Dead-Space Ventilation and Mortality in Acute Respiratory Distress Syndrome – Appendix

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Appendix A1: Search Strategy

MEDLINE (via National Library of Medicine) inception to 1 Nov 2022

#1 ("A-a gradient") OR ("Alveolar-arterial gradient") OR ("PAO2-PaO2") OR (Deadspace*) OR (Dead-space*) OR (Ventilatory Ratio) OR (VE/VCO2) OR (Vd/Vt) OR (Ventilatory efficiency) OR (PF Ratio)) OR (P:F Ratio)) OR (PaO2:FiO2) OR (PaO2/FiO2) OR (Oxygenation Index) OR (Volumetric Capnography)

#2 (ARDS) OR ("Acute Respiratory Distress Syndrome") OR ("Acute Lung Injury") OR (ALI)

#3 (Mortality)

#4 (("case reports"[Publication Type]) OR ("all child"[Filter]))

#1 AND #2 AND #3 NOT #4

CENTRAL inception to 1 Nov 2022

#1 ("A-a gradient") OR ("Alveolar-arterial gradient") OR ("PAO2-PaO2") OR (Deadspace*) OR (Dead-space*) OR (Ventilatory Ratio) OR (VE/VCO2) OR (Vd/Vt) OR (Ventilatory efficiency) OR (PF Ratio)) OR (P:F Ratio)) OR (PaO2:FiO2) OR (PaO2/FiO2) OR (Oxygenation Index) OR (Volumetric Capnography)

#2 (ARDS) OR ("Acute Respiratory Distress Syndrome") OR ("Acute Lung Injury") OR (ALI)

#3 (Mortality)

#4 (("case reports"[Publication Type]) OR ("all child"[Filter]))

#1 AND #2 AND #3 NOT #4

Google Scholar inception to 1 Nov 2022

((Deadspace*) OR (Dead-space*) OR (Ventilatory Ratio) OR (VE/VCO2) OR (Vd/Vt) OR (Ventilatory efficiency) OR (PF Ratio) OR (P:F Ratio) OR (PaO2:FiO2) OR (PaO2/FiO2) OR (Oxygenation Index) OR (Volumetric Capnography)) AND (((((ARDS)) OR ("Acute Respiratory Distress Syndrome")) OR ("Acute Lung Injury")) OR (ALI))) AND (Mortality))

Filters and reference screening

Search strategies were modified for each database to include database-specific descriptors and field names. Where available, we used search filters to exclude studies on children or

animals and case reports. References of included articles were hand searched for further eligible studies.

Appendix A2: Eligibility Criteria

Population

Patients aged 16 years or older with acute respiratory distress syndrome as defined by the Berlin criteria (1) or American European Consensus Conference Criteria (2).

1) Arterial partial pressure of Oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 with Positive end expiratory pressure (PEEP) $\geq$ 5
2) Bilateral opacities on radiographs not fully explained by effusion, nodules or collapse,
3) Respiratory failure not fully explained by cardiac failure or fluid overload,
4) within one week of a known clinical insult

ARDS diagnosed at time of admission to ICU, or during ICU stay. Measurements taken within 72 hours of diagnosis of ARDS.

Index prognostic factors

Index measurements of one of the following:

1) Deadspace fraction (V_D/V_T)- Either estimated or measured.
2) End-tidal carbon dioxide to arterial partial pressure of carbon dioxide (P_aCO2) ratio
3) End-tidal carbon dioxide to P_aCO2 gradient
4) Minute ventilation (V_E) to carbon dioxide production (V_{CO2}) ratio (V_E/V_{CO2}),
5) Corrected Minute Ventilation ($P_aCO2 \times V_E$/ 40 mmHg)
6) Ventilatory ratio ($V_E \times P_aCO2$/100 $ml^{-1}\,kg^{-1}$ predicted body weight x37.5 mmHg)

Measurements taken closest to time of enrollment will be prioritised if more than one measurement is reported (e.g. measurement performed on day 1 of study will be used as opposed to day 2).

Comparator

None

Outcome

Primary: Pooled unadjusted odds ratios or relative risk, or standardised mean differences (depending on how outcome is reported) for mortality up to 90 days following diagnosis of ARDS, inclusive of ICU and in-hospital mortality.

Secondary: Ventilator free days, ICU free days, duration of mechanical ventilation, ICU length of stay.

Setting

Intensive care unit

Appendix A3: Data Items for Extraction

We will extract information on first author, country, year of publication, year of study start, number of patients at baseline that were included in the analysis, their mean/median age, gender distribution, the baseline mean/median illness severity score defined as Acute Physiology and Chronic Health Evaluation (APACHE) Score, Sequential Organ Failure Assessment (SOFA) score/, or Simplified Applied Physiology Score (SAPS) II score (if any are applicable), details of treatment received, average levels of measured marker of dead-space ventilation at baseline (either mean with standard deviations or median with interquartile (IQR) range) in the whole sample and separately among those who did and did not subsequently survive, cut-off value used for analysis, type of dead-space ventilation measurement assessed, follow-up duration, and the number of deaths from which the crude risk or odds will be calculated, relative risk of death, odds of death, odds ratios, relative risk ratios, hazard ratios, ICU length of stay and hospital length of stay in the groups with impaired gas exchange measurement in comparison with the subgroup with normal measurements.

Appendix A4: Summary of Identified Studies

Pulmonary dead-space fraction (V_D/V_T)

Cohort	Study design & V_D/V_T method	ARDS definition	ARDS aetiology	Timing of measurement	Female (%)	Mean PaO_2/FIO_2	Sample size	Included in meta-analysis	Data obtained directly from authors	Cut-off	Adjusted variables	Mortality rate (%)	Mortality outcome
Nuckton 2002 (3)	Prospective observational (Measured-MM)	AECC	Sepsis, pneumonia, aspiration, trauma.	Within 24 hours	NR	147	179	Yes	No	0.61	PaO2/FiO2, pH, Compliance, LIS, OI, SAPS II, Vasopressor use, Medical reason for admission, Low volume ventilation, Cirrhosis, Non-pulmonary organ dysfunction.	72	In-Hospital
Kallet 2004 (4)	Prospective observational (Measured-VC)	AECC	Sepsis, pneumonia, aspiration, trauma.	Within 24 hours	22	139	59	Yes	Yes	0.6	NA	51	In-Hospital
Cepkova 2007 (5)	Prospective observational (Measured-VC)	AECC	Sepsis, pneumonia, aspiration.	Within 24 hours	55	177	42	No	NA	NA	NA	36	28-day
Lucangelo 2008 (6)	Prospective observational (Measured-VC)	AECC	Not reported	Within 24 hours	33	NR	36	No	NA	NA	NA	38.9	ICU
Siddiki (Mayo) 2010 (7)	Secondary analysis of prospective cohort (Estimated-SM)	AECC	Predominantly pneumonia and sepsis.	Within 24 hours	51	118	109	Yes	No	0.6	APACHE III, Shock, PaO2/FiO2, PEEP,	34	In-Hospital
Siddiki (ARDSNet) 2010 (7)	Secondary analysis of RCT (Estimated- SM)	AECC	Predominantly pneumonia and sepsis.	Within 24 hours	45	150	1896	Yes	No	0.6	APACHE III, Shock, PaO2/FiO2, PEEP,	29	In-Hospital

Raurich 2010 (8)	Prospective observational (Measured-DB)	AECC	Predominantly pneumonia and sepsis.	Within 72 hours	32	153	80	Yes	Yes	0.6	Age, SAPS II, SOFA, pH	43.75	In-Hospital
Kallet 2014 (9)	Secondary analysis of RCT (Measured-VC)	AECC	Predominantly pneumonia and sepsis.	Within 4 hours	47	166	115	No	NA	NA	PaO2/FiO2, OI, Vasopressor use	19.1	60-day
Beitler (ALTA, EPVENT, APC) 2015 (10)	Secondary analysis of RCT (Measured-VC)	AECC	Predominantly pneumonia and sepsis.	Within 24 hours	45	167	210	Yes	No	NA	APACHE II, ARDS Severity, PEEP, Clinical trial.	16	28-day
Beitler (ARDSNet) 2015 (10)	Secondary analysis of RCT (Estimated-HB)	AECC	Predominantly pneumonia and sepsis.	Within 24 hours	46	172	3135	Yes	No	NA	APACHE II, ARDS Severity, PEEP, Clinical trial.	22	28-day
Zhang 2016 (11)	Prospective observational (Measured-VC)	Berlin	Predominantly pneumonia and sepsis.	Within 24 hours	39	161	46	No	No	NA	NA	52.1	In-Hospital
Kallet 2017 (12)	Secondary analysis of prospective cohort (Measured-VC)	Berlin	Predominantly pneumonia and sepsis.	Within 12 hours	28	133	685	Yes	Yes	0.6	Driving pressure, OI, Age, SAPS II	38	In-Hospital

