

Electronic Supplementary material

Manuscript Title: Burden of Pertussis in Adults Aged 50 Years and Older: A Retrospective Database Study in England

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Text S1 Data sources

As previously described [1, 2], the Clinical Practice Research Datalink (CPRD) [3] – the United Kingdom (UK)’s research service – is funded by the National Institute for Health Research and the Medicines and Healthcare Products Regulatory Agency. GOLD, which is a primary care database held by the CPRD [4], contains longitudinal primary care data from > 500 real-world clinical practices. It covers approximately 8% of the population of the UK, including > 20 million patient lives, with > 5 million currently registered, active patients. Since August 2018, CPRD has offered access to CPRD Aurum practices using the EMIS Web electronic patient record system for data collection. In March 2020, CPRD Aurum included > 10 million patients from > 1000 contributing practices. Merged Aurum and GOLD data were used in the current study.

The CPRD offers a linkage with Hospital Episode Statistics (HES), which allows the same patient to be tracked in secondary care. The HES Admitted Patient Care database includes all hospitalisation information. HES outpatient data include records of outpatient specialist appointments in England only. The linkage is only available for practices in England and is only performed for those practices that opt into the linkage. The latest available linked HES data (containing patient records until November 2018; linkage set 17) were used for the current study.

Text S2 Propensity score matching

As previously described [1, 2], due to data minimisation requirements implemented by the CPRD, which limited requests for HES-linked data to approximately 600,000 patients, a list of potential comparators (without pertussis) was created before submitting the data linkage request. To pre-select close potential comparators, only patients with the same practice, sex, and year of birth of patients with a diagnosis of pertussis were retained and assigned the index date of the corresponding pertussis case.

Pertussis patients were then matched (1:1) to controls using a nearest-neighbour matching method with a calliper (i.e., the maximum permitted difference between matched subjects) equal to 1/4 of the pooled standard deviation of the propensity score. The propensity score was assigned to each patient using a logistic regression model with the incidence risk of pertussis as the dependent variable and covariates identified below as independent variables. Based on available literature [5] and expert clinical input, baseline variables used to calculate the propensity score were: age, sex, and environmental/socioeconomic deprivation (Index of Multiple Deprivation (IMD)) (all at index); smoking status and direct medical costs (DMC) (during months –18 to –6); hypertension, depression, diabetes mellitus, asthma, and chronic obstructive pulmonary disease (COPD) (any time before index); and the number of chronic conditions (≥ 2 vs 0/1 of those above plus heart failure, anxiety, chronic kidney disease, coronary heart disease and chronic/persistent cough, the latter of which was only counted up to –6 months).

Standardised mean differences (SMDs) were used to assess match quality and balance in baseline characteristics for continuous and binary variables. Standardised differences > 0.20 after matching were considered unbalanced. For multilevel categorical variables where the SMD could not be estimated, p -values were used to estimate the balance between matched cohorts. For ordinal or interval multilevel categorical variables, p -values from the Wilcoxon rank sum test (Mann-Whitney-U test) were calculated. For categorical values that were not ordinal or interval, the Fisher Exact test was used and if it was not possible to use the Fisher Exact test (due to large numbers of categories or observations), then the Chi Square test was used. Variables that remained unbalanced after matching were considered for inclusion as covariates in the DMC analysis.

Text S3 Methods of cost calculations

As previously described [1, 2], DMC included all costs associated with health care services and the five most common (in the pertussis cohort; during each time period shown in main Fig. 1), general practitioner (GP) prescriptions, and clinical assessments. The unit cost associated with each resource or service was calculated and applied to each health care resource utilisation (HCRU). Health care in the UK is financed by the National Health Service (NHS). Different publicly available sources were used to identify costs for different HCRU.

Unit costs for GP, nurse, and outpatient specialist visits were derived from the 2019 Unit Costs of Health and Social Care published by the Personal Social Services Research Unit of the University of Kent [6]. Unit costs for the five most commonly prescribed products (pertussis cohort; during each time interval shown in main Fig. 1) were derived from the September 2019 NHS Drug Tariff [7]. Unit costs for the five most common clinical assessments (e.g., blood pressure, weight, and laboratory tests) and accident and emergency costs were derived from the 2018/2019 National Schedule of NHS Reference Costs [8].

