International variation in radiation dose for computed tomography examinations: prospective cohort study

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ABSTRACT

OBJECTIVE
To determine patient, institution, and machine characteristics that contribute to variation in radiation doses used for computed tomography (CT).

DESIGN
Prospective cohort study.

SETTING
Data were assembled and analyzed from the University of California San Francisco CT International Dose Registry.

PARTICIPANTS
Standardized data from over 2.0 million CT examinations of adults who underwent CT between November 2015 and August 2017 from 151 institutions, across seven countries.

MAIN OUTCOME MEASURES
Mean effective doses and proportions of high dose examinations for abdomen, chest, combined chest and abdomen, and head CT were determined by patient characteristics (sex, age, and size), type of institution (trauma center, care provision 24 hours per day and seven days per week, academic, private), institutional practice volume, machine factors (manufacturer, model), country, and how scanners were used, before and after adjustment for patient characteristics, using hierarchical linear and logistic regression. High dose examinations were defined as CT scans with doses above the 75th percentile defined during a baseline period.

RESULTS
The mean effective dose and proportion of high dose examinations varied substantially across institutions. The doses varied modestly (10-30%) by type of institution and machine characteristics after adjusting for patient characteristics. By contrast, even after adjusting for patient characteristics, wide variations in radiation doses across countries persisted, with a fourfold range in mean effective dose for abdomen CT examinations (7.0-25.7 mSv) and a 17-fold range in proportion of high dose examinations (4-69%). Similar variation across countries was observed for chest (mean effective dose 1.7-6.4 mSv, proportion of high dose examinations 1-26%) and combined chest and abdomen CT (10.0-37.9 mSv, 2-78%). Doses for head CT varied less (1.4-1.9 mSv, 8-27%). In multivariable models, the dose variation across countries was primarily attributable to institutional decisions regarding technical parameters (that is, how the scanners were used).

CONCLUSIONS
CT protocols and radiation doses vary greatly across countries and are primarily attributable to local choices regarding technical parameters, rather than patient, institution, or machine characteristics. These findings suggest that the optimization of doses to a consistent standard should be possible.

STUDY REGISTRATION
Clinicaltrials.gov NCT03000751.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Radiation doses used for computed tomography (CT) are highly variable across patients, institutions, and countries

Lowering patients' exposure to radiation, a known carcinogen, requires an understanding of factors contributing to this variation

Owing to differences in patient populations and inconsistencies in data collection and analysis, accurately quantifying the dose variation or determining whether differences are primarily driven by specific factors has been difficult

WHAT THIS STUDY ADDS

Variation in doses used for CT scanning across patients is primarily driven by how CT scanners are used, and not to factors related to the patient, institution, or machine

The large variation in doses across countries is mainly attributable to institutional decisions regarding the technical parameters that are used rather than to underlying differences in the patients scanned or the machines used

These findings suggest that optimizing doses to a consistent standard is possible, which will probably require more education of individuals who create protocols for CT, recalibration of image quality expectations targeted to answering the clinical question at hand, and greater sharing of protocols across institutions

Introduction

Radiation doses for computed tomography (CT) vary substantially across patients, institutions, and countries.[1-4] Ionizing radiation is a known carcinogen,[5-10] and CT radiation is associated with increased cancer incidence.[11-14] Therefore, it is important to minimize exposure from medical imaging and reduce unnecessary variation by optimizing examination protocols. Evidence suggests that in many instances, CT doses can be reduced by 50% or more without reducing diagnostic accuracy.[15] However, differences in patient populations and inconsistencies in data collection and analysis have challenged both accurate quantification of dose variations and

determination if variability is driven primarily by patient characteristics (patient size, indications for imaging), institution type (eg, academic, private, trauma facility, or 24 h/day provider of CT), machine factors (eg, machine age, specific manufacturer and model, or use of updated software that permits dose reduction), or regional choices that affect dose optimization or image quality (or both). For example, the European Union collects dose levels in Europe, but differences in definitions and data collection techniques across member states confound the identification of factors that explain the observed variation.[3] To develop optimization activities likely to meaningfully affect CT doses, we must understand the factors that influence them.