Morales-Quinteros 2019 (13)	Secondary analysis of prospective cohort (Estimated-HB)	Berlin	Predominantly pneumonia and sepsis.	24-48 hours	38	203	940	Yes	No	NA	APACHEI IV, PaO2/FiO2, PEEP, Driving Pressure, Compliance	31.3	30-day
Lecompte-Osorio (Chicago) 2021 (14)	Secondary analysis of prospective cohort (Estimated-SE)	AECC & Berlin	Not reported	Within 24 hours	47	120	302	Yes	No	NA	Age, APACHE II, Vasopressor use, Ventilator mode.	57.3	In-Hospital
Lecompte-Osorio (ARDSNet) 2021 (14)	Secondary analysis of RCT (Estimated-SE)	Berlin	Not reported	Within 24 hours	45	176	124	Yes	No	NA	Age, APACHE II, Vasopressor use, Ventilator mode.	21	In-Hospital
Morales-Quinteros 2021 (15)	Secondary analysis of prospective cohort (Estimated-HB)	Berlin	COVID-19 ARDS	Within 24 hours	27	131	927	Yes	No	0.58	Age, Sex, BMI, PaO2/FiO2, Creatinine, Hypertension, Diabetes, ACE inhibitor use, Vasopressor/inotrope use, Fluid balance, pH, Mean arterial pressure, Heart rate, Compliance, and PEEP.	28.7	28-day
Fusina 2021 (16)	Secondary analysis of prospective cohort (Estimated-HB)	Berlin	COVID-19 ARDS	Within 24 hours	22	137	187	No	NA	NA	Age, Sex, BMI, No. of comorbidities, Non-respiratory SOFA, PaO2:FiO2, Compliance.	51.3	In-Hospital
Putra 2021 (17)	Retrospective observational (Estimated-HB)	Berlin	COVID-19 ARDS	24-48 hours	30	NR	77	No	NA	NA	NA	74	In-Hospital

Graf 2022 (18)	Secondary analysis of prospective cohort (Measured-VC)	Berlin	COVID-19 ARDS	Within 24 hours	17	175	60	No	NA	0.57	NA	45	28-day
Maj 2022 (19)	Retrospective observational (Estimated-HB)	Berlin	Predominantly COVID-19 ARDS	Within 24 hours	31	129	641	No	NA	NA	Ventilatory ratio, Carbon dioxide production, PaO2/FiO2.	35	ICU
Ventilatory ratio (VR)													
Cohort	**Study design**	**ARDS definition**	**ARDS aetiology**	**Timing of measurement**	**% Female**	**Mean PaO_2/FIO_2**	**Sample size**	**Included in meta-analysis**	**Data obtained from authors**	**Cut-off**	**Adjusted variables**	**Mortality rate (%)**	**Mortality outcome**
Sinha 2013 (20)	Secondary analysis of RCT	AECC	Predominantly pneumonia and sepsis.	Within 24 hours	NR	NR	1307	Yes	No	2	Shock, PaO2/FiO2, APACHE III, PEEP	31.6	In-hospital
Sinha 2014 (21)	Secondary analysis of prospective cohort	AECC	Predominantly pneumonia and sepsis.	Within 24 hours	NR	170	121	Yes	No	2	APACHE II, PEEP.	29.7	In-hospital
Morales-Quinteros 2019 (13)	Secondary analysis of prospective cohort	Berlin	Predominantly pneumonia and sepsis.	24-48 hours	38	203	940	Yes	No	NA	APACHE IV, PaO2/FiO2, PEEP, Driving Pressure, Compliance	31.3	30-day
Sinha (San Francisco) 2019 (22)	Prospective observational	Berlin	Predominantly pneumonia and sepsis.	Within 24 hours	26	NR	946	Yes	No	2	PaO2/FiO2, Driving pressure.	39	In-hospital
Sinha (FACTT) 2019 (22)	Secondary analysis of RCT.	AECC	Predominantly pneumonia and sepsis.	Within 24 hours	50	155	520	Yes	No	2	PaO2/FiO2, Driving pressure.	26.1	60-day

Grasselli 2020 (6)	Prospective observational	Berlin	COVID-19 ARDS	Within 24 hours	23	NR	301	Yes	Yes	2	NA	28.4	28-day
Morales-Quinteros 2021 (15)	Secondary analysis of prospective cohort	Berlin	COVID-19 ARDS	Within 24 hours	27	131	927	Yes	No	1.72	Age, Sex, BMI, PaO2/FiO2, Creatinine, Hypertension, Diabetes, ACE inhibitor use, Vasopressor/inotrope use, Fluid balance, pH, Mean arterial pressure, Heart rate, Compliance, PEEP.	28.7	28-day
Beloncle (COVID-19) 2021 (23)	Prospective observational	Berlin	COVID-19 ARDS	Within 24 hours	30	146	135	Yes	No	2	NA	19.3	28-day
Beloncle (EXPRESS) 2021 (23)	Secondary analysis of RCT.	AECC	Predominantly pneumonia and sepsis.	Within 24 hours	33	138	767	Yes	No	2	NA	23.5	28-day
Fusina 2021 (16)	Secondary analysis of prospective cohort	Berlin	COVID-19 ARDS	Within 24 hours	22	137	187	Yes	No	NA	Age, Sex, BMI, No. of comorbidities, Non-respiratory SOFA, PaO2/FiO2, Compliance.	51.3	In-Hospital
Ruan 2021 (24)	Retrospective observational	Berlin	Predominantly pneumonia and sepsis.	Within 24 hours	32	148	258	Yes	Yes	2	NA	43.4	30-day
Torres 2021 (25)	Prospective and retrospective observational cohort	Berlin	COVID-19 ARDS	Within 24 hours	29	123	1118	Yes	Yes	2	Age, Sex, Hypertension, Chronic respiratory disease, Cardiovascular SOFA , PaO2/FiO2, Creatinine, Lymphocyte count, Platelet count, D-dimer,	38.7	In-hospital
Kallet 2021 (26)	Secondary analysis of prospective cohort	Berlin	Predominantly pneumonia and sepsis.	Within 12 hours	28	133	685	Yes	No	NA	End tidal to arterial carbon dioxide ratio, Eligibility for randomised trial, OI, Age, APACHE II, Platelet, Bilirubin.	38	In-Hospital
Putra 2021 (17)	Retrospective observational	Berlin	COVID-19 ARDS	24-48 hours	77	109	77	No	NA	NA	NA	74	In-Hospital

Sedhai 2021 (27)	Secondary analysis of prospective cohort	Berlin	Predominantly pneumonia and sepsis.	Within 24 hours	39	155	340	No	NA	NA	NA	37	In-Hospital
Monteiro 2022 (28)	Secondary analysis of RCT.	Berlin	Predominantly pneumonia and sepsis.	Within 24 hours	44	99	1006	Yes	No	2	APACHE III, Vasopressor use, PaO2/FiO2, Sex	36.8	28-day
Maj 2022 (19)	Retrospective observational	Berlin	Predominantly COVID-19 ARDS	Within 24 hours	31	129	641	No	No	NA	Pulmonary dead-space fraction, Carbon dioxide production, PaO2:FiO2	35	ICU
Siegel 2022 (29)	Secondary analysis of prospective cohort	Berlin	Predominantly pneumonia and sepsis.	Within 24 hours	46	159	50	No	NA	NA	OI, APACHE III, RALE	56	28-day

ARDS, Acute respiratory distress syndrome; AECC, American European Consensus Conference Definition; Berlin, Berlin definition of acute respiratory distress syndrome; PaO_2/FIO_2, Arterial partial pressure of oxygen to fraction of inspired oxygen ratio; MM, Metabolic monitor; VC, Volumetric capnography; ICU, Intensive care unit; SM, Siddiki Method; DB, Douglas bag; HB, Harris-Benedict; LIS, Lung injury score; OI, Oxygenation index; SAPS, Simplified acute physiology score; APACHE, Acute physiology and chronic health evaluation; PEEP, Positive end expiratory pressure; SOFA, Sequential organ failure assessment; BMI, body mass index; ACE, angiotensin converting enzyme; RALE, Radiologic assessment of lung edema.