Hospitalisations are financed by Healthcare Resource Groups (HRGs) in the UK, so 2018/2019 HRG4+ Reference Costs Grouper software [9, 10] was used to assign an HRG code for each hospitalisation using the diagnosis and procedure codes associated with the episode, and the type of stay (day case, regular day or night admission, elective inpatient, non-elective long stay, non-elective short stay). Costs for hospitalisations were applied by matching the generated HRG code of each hospitalisation episode with those in the National Schedule of Reference Costs [11]. For HRG codes where no cost was available in the National Schedule of Reference Costs, the average cost per type of stay (day case, regular day or night admission, elective inpatient, non-elective long stay, non-elective short stay) was used. The 2017/2018 National Schedule of Reference Costs [12] was used to derive the costs for inpatient episodes from –18 to –6 months used for the propensity score matching. The 2018/2019 National Schedule of Reference Costs was used to derive costs for inpatient episodes from –6 months to +11 months [8].

Costs were calculated as:

$$\text{Direct medical costs per patient} = \text{HCRU unit cost} * \text{HCRU events}$$

If there were no events, costs were assumed to be zero. Total DMC were estimated as the sum of all the costs incurred. The mean (standard deviation) annualised costs in each cohort for all events occurring during the study period are reported.

Costs were annualised as:

$$\text{Annualized cost} = \frac{\text{Sum of direct medical costs per month}}{\text{Months of available follow-up}} * 12$$

All matched patients were included in the descriptive cost analysis and minimum follow-up time was applied.

As HCRU and DMC were expected to have skewed distributions, non-normality tests were performed: the Kolmogorov-Smirnov test, the Anderson-Darling test, and the Cramér-von Mises test. As the results showed a non-normal distribution of HCRU and the distribution of cost data was skewed, the Wilcoxon rank sum test was used to compare these between the pertussis and control cohorts.

Text S4 DMC statistical methods

Excess DMC among the pertussis vs control cohorts during months –1 to +11 were estimated using a generalised linear model analysis. For this analysis, cohorts were matched on a propensity score model including age, sex, IMD, baseline DMC, smoking status, asthma, COPD, hypertension, depression, and diabetes. DMC were initially modelled with a log-link and normal distribution, a gamma distribution and Tweedie distribution. Model performance was tested using histograms and residual plots for residuals and Akaike Information Criterion. The Tweedie distribution was selected for the final model, which is well suited for modelling left-skewed cost data. Total DMC was the dependent variable, with logarithm-transformation of the year as an offset; no additional covariates were included because baseline characteristics were well balanced after matching in both cohorts. The threshold for statistical significance was $p < 0.05$.

Table S1 History of pertussis read codes

MEDCODE	READ CODE	READ TERM
7019	1419.00	H/O: pertussis
7527	1419.11	H/O: whooping cough

H/O history of, *MedCode* Medical code

As previously disclosed [1, 2]

Table S2 History of pertussis SNOMED/Medcodes codes

MedCode	Term	Original Read Code	Cleansed Read Code	SNOMED Code CT Concept ID	SNOMED Code CT Description ID
4539371000006114	H/O: pertussis	^ESCTHI453937		161422003	2986334016
251550018	H/O: whooping cough	1419-1	1419.11	161422003	251550018

CT clinical term, *H/O* history of, *ID* identification, *MedCode* Medical code, *SNOMED* Systematized Nomenclature of MEDicine

As previously disclosed [1, 2]

Table S3 Pertussis read codes

MEDCODE	READ CODE	DESCRIPTION
7267	65VA.00	Notification of whooping cough
763	A33..00	Whooping cough
3842	A330.00	<i>Bordetella pertussis</i>
15761	A331.00	<i>Bordetella parapertussis</i>
53897	A33y.00	Whooping cough - other specified organism
64286	A33yz00	Other whooping cough NOS
42548	A33z.00	Whooping cough NOS
100943	Ayu3A00	Whooping cough, unspecified
56366	F007800	Meningitis due to pertussis
30437	H243.00	Pneumonia with whooping cough
35082	H243.11	Pneumonia with pertussis

MedCode Medical code, *NOS* not otherwise specified

As previously disclosed [1, 2]