Various approaches have been used to optimize CT radiation doses. For example, doses for individual patients can be minimized by refining the scan coverage, altering technical parameters (eg, the machine's x ray tube current) or by techniques such as iterative reconstruction.[16] One widely used approach to standardize radiation doses is the creation of target dose levels[17] or diagnostic reference levels. Levels are defined for groups of patients receiving broadly defined study types with the expectation that under best practices, levels will not be exceeded for average sized patients.[3] Levels are frequently the 75th percentile of the observed dose distribution for a geographical area.[3 18 19] Target doses and diagnostic reference levels are often set locally, on the assumption that dose variation is driven by differences in equipment or patients.[20 21] However, without understanding precise factors behind variation in reported doses, it is unknown whether the setting of target levels locally is needed. For example, if dose variations between localities reflect differences in how CT machines are used rather than differences in underlying patient populations or machine manufacturer or specific models, setting standards and targets locally needlessly complicates optimization activities.

The University of California San Francisco CT International Dose Registry collects data from participating healthcare institutions worldwide that perform CT. In this study, we sought to use registry data to understand factors that influence CT dose, to inform development of dose optimization approaches, and to ultimately investigate the need (or lack of) to localize target levels.

Methods
Registry
The University of California San Francisco CT International Dose Registry was created to pool CT dose data from collaborating institutions on 100% of CT scans performed. Radiation and imaging data stored in digital imaging and communications in medicine (DICOM) format are exported onto a local server directly from the CT machines or via the picture archiving and communication systems (PACS) used to review these examinations. Data are stripped of patient identifying information other than study date and time, and transferred to the dose registry in real time.

Collaborating institutions
All healthcare institutions that used Radimetrics software (Bayer) in 2015 to monitor medical imaging radiation dose were invited by email to participate in the registry. The registry is a convenience sample and includes data from sites that expressed interest in participating and who were able to complete the logistical requirements of establishing data connections, complete data use agreements, receive institutional review board approval, and agree to complete the study aims. Institutions from seven countries were included.

Study population
We included diagnostic CT examinations of the abdomen (including any imaging through the abdomen or pelvis), chest, combined chest and abdomen, and head in adults aged 18 years and older between 1 November 2015 and 22 August 2017. Cardiac exams were excluded. The four groups included anatomical areas reflecting about 92% of all diagnostic CT exams during the study period. Spine CT, and exams performed across multiple anatomical areas comprised most of the excluded exams. CT exams for research, radiation oncology guidance, surgical or interventional procedures, or that were part of combined positron emission tomography-CT exams or single photon emission tomography-CT exams were excluded because of expected heterogenous doses for these study types.

Variables
Analyses were at the CT examination level, defined as a complete CT study, which could include several CT scans such as with and without intravenous contrast. Statistical analyses were performed separately for each anatomical area.

The analyses adjusted for a range of variables that we hypothesized might be associated with radiation doses. Patient characteristics extracted for each examination were age, sex, and size. Sex and size might be factors because the larger a patient, the greater the doses of radiation that must be used to generate an image equal in quality compared with doses needed in a smaller patient. Patient diameter, the proxy for size, was calculated as the average of the water equivalent diameter from each CT acquisition over the entire imaging range.[22] Age could be important because institutions might lower doses for younger patients. Scanning indication could influence the radiation doses needed, because greater imaging quality might be needed for particular clinical questions, but was known for only a subset of examinations and could not be used to adjust for possible case mix differences across institutions. Instead, differences in dose were assessed by examination time of day, because those taking place at night (between 10 pm and 5 am) should primarily reflect acute imaging.