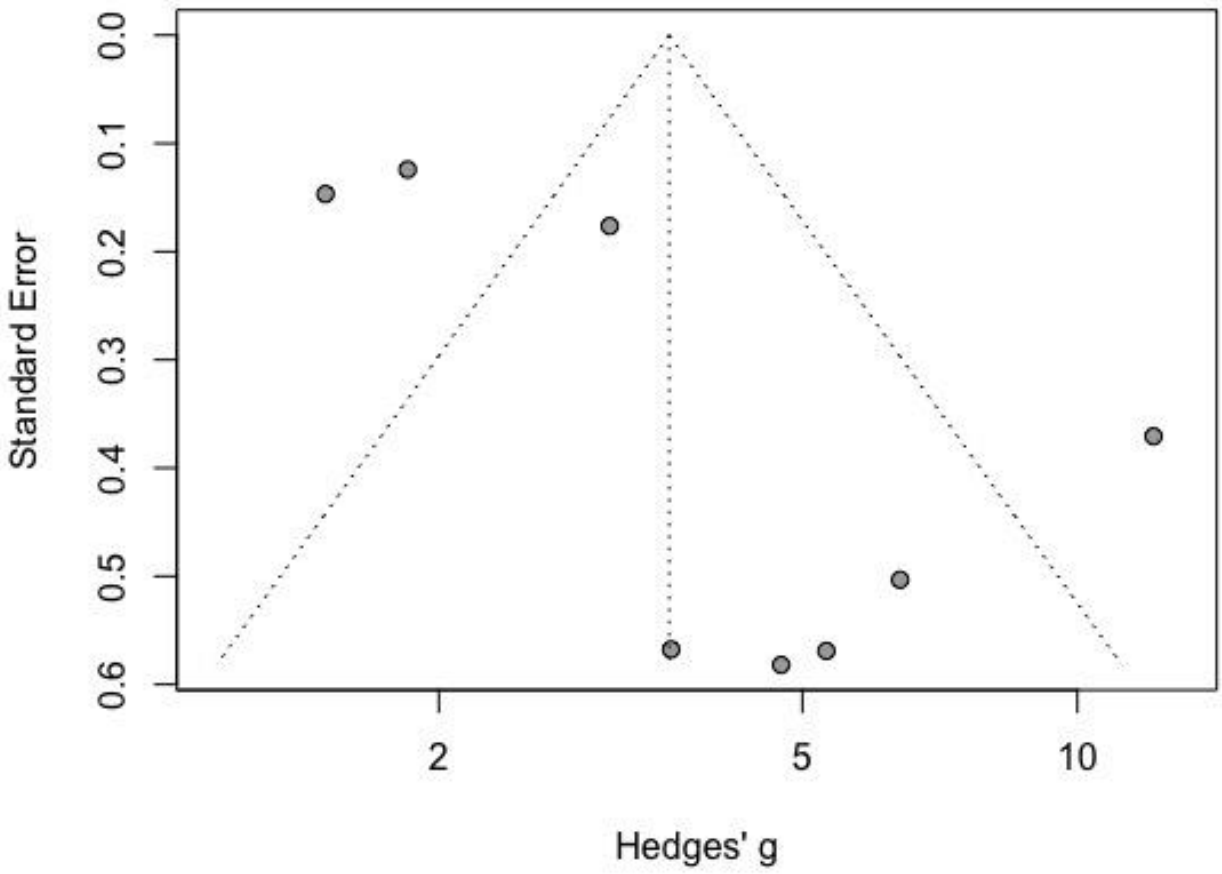
Appendix A5. Risk of Bias Assessment (QUIPS Tool)

Study	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Statistical analysis reporting
Pulmonary dead-space fraction (V_D/V_T)						
Nuckton 2002	Low	Low	Low	Low	Low	Low
Kallet 2004	Low	Low	Low	Low	Mod[1]	Low
Cepkova 2007	Low	Low	Mod[2]	Low	Mod[1]	Low
Lucangelo 2008	Low	Low	Low	Low	Mod[1]	Low
Siddiki 2010 (Mayo)	Low	Low	Mod[3]	Low	Low	Low
Siddiki 2010 (ARDSNet)	Low	Low	Mod[3]	Low	Low	Low
Raurich 2010	Low	Low	Low	Low	Low	Low
Kallet 2014	Low	Low	Low	Low	Low	Low
Beitler (ALTA, EPVENT, APC) 2015	Low	Low	Low	Low	Low	Low
Beitler (ARDSNet) 2015	Low	Low	Low	Low	Low	Low
Kallet 2017	Low	Low	Low	Low	Low	Low
Morales-Quinteros 2019	Low	Low	Low	Low	Low	Low
Lecompte-Osorio 2021 (Chicago)	Low	Low	Mod[3]	Low	Low	Low
Lecompte-Osorio 2021 (ARDSNet)	Low	Low	Mod[3]	Low	Low	Low
Morales-Quinteros 2021	Low	Low	Mod[4]	Low	Low	Low
Fusina 2021	Low	Low	Low	Low	Low	Low
Putra 2021	Low	Low	Mod[3]	Low	Mod[1]	Low
Graf 2022	Low	Low	Low	Low	Mod[1]	Low
Maj 2022	Low	Low	High[5]	Low	Low	Low
Ventilatory Ratio (VR)						
Sinha 2013	Mod[6]	Low	Low	Low	Low	Mod[6]
Sinha 2014	Low	Low	Low	Low	Low	Low
Morales-Quinteros 2019	Low	Low	Low	Low	Low	Low
Sinha (San Francisco) 2019	Low	Low	Low	Low	Low	Low
Sinha (FACTT) 2019	Low	Low	Low	Low	Mod[7]	Low
Morales-Quinteros 2021	Low	Low	Mod	Low	Low	Low
Beloncle (COVID-19) 2021	Low	Low	Low	Low	Mod[1]	Low
Beloncle (EXPRESS) 2021	Low	Low	Low	Low	Mod[1]	Low
Fusina 2021	Low	Low	Low	Low	Low	Low
Ruan 2021	Mod[1]	Low	Low	Low	Mod[1]	Low
Torres 2021	Mod	Low	Low	Low	Low	Low
Kallet 2021	Low	Low	Low	Low	Low	Low
Putra 2021	Low	Low	Mod[3]	Low	Mod[1]	Low
Sedhai 2021	Low	Low	Low	Low	Mod[1]	Low

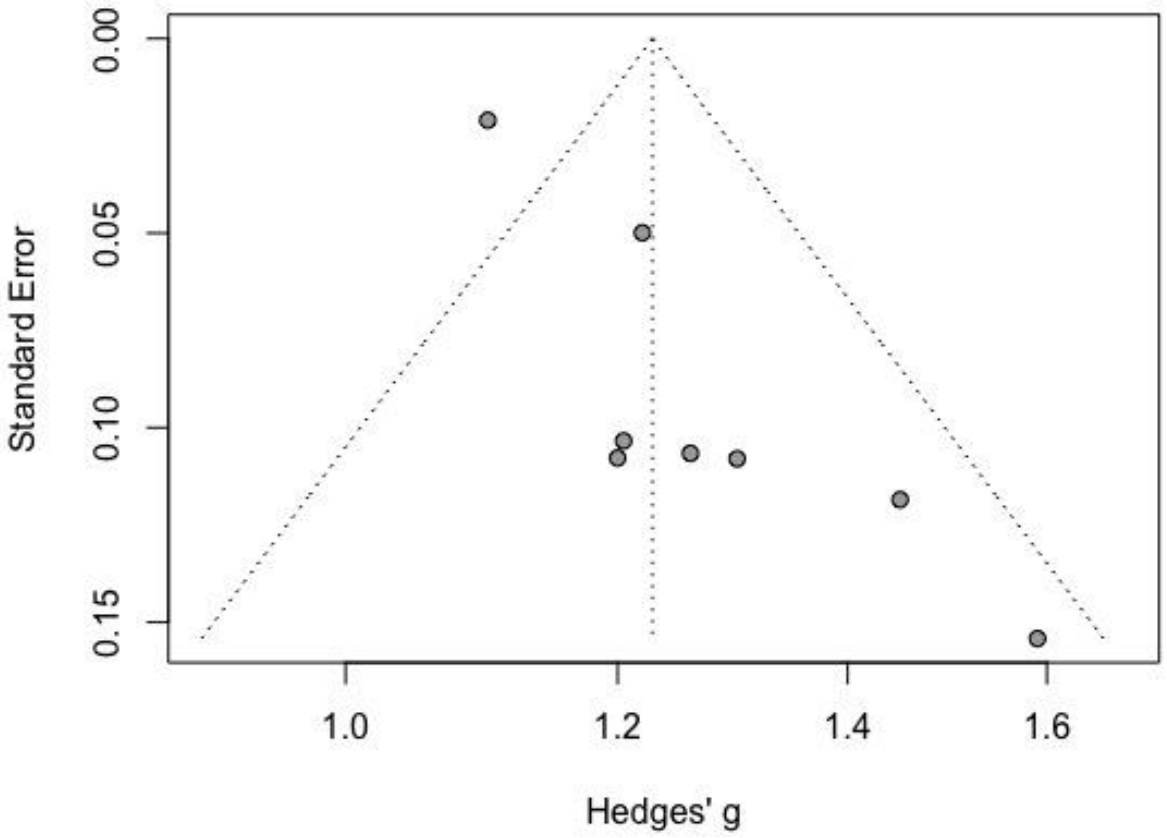
Graselli 2022	Low	Low	Low	Low	Mod[1]	Low
Monteiro 2022	Low	Low	Low	Low	Low	Low
Maj 2022	Low	Low	Low	Low	Low	Low
Seigel 2022	Low	Low	Low	Low	Low	Low