Table S4 Pertussis ICD-10 codes

ICD-10	DESCRIPTION
A37.0	Whooping cough due to <i>Bordetella pertussis</i>
A37.1	Whooping cough due to <i>Bordetella parapertussis</i>
A37.8	Whooping cough due to other <i>Bordetella</i> species
A37.9	Whooping cough, unspecified

ICD-10, International Classification of Diseases, 10th revision

As previously disclosed [1, 2]

Table S5 Pertussis SNOMED/MedCodes

MedCode ID	Term	Original Read Code	Cleansed Read Code	SNOMED Code CT Concept ID	SNOMED Code CT Description ID
296787017	Meningitis due to pertussis	F0078	F007800	192650000	296787017
476768100006117	Meningitis caused by pertussis	^ESCTM E476768		192650000	3296612019
1231962012	Pneumonia with pertussis	H243-1	H243.11	59475000	1231962012
346596100006115	Pneumonia in pertussis	^ESCTP N346596		59475000	98793016
88522100006117	Whooping cough pneumonia	H243-99	H243.99	59475000	885221000006117
1231963019	Pneumonia with whooping cough	H243	H243.00	59475000	1231963019
9799018	<i>Bordetella pertussis</i>	A330	A330.00	26484003	483240018
46589015	Whooping cough	A33	A33..00	27836007	46589015
43868014	<i>Bordetella parapertussis</i>	A331	A331.00	27836007	46586010
288039014	Whooping cough due to other <i>Bordetella</i> species	Ayu39	Ayu3900	27836007	46586010
288040011	Whooping cough, unspecified	Ayu3A	Ayu3A00	27836007	46586010
286448015	Whooping cough - other specified organism	A33y	A33y.00	27836007	46586010
294676100006112	WC - Whooping cough	^ESCTW C294676		27836007	483685011
294674100006113	Infection due to <i>Bordetella pertussis</i>	^ESCTIN 294674		27836007	46588011
286452015	Whooping cough NOS	A33z	A33z.00	27836007	46589015
286451010	Other whooping cough NOS	A33yz	A33yz00	27836007	46586010
264414014	Notification of whooping cough	65VA	65VA.00	170526005	264414014
92573100006112	Notification of whooping cough	PCNQN O12		925731000006108	925731000006112
90754100006113	[RFC] Whooping cough	HNG023 0		907541000006109	907541000006113
644421000033117	Pertussis	DRGC62 20BRIDL		644421000033101	644421000033117
296787017	Meningitis due to pertussis	F0078	F007800	192650000	296787017
476768100006117	Meningitis caused by pertussis	^ESCTM E476768		192650000	3296612019
1231962012	Pneumonia with pertussis	H243-1	H243.11	59475000	1231962012
346596100006115	Pneumonia in pertussis	^ESCTP N346596		59475000	98793016
88522100006117	Whooping cough pneumonia	H243-99	H243.99	59475000	885221000006117
1231963019	Pneumonia with whooping cough	H243	H243.00	59475000	1231963019
9799018	<i>Bordetella pertussis</i>	A330	A330.00	26484003	483240018
46589015	Whooping cough	A33	A33..00	27836007	46589015
43868014	<i>Bordetella parapertussis</i>	A331	A331.00	27836007	46586010
288039014	Whooping cough due to other <i>Bordetella</i> species	Ayu39	Ayu3900	27836007	46586010
288040011	Whooping cough, unspecified	Ayu3A	Ayu3A00	27836007	46586010
286448015	Whooping cough - other specified organism	A33y	A33y.00	27836007	46586010

2946761000 0 06112	WC - Whooping cough	^ESCTW C294676		27836007	483685011
2946741000 0 06113	Infection due to <i>Bordetella pertussis</i>	^ESCTIN 294674		27836007	46588011
286452015	Whooping cough NOS	A33z	A33z.00	27836007	46589015
286451010	Other whooping cough NOS	A33yz	A33yz00	27836007	46586010
264414014	Notification of whooping cough	65VA	65VA.00	170526005	264414014
9257310000 06112	Notification of whooping cough	PCNQN O12		925731000006 108	925731000006 112
9075410000 06113	[RFC] Whooping cough	HNG023 0		907541000006 109	907541000006 113
6444210000 33117	Pertussis	DRGC62 20BRIDL		644421000033 101	644421000033 117

