of statistically rigorous analysis for the contribution of this factor to EE. In considering further study of this factor, researchers have to consider the evidence that suggests that the effect of muscle relaxants on EE is influenced by the depth of sedation, in both human studies [121] and animal studies [122]. Inotropes and vasopressors were evaluated frequently with 74% of those being an effect size evaluation [23,47,50,57,64,90]. The relationship with EE can be explained by the change in oxygen consumption noted with infusions or intrinsic increases of inotropes or vasopressors [123–126]. Clinical scores were evaluated frequently in this review, two of those were in the indeterminate category for their relationship with EE, APACHE [39,41,46,49,95,105,117,127] and SAPS [88,90,113,117,127]. Both of these scores summarize the extent of organ failure based on multiple criteria that may be better treated as separate factors in future studies. The relationship between EE and cytokines is indeterminate since evaluations of cytokines were largely derived from one study [57]. The inflammatory state and its relationship with EE is best described in obesity in both animal studies with an increase in EE associated with the increase in inflammation [128,129].

Nutritional support representing protein intake and route of nutritional intake had an indeterminate relationship with EE [22,50,57,69,77,80,90,130]. This factor requires additional consideration for it evaluation strategy in future studies of energy expenditure. Finally, several other factors were evaluated in small sample sizes limiting the ability to conclude the nature of their relationship with EE [22,23,34,35,37,43,48,50,51,53,56–58,60,62–68,72,75,76,81,84,86,87,90–93,95,116–119,127,131–136]. These factors were summarized in the results section and further evaluation is warranted with a specific focus on the power required to determine the exact relationship with EE.

Fourth, this study identified several factors with no association with EE. These factors were heart rate [34,58,63,70,83,90,92,95,106,116,118,137], $FiO_2$ [70,90,91,138], respiratory rate [70,90,95], respiratory disease diagnosis [22,70,90], PEEP [90,138], CRP [23,52,59,91,134], size [22,51,74,109], and ICU days [22,23,113,116]. Physiologically, heart rate changes and inflammation represented by CRP result in a change in oxygen consumption and hence EE. However, both of those factors were sufficiently evaluated by regression methods and the lack of association with EE is evident. The remaining factors do not represent distinct physiologic states and that absence of an association with EE is expected.

Fifth, this study demonstrated differences in EE and factor assessments between studies. The units utilized for EE and factor measurements limited our ability to form generalizations about relationships. The lack of consistent reporting on variability of correlation coefficients from regression equations limits the meta-analysis of valuable data reported in the literature. Lastly, the lack of consistent reporting on calibration and steady state results question the validity of many of the EE measurements reported in the studies. These findings highlight the need for more formalized reporting in studies of energy expenditure in the critically ill.

There are three main strengths of this review. First, this is the only review that summarizes all factors evaluated in association with EE in the critically ill patient population. This offers an explanation of why current EE prediction formulae are inaccurate. Second, the review collected all types of relationships evaluated and then focused on effect sizes to better understand the strength of the relationship. Third, the review summarizes potential explanations for relationships with EE or the lack thereof with evidence published in humans and animals and forms a basis for additional rigorous studies in this field.

There are five main limitations of this review. First, the data are heterogeneous and represents different patient populations with a wide range of disease phenomena. This is a strength for universally associated factors however may conceal population specific factors. Second, many factors were classified as indeterminant. This may be due to underpowered evaluations of the factor-EE relationship and our selection of arbitrary cutoffs for significance levels (75% significance). Third, indirect calorimetry calibration and patients' steady state were not uniformly reported, with 53% of studies describing calibration and 37% reporting on steady state. Both are required for accurate EE measurement, therefore study quality was variable [139]. Fourth, five of the included studies contributed the largest number of indirect calorimetry measurements performed resulting in potential measurement bias. Fifth, the best statistical method to evaluate for relationships between EE and factors is not clear. This study considered regression analysis with incorporation of potential confounders as the most reliable method.

## 5. Conclusions

To our knowledge, this is the only review that has summarized published literature on the association of clinical factors with EE in the critically ill. Understanding relationships between patient and clinical factors and EE, is an important interval step in the development of accurate formulae to predict EE. The review highlights the limitations of currently available data, and identifies important factors that are not included in existing predictive models of EE. Rigorous studies of relevant factors, populations, sample sizes, and statistical methods are required to support deriving formulae to predict EE.

## Statement of authorship

HM, MJSA, JPA, PP, EP, CP provided substantial contributions to the conception or design of the work; MC to acquisition, analysis, or interpretation of data for the work; HM, MJSA, MC, JPA, PP, EP, CP to drafting the work or revising it critically for important intellectual content; HM, MJSA, MC, JPA, PP, EP, CP to final approval of the version to be published; HM, MJSA, MC, JPA, PP, EP, CP to agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Conflicts of interest

HM, MJSA, MC, JPA, PP, EP, CSP: No conflicts of interest to declare.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.06.009.

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