1. Not controlled for any possible confounding variables.
2. 3 patients Vd/Vt not measured. Not reported how this was accounted for in analysis.
3. Novel unvalidated method of estimation.
4. Some estimation values do not seem consistent with all other studies (Direct measurements
5. Not all patients had Vd/Vt measured the same way. 20% were measured, 80% estimated.
6. Multivariable analysis performed with each individual comparator, not together in a model. Conclusions drawn could be misinterpreted.
7. No adjustment for confounding apart from stratification by PF ratio

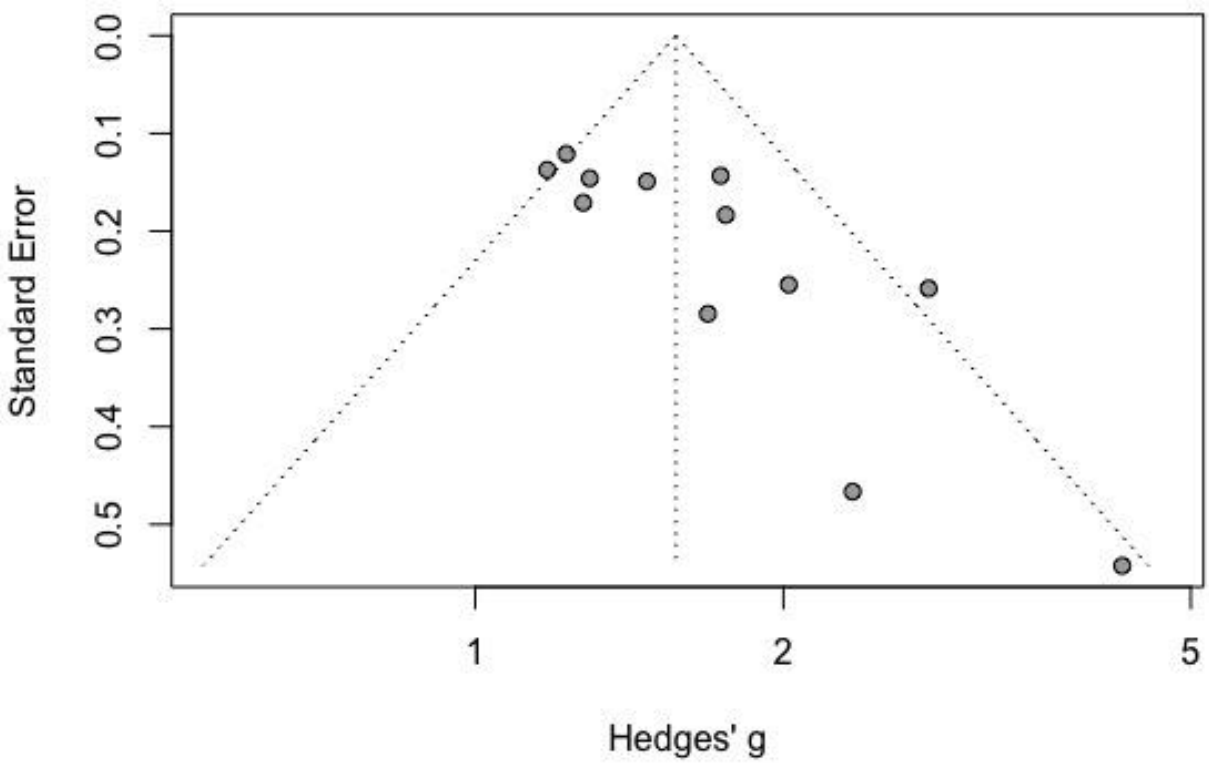
Appendix A6: Funnel Plot High vs Low V_D/V_T and Mortality



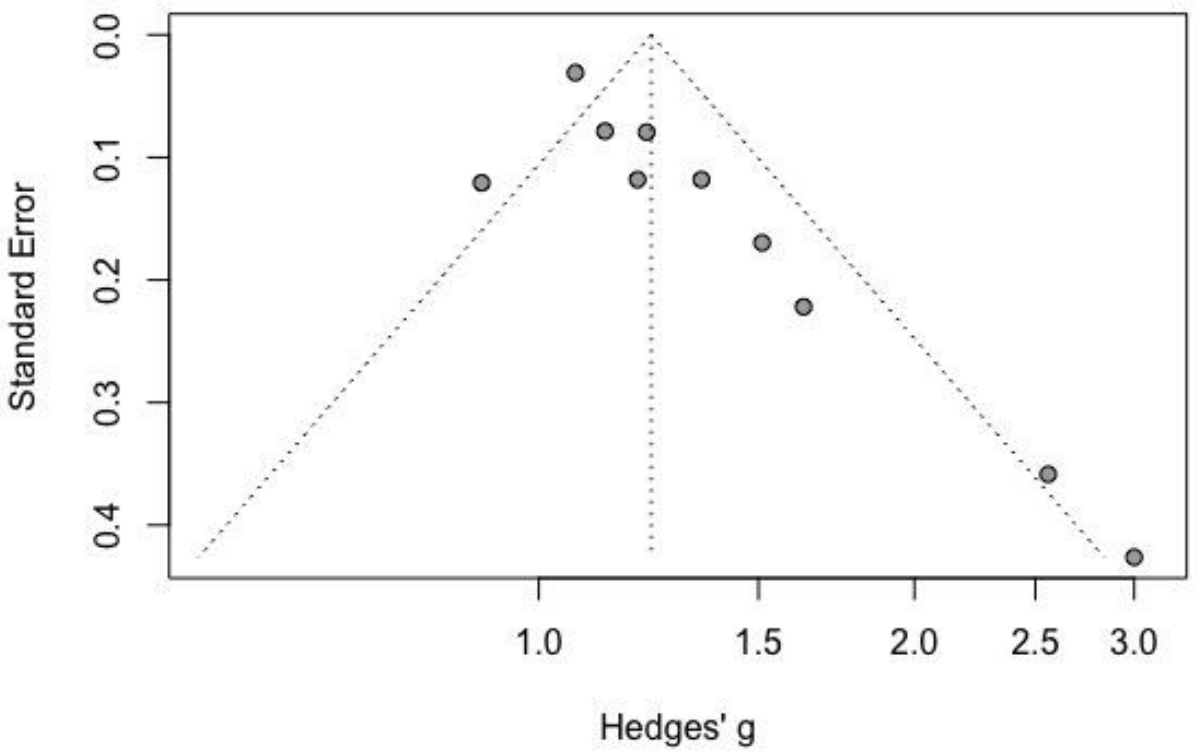
Appendix A7: Funnel Plot V_D/V_T and Adjusted Mortality



Appendix A8: Funnel Plot High vs Low VR and Mortality



Appendix A9: Funnel Plot VR and Adjusted Mortality



Appendix A10: Egger's Test

Meta-analysis	Egger's Test p-value
High vs low V_D/V_T	0.0341
V_D/V_T and adjusted mortality	0.002
High vs low VR	0.004
VR and adjusted mortality	0.008