CT clinical term, ID identification, MedCode Medical code, NOS not otherwise specified, RFC request for change, SNOMED Systematized Nomenclature of MEDicine, WC whooping cough
As previously disclosed [1, 2]

Table S6 Use of the five most common outpatient services (in the pertussis cohort during each time period) in the pertussis and control cohorts during each time period around the index date

		-6 to -1 month		-1 month to index		Index to 2 months		2-5 months		5-11 months	
	<i>n</i> (%)	Rate per 100 PY (95% CI)	<i>n</i> (%)	Rate per 100 PY (95% CI)	<i>n</i> (%)	Rate per 100 PY (95% CI)	<i>n</i> (%)	Rate per 100 PY (95% CI)	<i>n</i> (%)	Rate per 100 PY (95% CI)	
Thoracic medicine											
Pertussis	NA	NA	28 (1.9)	25 (17-36)^a	51 (3.4)	25 (19-34)^a	70 (4.8)	22 (17-29)^a	65 (4.5)	14 (10-18)^a	
Control	NA	NA	5 (0.3)	4 (1-10)	12 (0.8)	5 (3-9)	15 (1.0)	6 (3-10)	27 (1.9)	6 (5-8)	
Diagnostic imaging											
Pertussis	56 (3.8)	11 (8-14) ^b	46 (3.1)	40 (30-53)^a	NA	NA	NA	NA	NA	NA	
Control	32 (2.2)	7 (4-9)	6 (0.4)	5 (2-11)	NA	NA	NA	NA	NA	NA	
Ear, nose and throat											
Pertussis	NA	NA	28 (1.9)	26 (17-38)^a	38 (2.6)	16 (12-22)^a	NA	NA	NA	NA	
Control	NA	NA	8 (0.5)	7 (3-13)	11 (0.7)	4 (2-8)	NA	NA	NA	NA	
Cardiology											
Pertussis	58 (3.9)	14 (10-19)	NA	NA	48 (3.2)	22 (16-30) ^b	56 (3.8)	18 (14-24) ^b	59 (4.1)	11 (9-15)	
Control	40 (2.7)	10 (7-14)	NA	NA	25 (1.7)	12 (8-19)	32 (2.2)	12 (8-18)	46 (3.2)	11 (7-15)	
Trauma and orthopaedics											
Pertussis	80 (5.4)	23 (18-31)	25 (1.7)	21 (14-32)	37 (2.5)	18 (12-25)	54 (3.7)	23 (16-31)	81 (5.6)	24 (18-32)	
Control	85 (5.7)	24 (18-31)	23 (1.6)	20 (13-30)	39 (2.6)	20 (14-28)	50 (3.4)	20 (15-28)	72 (5.0)	17 (13-23)	
Physiotherapy											
Pertussis	43 (2.9)	22 (14-34)	NA	NA	NA	NA	33 (2.2)	18 (12-28)	36 (2.5)	17 (10-28)	
Control	33 (2.2)	12 (7-18)	NA	NA	NA	NA	23 (1.6)	14 (8-25)	33 (2.3)	11 (7-17)	
Ophthalmology											
Pertussis	62 (4.2)	16 (12-21)	21 (1.4)	19 (12-30)	42 (2.8)	20 (15-28)	40 (2.7)	17 (12-25)	63 (4.3)	15 (11-20)	
Control	68 (4.6)	20 (15-26)	28 (1.9)	26 (18-39)	44 (3.0)	23 (16-32)	46 (3.1)	18 (13-25)	80 (5.5)	22 (17-30)	

Rates of outpatient services per 100 PY (95% CI) were estimated by fitting a negative binomial model

CI confidence interval, *n* (%) number (percentage) of patients with at least one event, NA not available (as only data for the top five outpatient services in the pertussis cohort in each time period were compiled), PY person-years

^aUnadjusted *p* < 0.001 shown in bold (statistically significant after adjustment for multiplicity) derived using the Wilcoxon rank-sum test

^bUnadjusted *p* < 0.05 (suggestive of a trend) derived using the Wilcoxon rank-sum test

Table S7 Use of the five most common prescriptions (in the pertussis cohort during each time period) in the pertussis and control cohorts during each time period around the index date