The type of institution might reflect the types and complexity of the patients seen at that institution, and therefore could predict doses use for imaging. The type of institution was extracted from a survey completed by each institution, which also included trauma center status, whether imaging was provided 24 h/day and 7 days/week (24/7), and self identification as an academic or private institution. Average machine and institutional practice volumes could be associated with dose based on volume-outcome associations described in many other areas of medical practice. Volumes were calculated on the basis of all CT examinations performed on weekdays.

Machine characteristics included manufacturer and model. These factors could be associated with dose because the technical capacity of machines have changed over time. Further, newer machines sometimes offer dose reduction software.

The technical parameters[23] (including x ray tube parameters (kV and mAs), acquisition parameters (pitch and acquired slice thickness), scan length, and number of scans per examination) and CT dose metric parameters (volumetric CT dose index and dose length product) were stored for each CT scan. The volumetric CT dose index reflects the average dose value within a section (slice) of the scanned volume, whereas the dose length product reflects the total emitted radiation imparted to the patient (defined as volumetric CT dose index×scan length). Effective dose, which is proportional to total imparted radiation, is an estimate that accounts for estimated future cancer risk based on irradiated organs. If multiple CT scans were performed during an examination, a weighted average of the technical parameters was used. The number of CT scans did not include localizers or contrast bolus timing scans, although the radiation from the contrast bolus was included in the dose calculations. Effective dose was calculated for each examination by use of the dose length product and published conversion factors.[22]

Statistical analysis

We calculated descriptive statistics for CT scans by patient, institution, practice volume, machine, and country. The dose metrics of interest were effective dose (mean, standard deviation, median, and interquartile range) and the prevalence of high dose studies, defined as studies whose effective dose exceeded the 75th percentile during the first six months of study (1 November 2015 to 30 April 2016). Variation by less than 50% was considered modest variation.

Variation in radiation doses across institutions and countries and by predictive variables

We calculated the distribution in radiation doses for abdominal CT by institution and for all anatomical areas by country after adjusting for patient characteristics. The mean effective dose (and standard deviation) and proportion of high dose studies by institution, practice volumes, machine, and country are shown unadjusted and adjusted for patient characteristics to show how the doses vary by these factors. The adjusted effective dose and adjusted prevalence of high dose examinations were estimated by log-linear regression and logistic regression, respectively.

Multivariate analysis to identify factors that are associated with dose

To understand the contribution of patient, institution, practice volume, machine, country, and technical factors to the variation of effective dose between machines and countries, we fit a series of log-linear mixed effects models predicting effective dose. We graphically show a series of models displaying how the doses vary across the 290 machines included in the University of California San Francisco CT International Dose Registry. The first model contained no predictors except for a random effect accounting for clustering by machine and showed the average dose for each machine for abdomen CT. The second model added patient characteristics, showing the average dose for each machine after accounting for patient characteristics. Additional predictors were subsequently added to each model so that the final fully adjusted model included all of the predictor variables and log-transformed technical parameters (kVp, mAs, pitch, number of CT scans, scan length, and slice thickness).

To quantify variation in dose across the different machines and the reduction in variation after accounting for each predictor variable, we randomly sampled random effects for 10 000 pairs of machines from the estimated distribution and computed the ratio of the estimates for each pair. We presented the median, 75th percentile, and 95th percentile of these 10 000 bootstrapped ratios as relative doses. The 95% in the relative dose was used to quantify the variation between two randomly selected machines. The larger the ratio between two randomly selected machines, the greater the variation in dose across machines in the registry. A sharp decline in the variability of relative dose among machines and countries after a predictor was added indicates that the predictor accounted for a large amount of the variation. We also computed the expected mean effective dose in each country for each model, also shown in the figures.

The magnitude of the associations between dose and patient, institution, practice volume, machine, and country are also shown. The effect sizes were defined as the multiplicative change in dose for each standard deviation change in the associated covariate; the larger the estimated effect, the more important the variable. Lastly, we showed the effect of the inclusion of technical factors on the observed variation in dose across countries.