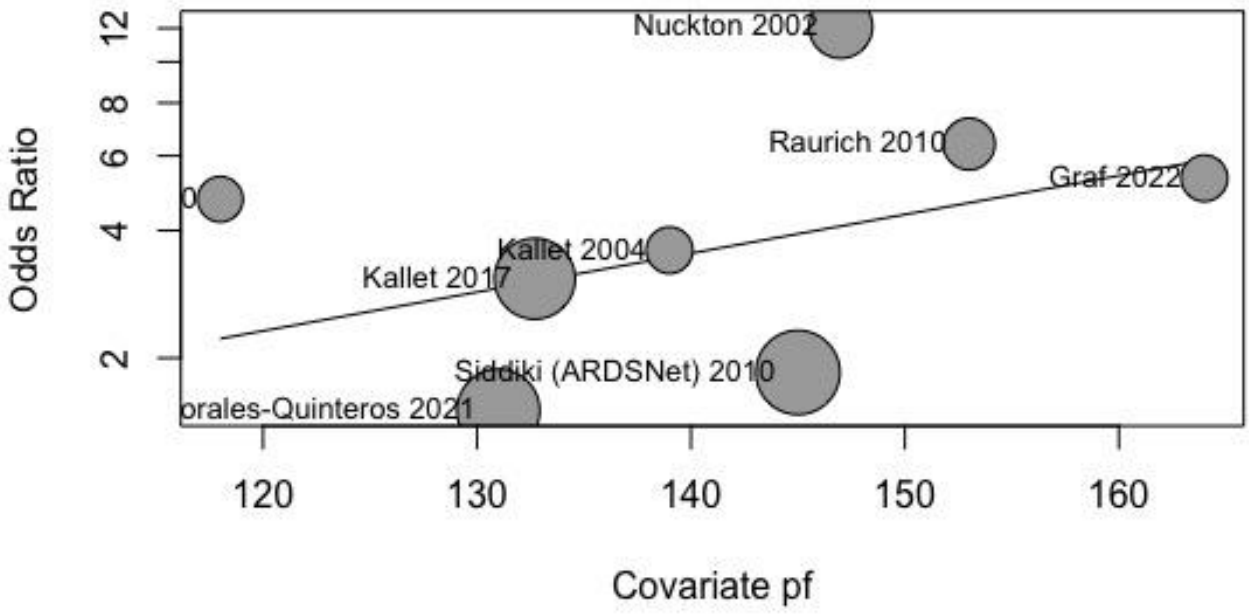
V_D/V_T, Pulmonary dead-space fraction; VR, Ventilatory Ratio.

Appendix A11: GRADE Assessment of Dead-space Ventilation Indices.

Dead-space ventilation index	No. of patients	No of cohorts	Univariate			Multivariate			Phase	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/large effect size	Dose effect	Overall quality
			+	0	-	+	0	-									
Pulmonary dead-space fraction (V_D/V_T)	9,850	20	15	2	0	10	4	0	2	No	Yes	No	No	Yes	Yes	Yes	+++
Ventilatory Ratio	10,362	18	12	3	0	7	4	0	2	No	Yes	No	No	Yes	No	Yes	+++
End-tidal to arterial carbon dioxide ratio	885	2	2	0	0	1	0	0	1	Yes	Yes	No	Yes	Yes	No	No	++
Arterial to end-tidal carbon dioxide gradient	426	1	1	0	0	1	0	0	1	Yes	Yes	No	Yes	Yes	No	No	++
Corrected Minute Ventilation	187	1	1	0	0	1	0	0	1	Yes	Yes	No	Yes	Yes	No	No	+

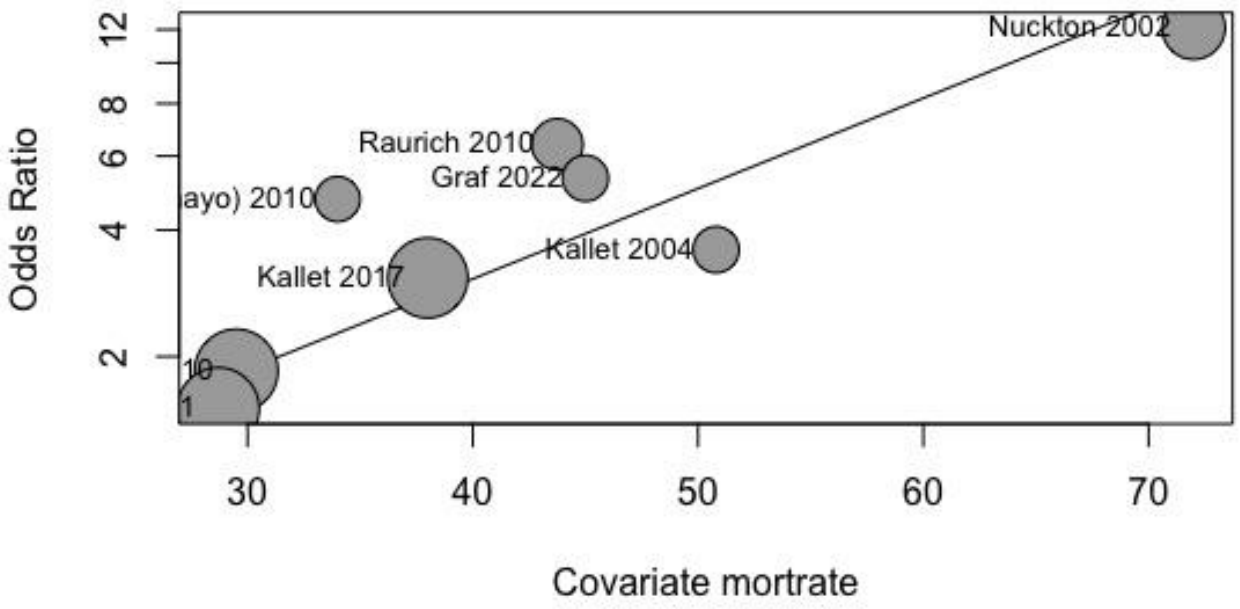
Phase, phase of investigation: Phase 1, outcome prediction research or explanatory research aimed to identify associations between potential prognostic factors and the outcome; Phase 2, explanatory research aimed to confirm independent associations between potential prognostic factor and the outcome; Phase 3, explanatory research aimed to understand prognostic pathways. For univariate and multivariate analyses: +, number of significant effects with a positive value; 0, number of non-significant effects; -, number of significant effects with a negative value. For GRADE factors: For overall quality of evidence: +, very low; ++, low; +++, moderate; ++++, high.

Appendix A12: Meta-regression of PaO_2/FIO2 vs Effect Estimate (High vs Low V_D/V_T and Mortality)



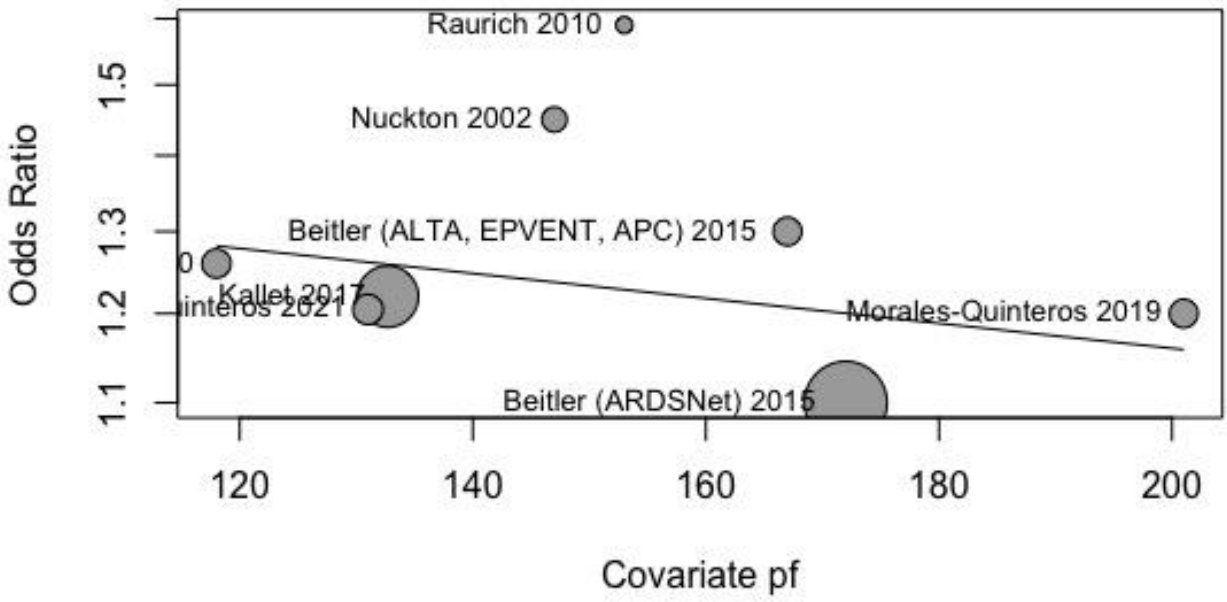
R^2 (amount of heterogeneity accounted for) = 0.00%
Estimate = 0.0232, Standard error = 0.0285 (p = 0.4533)