	-6 to -1 month		-1 month to index		Index to 2 months		2-5 months		5-11 months	
	<i>n</i> (%)	Rate per 100 PY (95% CI)	<i>n</i> (%)	Rate per 100 PY (95% CI)	<i>n</i> (%)	Rate per 100 PY (95% CI)	<i>n</i> (%)	Rate per 100 PY (95% CI)	<i>n</i> (%)	Rate per 100 PY (95% CI)
Amoxicillin 500 mg capsules										
Pertussis	333 (22.5)	63 (57-70)^a	167 (11.3)	143 (123-166)^a	NA	NA	NA	NA	NA	NA
Control	85 (5.7)	16 (13-20)	16 (1.1)	13 (8-21)	NA	NA	NA	NA	NA	NA
Clarithromycin 500 mg tablets										
Pertussis	NA	NA	261 (17.6)	230 (205-259)^a	226 (15.3)	96 (84-108)^a	NA	NA	NA	NA
Control	NA	NA	12 (0.8)	10 (5-17)	8 (0.5)	3 (1-6)	NA	NA	NA	NA
Omeprazole 20 mg gastro-resistant capsules										
Pertussis	227 (15.3)	102 (85-122)^a	171 (11.6)	165 (142-193)^a	161 (10.9)	105 (88-126) ^b	184 (12.5)	107 (89-129) ^b	217 (15.0)	105 (87-128) ^b
Control	142 (9.6)	78 (61-100)	65 (4.4)	72 (55-94)	117 (7.9)	80 (64-99)	142 (9.7)	88 (71-110)	162 (11.2)	86 (68-109)
Salbutamol 100 µg/dose inhaler CFC free										
Pertussis	NA	NA	128 (8.6)	113 (95-134)^a	103 (7.0)	53 (43-65)^a	NA	NA	NA	NA
Control	NA	NA	25 (1.7)	23 (15-35)	37 (2.5)	20 (14-29)	NA	NA	NA	NA
Prednisolone 5 mg tablets										
Pertussis	NA	NA	139 (9.4)	137 (115-162)^a	NA	NA	NA	NA	NA	NA
Control	NA	NA	15 (1.0)	17 (9-29)	NA	NA	NA	NA	NA	NA
Bendroflumethiazide 2.5 mg tablets										
Pertussis	83 (5.6)	53 (38-75)	NA	NA	81 (5.5)	62 (47-82)	83 (5.7)	56 (41-75)	80 (5.5)	55 (39-79)
Control	79 (5.3)	41 (29-56)	NA	NA	71 (4.8)	45 (34-59)	72 (4.9)	42 (31-58)	76 (5.3)	44 (31-62)
Amlodipine 5 mg tablets										
Pertussis	NA	NA	NA	NA	NA	NA	84 (5.7)	47 (36-62)	107 (7.4)	53 (40-70)
Control	NA	NA	NA	NA	NA	NA	75 (5.1)	47 (35-64)	89 (6.2)	50 (36-70)
Simvastatin 40 mg tablets										
Pertussis	111 (7.5)	62 (47-82)	NA	NA	88 (5.9)	60 (47-77)	89 (6.1)	58 (44-78)	84 (5.8)	53 (38-75)
Control	102 (6.9)	62 (46-83)	NA	NA	93 (6.3)	63 (49-81)	97 (6.6)	60 (46-79)	97 (6.7)	59 (43-81)
Paracetamol 500 mg tablets										
Pertussis	NA	NA	NA	NA	NA	NA	NA	NA	115 (7.9)	51 (39-66)
Control	NA	NA	NA	NA	NA	NA	NA	NA	94 (6.5)	47 (35-64)
Aspirin 75 mg dispersible tablets										
Pertussis	83 (5.6)	49 (35-68)	NA	NA	NA	NA	79 (5.4)	51 (38-69)	NA	NA
Control	82 (5.5)	54 (38-75)	NA	NA	NA	NA	84 (5.7)	54 (40-72)	NA	NA

Rates of prescriptions per 100 PY (95% CI) were estimated by fitting a negative binomial model

CFC chlorofluorocarbon, CI confidence interval, *n* (%) number (percentage) of patients with at least one event, NA not available (as only data for the top five prescriptions in the pertussis cohort in each time period were compiled), PY person-years

^aUnadjusted *p* < 0.001 shown in bold (statistically significant after adjustment for multiplicity) derived using the Wilcoxon rank-sum test

^bUnadjusted $p < 0.05$ (suggestive of a trend) derived using the Wilcoxon rank-sum test