Sensitivity analysis

To remove the potential effect of case mix (that is, different reasons why patients underwent CT), we illustrated the variation in effective doses for one specific imaging indication: suspected pulmonary embolism. We also did a subanalysis for this indication using

data from one machine model (Somaton Definition AS, Siemens Healthineers) to illustrate representative differences in technical parameters chosen by institutions for this indication and on this scanner. The main analyses were repeated using volumetric CT dose index as the outcome, and restricting to single phase CT examinations. We compared doses in the registry to published benchmarks, extracting combined data across age, sex, and size categories.[3] [4] [24-28] We abstracted effective doses from published reports, or calculated these from dose length product values using published conversion factors.[22]

Patient and public involvement
Patients were included as stakeholders in the project and contributed as part of in-person meetings and webinars to help guide the project direction.

Results
During the study period, 151 institutions from seven countries (Switzerland, Netherlands, Germany, United Kingdom, United States, Israel, and Japan) performed just over 2.0 million CT scans on about 1.7 million adults. Examinations were performed on 290 machines from four machine manufacturers and 49 machine models (table 1). Of the included CT scans, about one third were abdomen (n=724 627, 36%), one third head (682 701, 34%), and one third chest (n=515 007, 26%) or combined chest and abdomen (n=83 124, 4%). Numbers of examinations by patient, institution, practice volumes, machine, and country are shown in table 1.

Factors associated with CT dose
After accounting for patient characteristics, the median effective doses for abdominal CT across institutions ranged from 5 to 32 mSv (fig 1). The distribution in effective dose by country for each anatomical area (fig 2) demonstrated the greatest variation in median doses for abdomen and combined chest and abdomen CT.

The mean effective dose and proportion of high dose examinations by institution, practice volume, machine, and country after adjustment for patient characteristics are shown in table 2 (corresponding unadjusted values in table S1). The adjusted mean effective doses varied modestly (typically by 10-20%; occasionally by up to 40%) by institutional characteristics and practice volumes. For example, mean effective dose for abdomen CTs was 12.1 mSv at trauma centers compared with 12.5 mSv at a non-trauma center (relative dose 0.97 mSv). The adjusted mean effective dose also varied modestly by manufacturer. In contrast with other factors considered, mean doses varied widely across countries, particularly for abdomen, chest, and combined chest and abdomen CT. Mean effective dose for abdomen CT ranged fourfold across countries (7.0 mSv in the Netherlands to 25.7 mSv in Japan), and the relative proportion of high dose studies varied more than 17-fold (4-69%). Variation was similar for effective dose for chest and combined chest and abdomen CT, with fourfold differences in mean

dose across countries. Dose variation in head CT was more modest, with a relative mean dose between the highest dose and lowest dose countries of 1.3 (range 1.4-1.9 mSv).

In the subanalysis of patients who underwent CT for suspected pulmonary embolism scans, the variation in effective dose was substantial across countries (table 2). Mean effective dose ranged from 2.2 mSv to 33.2 mSv, and the relative proportion of high dose studies ranged from 0% to 89% (table 2). Variation in doses across countries were generally greater, rather than reduced, after adjustment for patient factors (table 2v table S1).

Factors explaining CT dose variation
The multivariable analyses highlighted that most factors considered (patient, practice volumes, machine factors) had only a small effect on the dose variation across different machines in the registry or between the different countries (fig 3, figures S1a-d). For abdomen CT examinations, the unadjusted 95th percentile of relative dose was 2.65, and the mean effective dose ranged from 7.3 mSv in Switzerland and Germany to 15.7 mSv in Israel, reflecting large variation between machines and countries. Subsequent adjustment for patient factors had no effect on relative dose (2.65) and resulted in a small increase (rather than decrease) in the differences in mean dose by country (range of 8.1 to 22.9 mSv). This suggests that despite the effective dose being highly correlated with patient characteristics (specifically patient size; table S1, table 3), patient size does little to explain the variability across machines or countries (fig 3, model 2). Sequential adjustment for institution and machine characteristics also had little effect on relative dose, although these adjustments slightly attenuated dose variation across countries (fig 3, models 3-5).