Appendix A13: Meta-regression of Cohort Mortality Rate vs Effect Estimate (High vs Low V_D/V_T and Mortality)



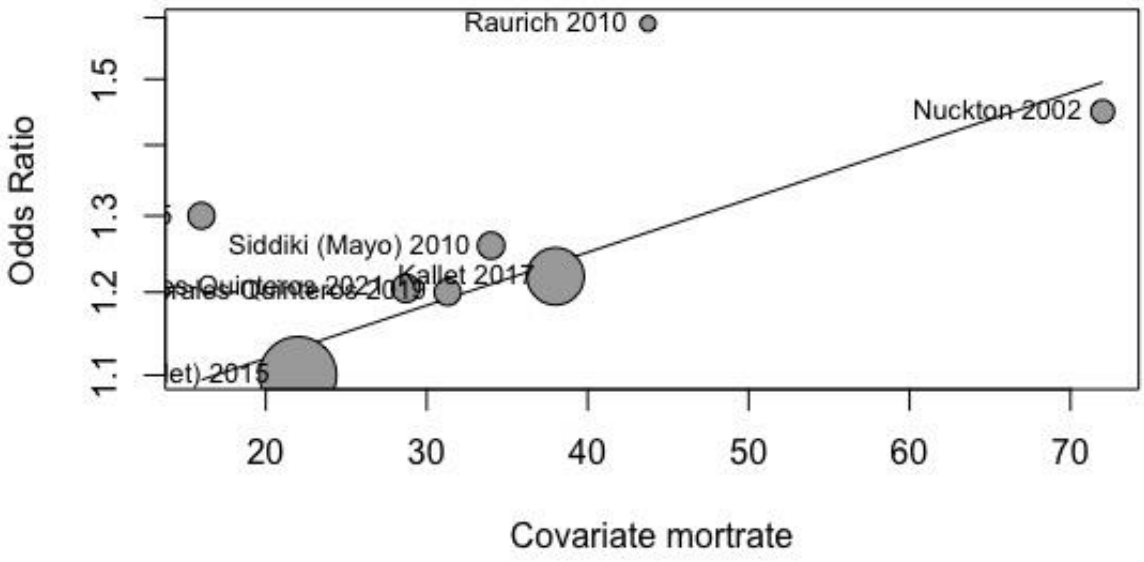
R^2 (amount of heterogeneity accounted for) = 100%
Estimate = 0.0495, Standard error = 0.0076 (p = 0.0006)

Appendix A14: Meta-regression of PaO_2/FIO2 vs Effect Estimate (V_D/V_T and Adjusted Mortality)



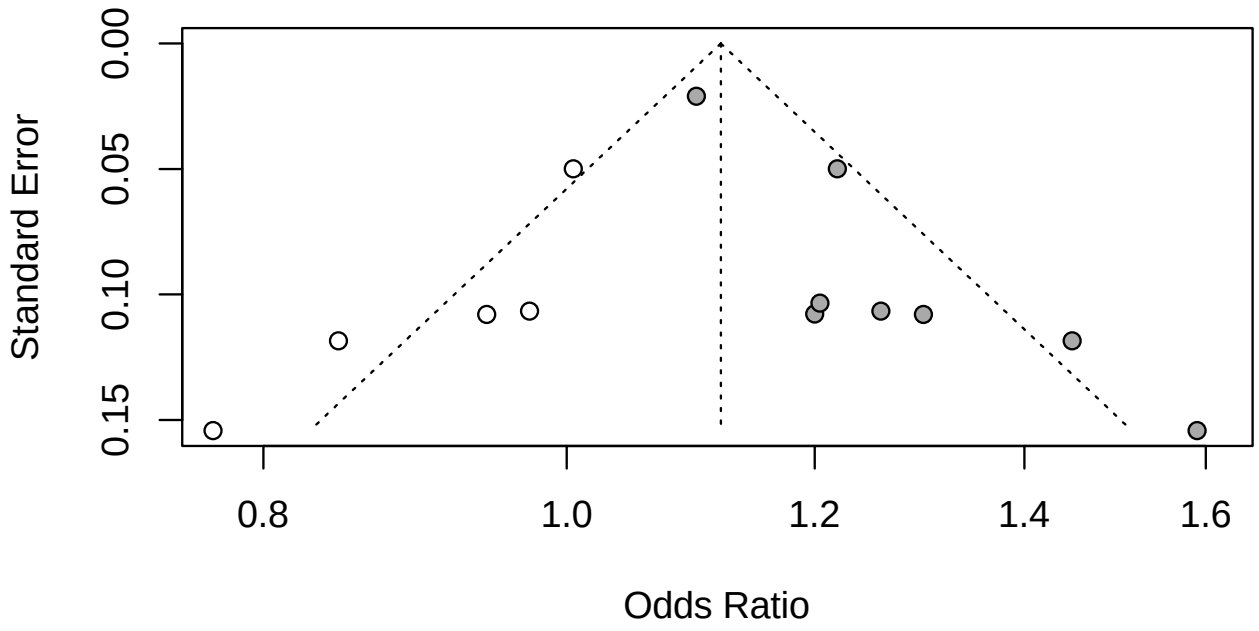
R^2 (amount of heterogeneity accounted for) = 6.35%
Estimate =-0.0012, Standard error = 0.0016 (p = 0.47)

Appendix A15: Meta-regression of Cohort Mortality Rate vs Effect Estimate (V_D/V_T and Adjusted Mortality)

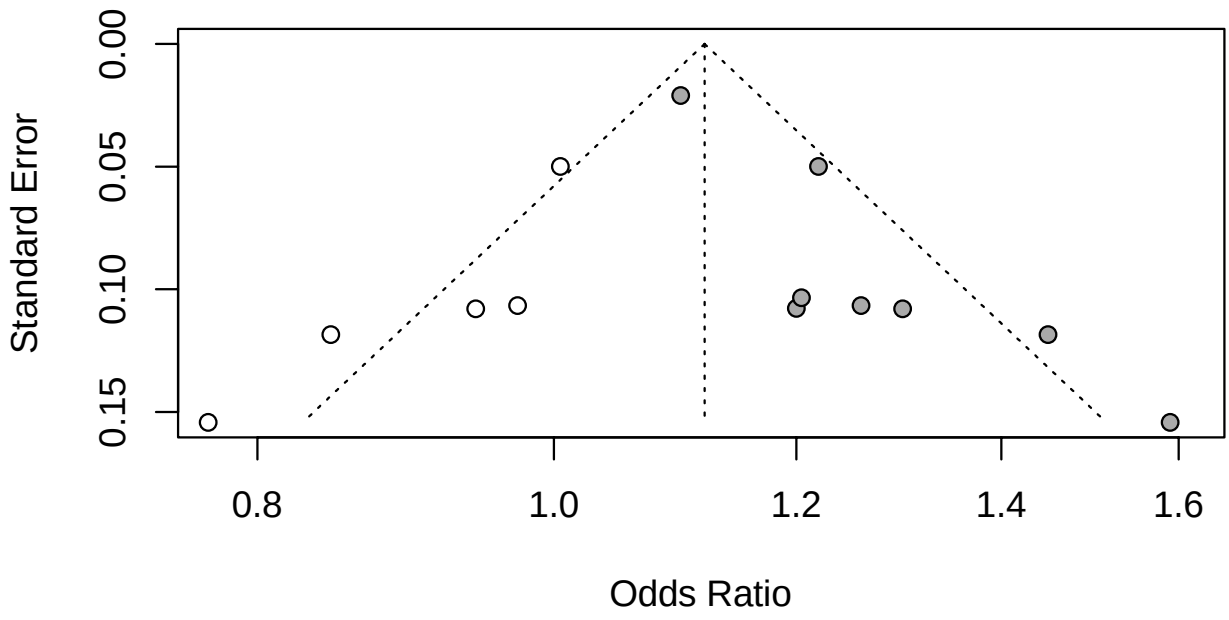


R^2 (amount of heterogeneity accounted for) = 84.66%
Estimate = 0.0056 Standard error= 0.002 (p = 0.034)