Table S8 Individuals in the pertussis and control cohorts with ≥ 1 of each type of HCRU during different time periods around the index date

	-6 to -1 month	-1 month to index	Index to 2 months	2 to 5 months	5 to 11 months
Time period (months)	5	1	2	3	6
GP/nurse, <i>n</i> (%)					
Pertussis	1288 (87.0)	1270 (85.8)	1416 (95.7)	1040 (70.8)	1195 (82.4)
Control	1076 (72.7)	509 (34.4)	777 (52.5)	910 (62.1)	1124 (77.7)
GP prescriptions, <i>n</i> (%)					
Pertussis	1254 (84.7)	1164 (78.6)	1165 (78.7)	1110 (75.6)	1178 (81.2)
Control	1104 (74.6)	715 (48.3)	977 (66.0)	1044 (71.2)	1123 (77.7)
Clinical assessments, <i>n</i> (%)					
Pertussis	997 (67.4)	933 (63.0)	712 (48.1)	669 (45.5)	936 (64.5)
Control	807 (54.5)	284 (19.2)	476 (32.2)	585 (39.9)	864 (59.8)
Outpatient, <i>n</i> (%)					
Pertussis	495 (33.4)	252 (17.0)	372 (25.1)	440 (30.0)	553 (38.1)
Control	447 (30.2)	170 (11.5)	275 (18.6)	342 (23.3)	471 (32.6)
A&E, <i>n</i> (%)					
Pertussis	172 (11.6)	93 (6.3)	78 (5.3)	93 (6.3)	138 (9.5)
Control	110 (7.4)	33 (2.2)	49 (3.3)	77 (5.3)	116 (8.0)
Hospitalisation, <i>n</i> (%)					
Pertussis	153 (10.3)	49 (3.3)	108 (7.3)	117 (8.0)	161 (11.1)
Control	144 (9.7)	51 (3.4)	71 (4.8)	105 (7.2)	162 (11.2)

A&E accident and emergency, *GP* general practitioner, *HCRU* health care resource utilisation, *n* (%) number (percentage) of patients with at least one event

Table S9 Annualised mean $\pm$ SD DMC per individual in the pertussis and control cohorts during the various time periods of the study

	-6 to -1 month	-1 month to index	Index to 2 months	2 to 5 months	5 to 11 months
GP/nurse (£)					
Pertussis	417±398^a	1378±1070^a	765±601^a	381±467^a	350±379^a
Control	286±363	275±530	284±461	301±433	304±395
GP prescriptions ^b (£)					
Pertussis	4±7^a	16±27^a	7±14^a	4±8	5±10
Control	3±10	3±14	4±12	4±11	4±11
Clinical assessments ^b (£)					
Pertussis	3±6 ^c	40±67^a	7±17 ^c	3±7	3±6
Control	3±5	8±34	5±14	3±7	3±6
Outpatient specialist (£)					
Pertussis	265±533	356±888^a	340±770^a	350±960^a	304±612 ^c
Control	264±634	272±927	275±835	269±723	255±559
A&E (£)					
Pertussis	54±171^a	136±561^a	58±275 ^c	43±179	37±135
Control	38±163	46±321	33±196	38±172	34±144
Hospitalisations (£)					
Pertussis	446±2673	410±3555	640±3422^a	628±3641	2700±82,153
Control	533±2826	588±4354	568±4566	654±3888	567±3716
Total ^d (£)					
Pertussis	1190±3054^a	2336±4235^a	1817±4036^a	1410±4133^a	3400±82,150^a
Control	1128±3270	1192±4914	1169±4963	1268±4300	1168±4025

Data are mean $\pm$ SD annualised DMC per individual, in 2019 £

^aUncorrected $p < 0.001$ (shown in bold) vs the control cohort (statistically significant after cut-off adjustment for multiplicity) derived using the Wilcoxon rank-sum test

^bTop five prescription medications or clinical assessments (in the pertussis cohort; during each time period)

^cUncorrected $p < 0.05$ vs the control cohort (suggestive of a trend) derived using the Wilcoxon rank-sum test

^dTotals may not be the exact sum of the components due to rounding

A&E accident and emergency, DMC direct medical costs, GP general practitioner, SD standard deviation

Trademarks

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Supplementary references

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