The final adjustment including the specific technical factors substantially reduced or eliminated large differences in relative dose between machines and reduced or eliminated the large differences across countries. In model 6 (fig 3), the technical factors explained nearly all dose variation (95th percentile relative dose 1.42), and average doses among countries were similar after this final adjustment. Results were similar for the chest, combined chest and abdomen, and the subanalysis for pulmonary embolisms (figures S1a, b, and d). We saw large differences in the relative doses across machines and countries that were reduced or eliminated only after inclusion of the technical parameters. We found less variation in doses for head CT even without adjustment (figures S1c).

Effect of each predictive factor in multivariable models
Table 3 shows the magnitude of the association between effective dose and patient, institution, practice volume, machine, and country characteristics, based on the multivariate results. Patient size was a significant predictor of mean dose in the fully adjusted multivariable models with large effect sizes; for each

Table 1 | Characteristics of computed tomography (CT) examinations, institutions, and machines included in analyses

	CT examinations (n=2 005 459)	Institutions (n=151)	Machines (n=290)
Anatomical area			
Abdomen	724 627 (36)	—	—
Chest	515 007 (26)	—	—
Combined abdomen and chest	83 124 (4)	—	—
Head	682 701 (34)		
Patient characteristics			
Age (years)			
18-29	179 889 (9)	—	—
30-39	177 964 (9)	—	—
40-49	251 366 (13)	—	—
50-59	385 556 (19)	—	—
60-69	439 115 (22)	—	—
70-79	337 904 (17)	—	—
≥80	233 665 (12)	—	—
Sex			
Female	1 056 929 (53)	—	—
Male	948 530 (47)	—	—
Size*			
Smallest	369 967 (20)	—	—
Small	369 938 (20)	—	—
Medium	369 939 (20)	—	—
Large	369 925 (20)	—	—
Largest	369 934 (20)	—	—
Time of scanning			
Daytime	1 783 910 (89)	—	—
Night time	221 549 (11)	—	—
Institutional characteristics†			
Trauma center	790 912 (39)	25 (17)	—
Institution scans 24/7	1 605 234 (80)	64 (42)	—
Academic	967 012 (48)	41 (27)	—
Private	204 962 (10)	12 (8)	—
Machine daily volume			
1-6	112 847 (6)	—	98 (34)
>6-9	108 127 (5)	—	33 (11)
>9-12	157 327 (8)	—	34 (12)
>12-20	583 851 (29)	—	71 (24)
>20-60	1 043 307 (52)	—	54 (19)
Facility daily volume			
1-6	77 001 (4)	58 (38)	—
>6-9	40 386 (2)	13 (9)	—
>9-20	113 142 (6)	20 (13)	—
>20-50	583 408 (29)	32 (21)	—
>50-600	1 191 522 (59)	28 (19)	—
Manufacturer‡			
GE	873 965 (44)	92 (61)	147 (51)
Philips	381 917 (19)	28 (19)	44 (15)
Siemens	552 222 (28)	43 (28)	78 (27)
Toshiba	197 355 (10)	16 (11)	21 (7)
Country			
Switzerland	37 119 (2)	2 (1)	4 (1)
Netherlands	38 034 (2)	1 (1)	5 (2)
Germany	45 599 (2)	4 (3)	7 (2)
UK	61 888 (3)	3 (2)	9 (3)
USA	1 627 834 (81)	133 (88)	253 (87)
Israel	133 031 (7)	5 (3)	5 (2)
Japan	61 954 (3)	3 (2)	7 (2)