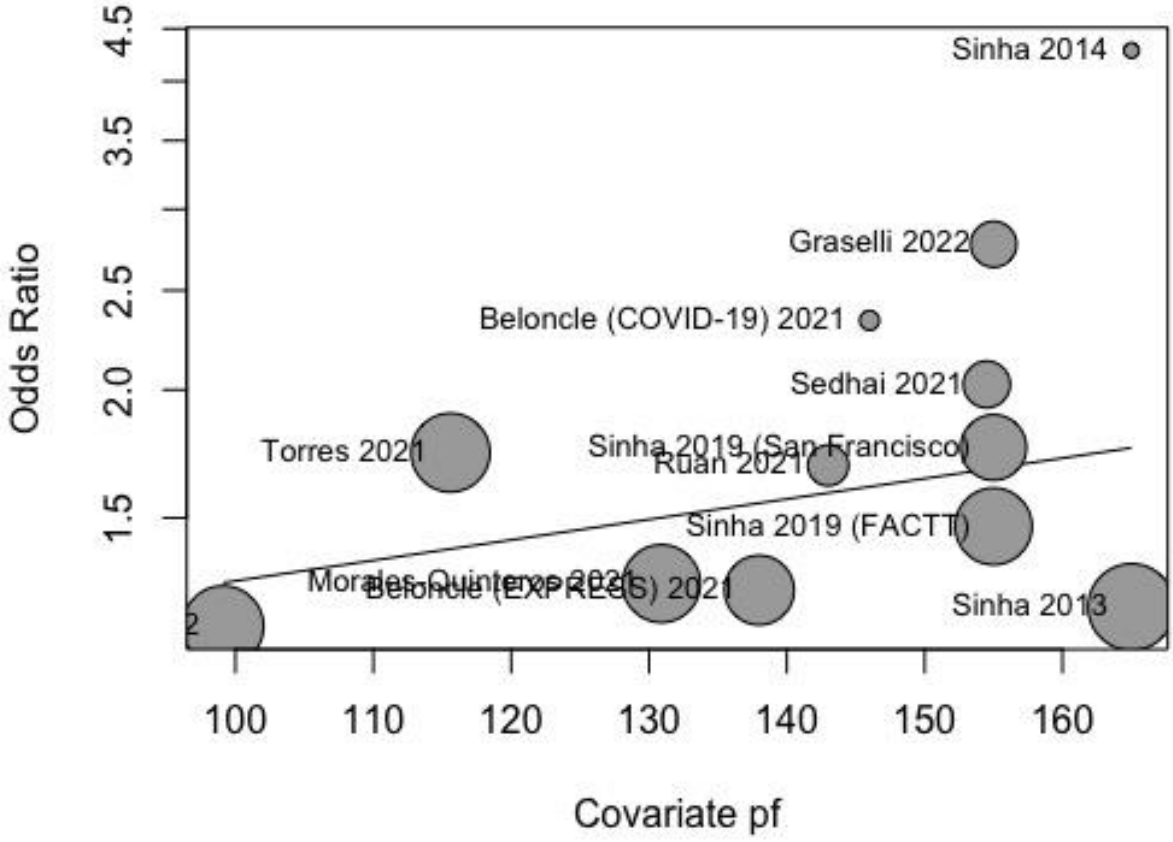
Appendix A16: Trim and Fill Funnel Plot High vs Low V_D/V_T and Mortality



Appendix A17: Trim and Fill Funnel Plot V_D/V_T and Adjusted Mortality

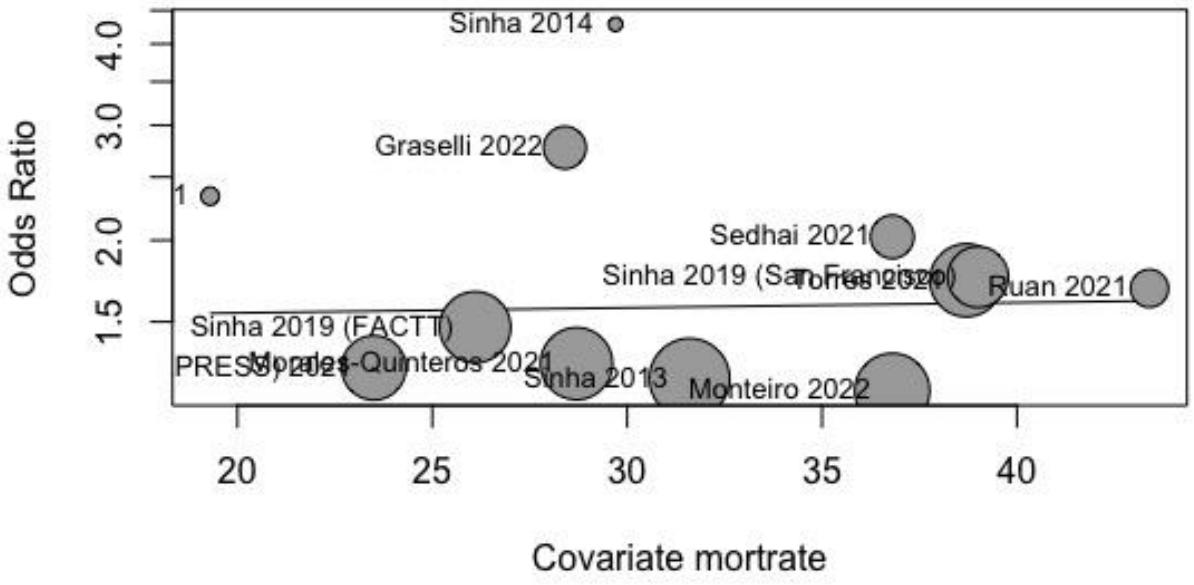


Appendix A18: Meta-regression of PaO_2/FIO2 vs Effect Estimate (High vs Low VR and Mortality)



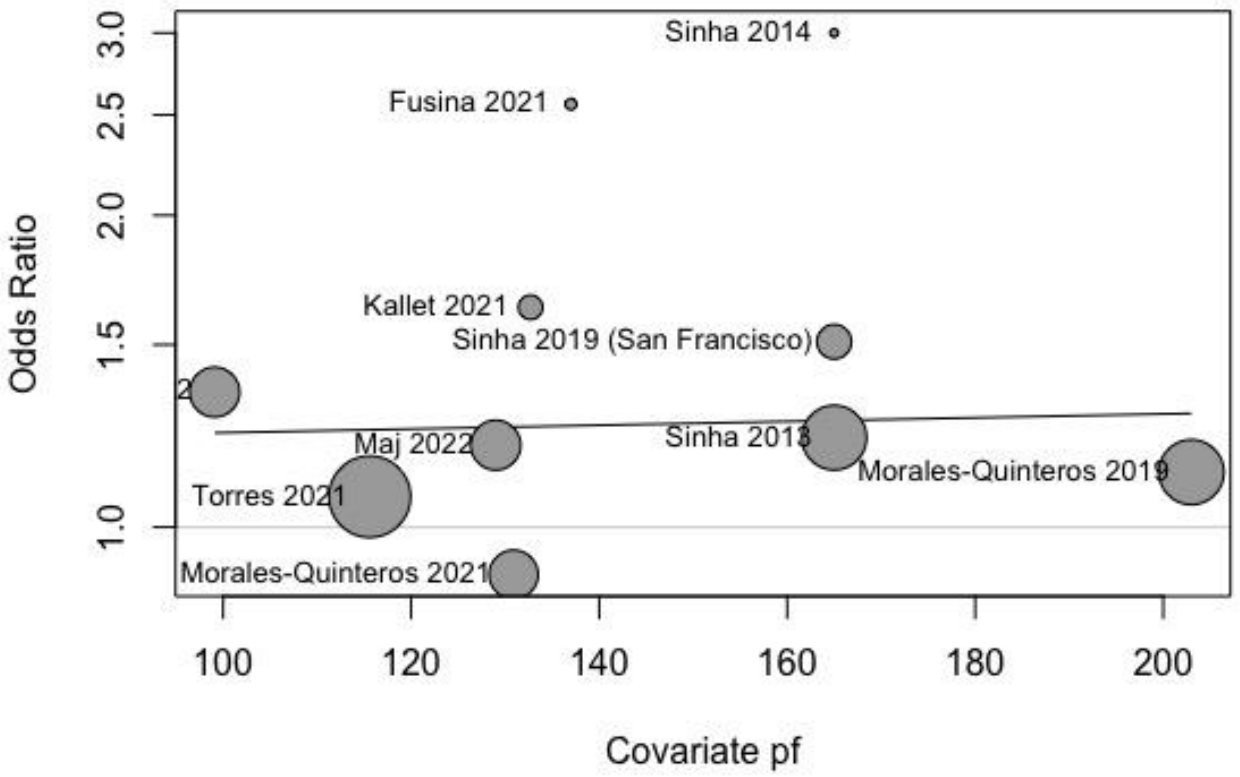
R^2 (amount of heterogeneity accounted for) = 0.00%
Estimate = 0.0232 Standard error= 0.0285 (p = 0.453)