Data are number (%). Percentages might not add to 100% owing to rounding. 24/7=24 h/day, 7 days/week.
*Size could not be calculated for 8% of scans. Based on average scan diameter, abdominal size categories were smallest (<26.6 cm), small (26.6-29.1 cm), medium (>29.1-31.3 cm), large (>31.3-34.2 cm), and largest (>34.2 cm); chest size categories were <25.7 cm, 25.7-28.2 cm, >28.2–30.1 cm, >30.1-32.3 cm, and >32.3 cm, respectively; combined chest and abdomen size categories were <26.2 cm, 26.2-28.6 cm, >28.6-30.6 cm, >30.6-33.1 cm, and >33.1 cm, respectively; and head size categories were <16.4 cm, 16.4-17.0 cm, >17.0-17.4 cm, >17.4-17.9 cm, and >17.9 cm, respectively.
†Institutional characteristics were not mutually exclusive. Institutions can report 0-4 institutional characteristics therefore the total number of institutions does not sum to 151.
‡Machine characteristics were not mutually exclusive. Institutions could have more than one manufacturer's machines and therefore the total number of institutions does not add up to 151.

standard deviation increase in patient size, mean dose increased by 36-47% for chest, abdomen, and combined chest and abdomen CT, and increased by 19% for head CT. We saw only small differences in dose by institutional characteristics; mean doses were slightly but significantly higher for chest and head CT
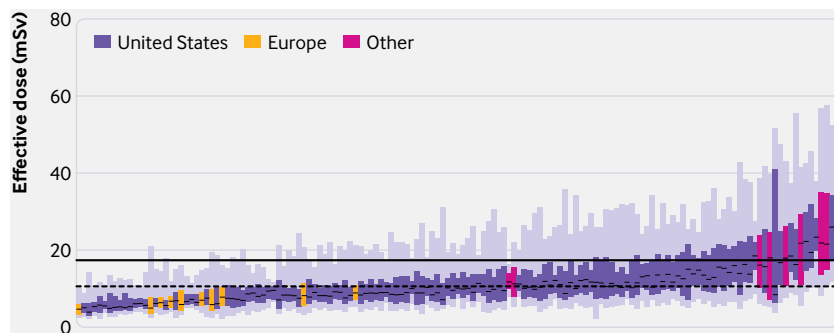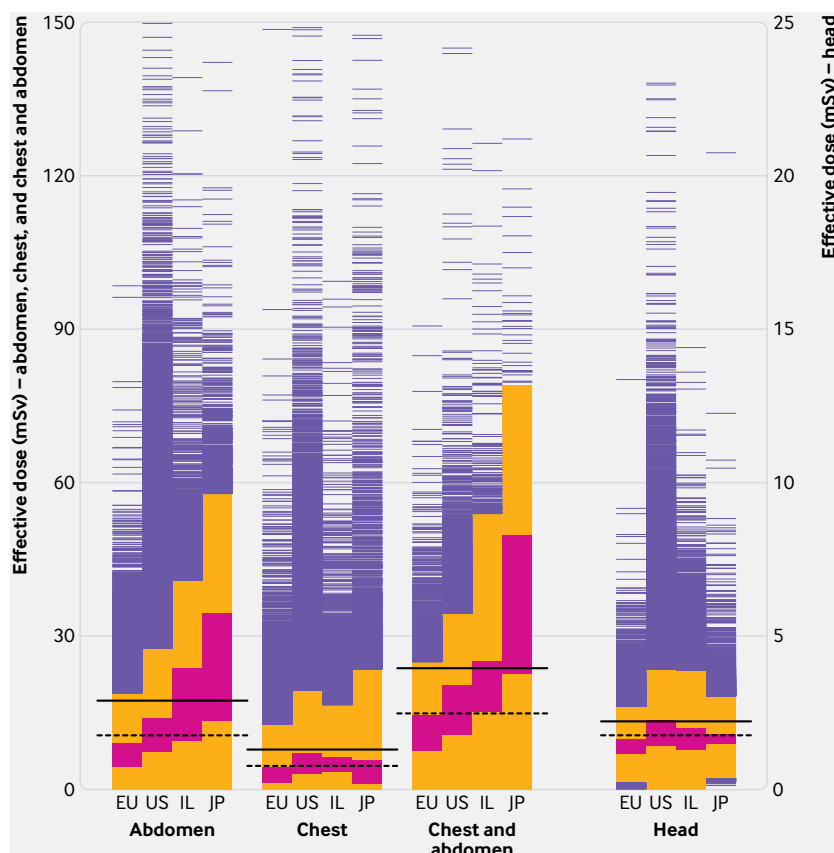
Fig 1 | Distribution in effective radiation dose by institution for abdomen CT, after adjustment for patient characteristics. Each column signifies one institution, ranked by mean effective dose. Light purple columns=5th and 95th percentiles of effective dose; dark purple, pink, and yellow column sections=25th and 75th percentiles of effective dose; lines=medians; horizontal solid line and dashed line=benchmark and target doses for abdomen, defined as the 75th and 50th percentiles of dose for all abdominal scans performed before 30 April 2016

at trauma centers, and head CT doses were higher at private institutions and those with scanning provided 24 h/day and 7 days/week. Most other institutional characteristics were not significantly associated with mean dose.

Fig 2 | Distribution of effective radiation dose by country and scan region, after adjustment for patient characteristics. Each column signifies one country or the European Union, with one horizontal line denoting each observation within the country. IL=Israel; JP= Japan; pink lines=within 25th and 75th percentiles; orange lines=two standard deviations from the mean; purple lines=outliers; horizontal solid line and dashed line=benchmark and target doses for each anatomical area, defined as the 75th and 50th percentiles of dose for all scans of that type performed before 30 April 2016

Abdomen, chest, and combined chest and abdomen CT doses did not differ significantly by manufacturer, although machines from Canon Medical Systems (Toshiba) were associated with modestly increased doses for head scans and machines from Siemens were associated with modestly reduced doses for suspected pulmonary embolism scans.

Although most predictive factors had relatively small effects on dose, large differences in dose persisted among countries for abdomen, chest, and combined chest and abdomen CT and for pulmonary embolism CT. The differences among countries was largest for suspected pulmonary embolism CT. We saw no significant differences in mean effective dose by country for head CT after accounting for other factors, suggesting a greater degree of protocol standardization for head imaging. The addition of specific scan parameters to the multivariable models (eg, x ray tube and acquisition parameters; table 4) attenuated or eliminated the differences between countries. This suggests that the differences among countries in the mean doses were not attributable to patient, institution, or machine factors (which all had small effects in table 3), but to the technical parameters.

Effect of technical parameters on CT dose for one indication

Subanalysis of one specific indication (suspected pulmonary embolism) highlighted differences in technical parameters chosen by different institutions using the same machine make and model that resulted in the large observed differences in effective dose (table 5). We found a greater than 15-fold difference in mean effective doses between the institutions with the highest tenth versus lowest tenth in dose (mean effective dose 31.0 v 2.0 mSv). Accounting for patient size resulted in a slightly greater difference between the highest tenth and lowest tenth in protocols (mean effective dose 27.5 v 1.6 mSv). Compared with institutions in the highest tenth of effective dose, those in the lowest tenth had a lower adjusted CT dose index (3.8 v 15.9 mGy), tube potential (102 v 119 kVp), tube current (113 v 188 mAs), slice thickness (1.9 v 3.9), number of CT scans per examination (1.0 v 2.7), and had higher pitch (1.2 v 0.8). Thus, as shown for the analyses at the anatomical area level, dose variations in pulmonary embolisms CT, even when restricted to the same machine model, were explained by differences in technical parameters rather than patient characteristics.