Appendix A19: Meta-regression Cohort Mortality Rate vs Effect Estimate (High vs Low VR and Mortality)



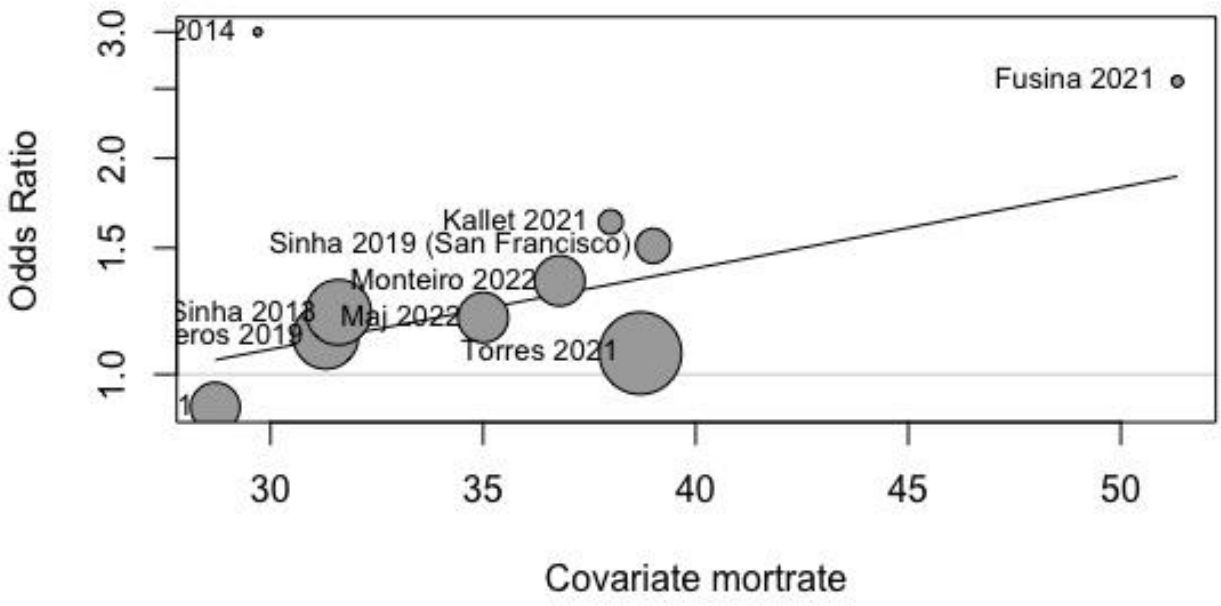
R^2 (amount of heterogeneity accounted for) = 0.00%
Estimate = 0.0018 Standard error= 0.0145 (p = 0.903)

Appendix A20: Meta-regression PaO_2/FIO2 vs Effect Estimate (VR and Adjusted Mortality)



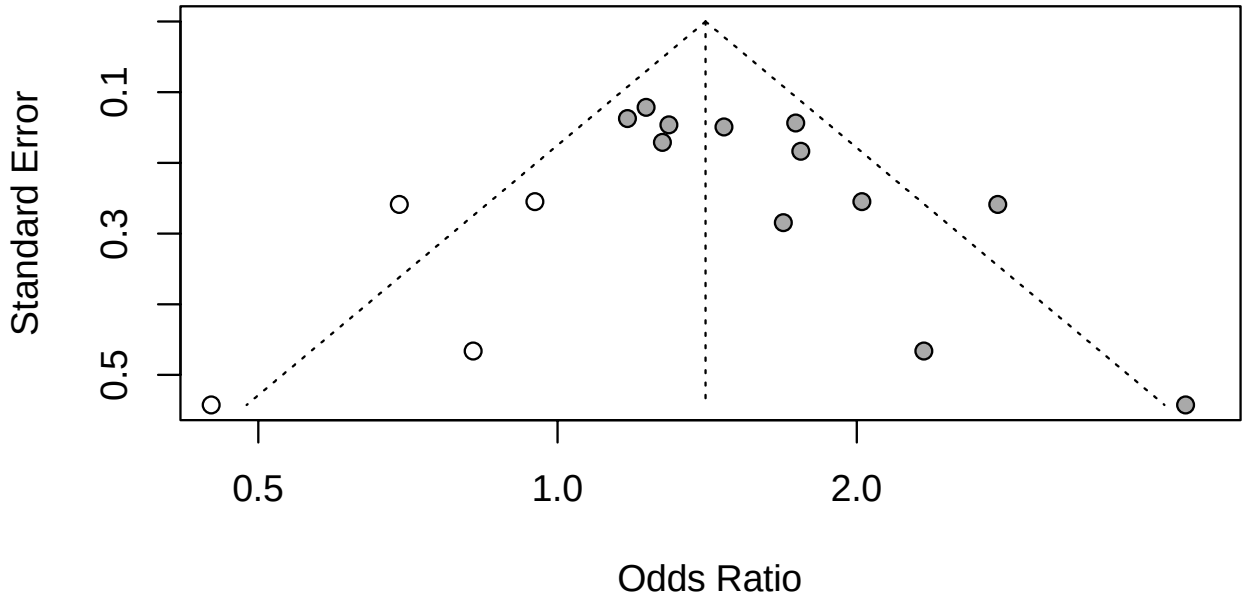
R^2 (amount of heterogeneity accounted for) = 0.00%
Estimate = 0.0124 Standard error= 0.0102 (p = 0.308)

Appendix A21: Meta-regression Cohort Mortality Rate vs Effect Estimate (VR and Adjusted Mortality)

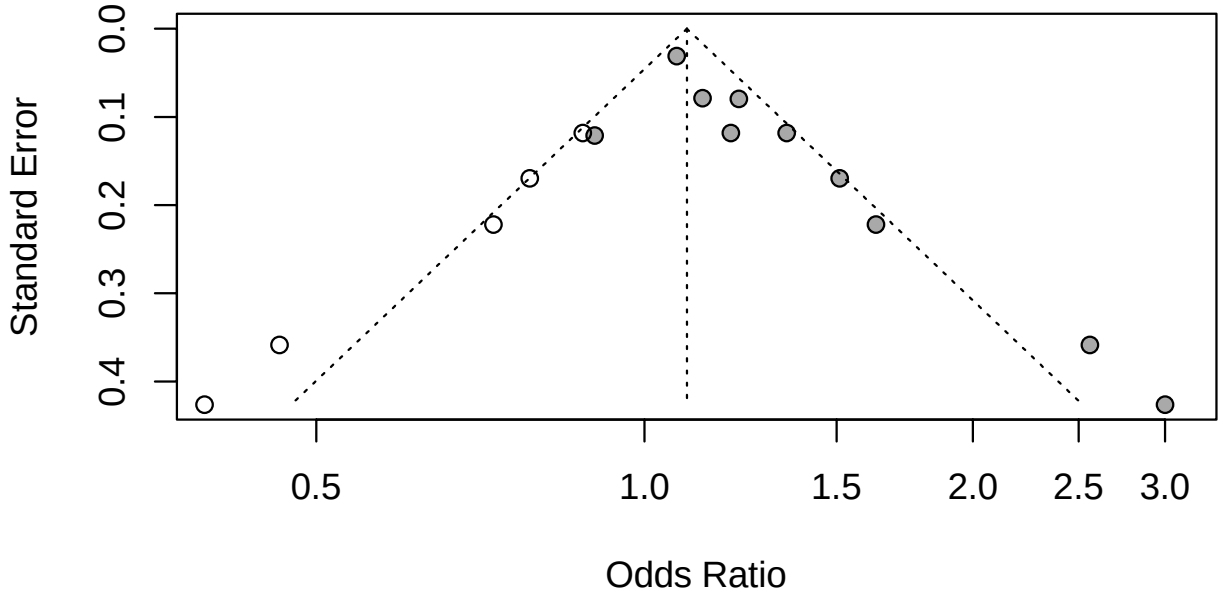


R^2 (amount of heterogeneity accounted for) = 0.00%
Estimate = 0.0260 Standard error= 0.0157 (p = 0.136)

Appendix A22: Trim and Fill Funnel Plot High vs Low VR and Mortality



Appendix A23: Trim and Fill Funnel Plot VR and Adjusted Mortality



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