Sensitivity analyses

Results were similar when we used the volumetric CT dose index as the outcome dose metric (results not shown), and when limited to single CT scan examinations (results not shown). The unadjusted doses in the University of California San Francisco CT International Dose Registry were similar to data in the literature (table S2). For example, the published benchmark abdomen dose in Switzerland is 10 mSv, and is 10.3 mSv (95% confidence interval 9.9 to 10.6) in the University of California San Francisco registry.
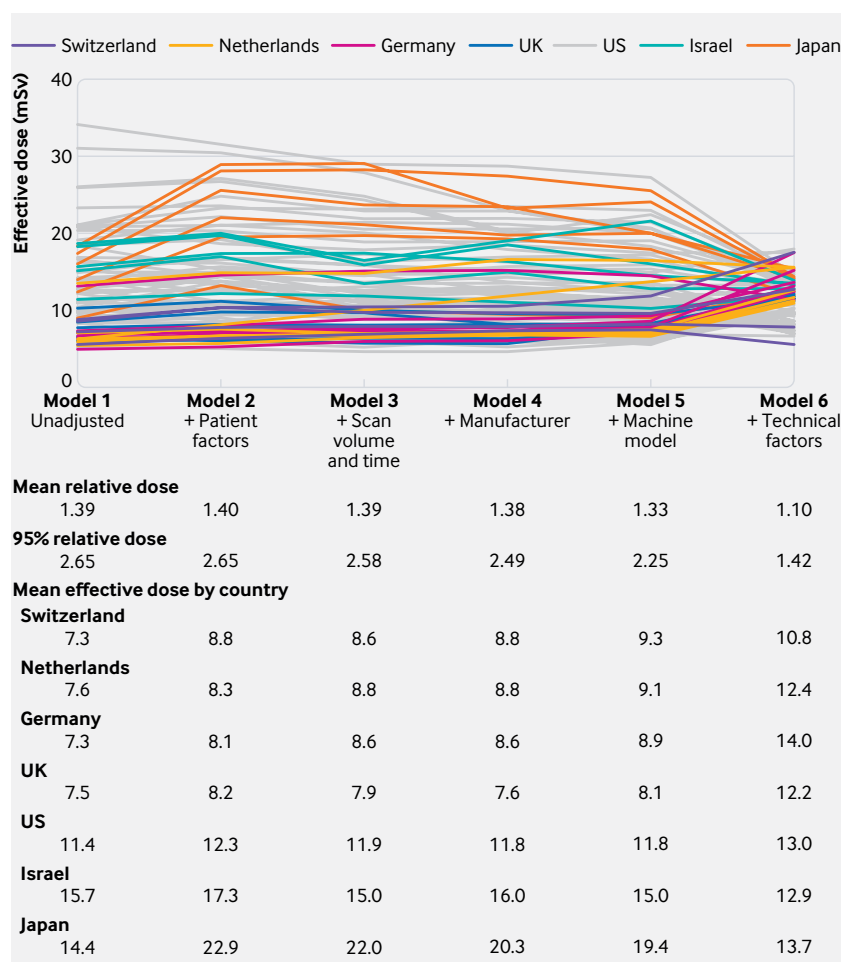
Fig 3 | Mean effective radiation dose by machine in abdomen computed tomography (CT) scans, with different levels of adjustment. Model 1=unadjusted results; subsequent adjustments included: model 2, patient characteristics; model 3, institutional characteristics; model 4, machine manufacturer; model 5, machine model; and model 6, technical parameters. Rows=mean relative effective dose and 95th percentile of relative dose for two randomly chosen machines, with mean dose by country at the corresponding level of adjustment within multivariable model. Lines=dose for single machines. For abdomen examinations in model 1, 95th percentile of relative dose was 2.65 and mean effective dose ranged from 7.3 mSv (Switzerland) to 15.7 mSv (Israel)

Discussion

Principal findings

Using an international registry of CT doses, we found large variation in doses across the included countries even after accounting for patient characteristics, numerous institutional characteristics, average machine and institutional practice volumes, and machine factors. The variation in dose persisted when we limited our analysis to one clinical question where the radiation dose requirements would have been the same across the included countries. To better understand reasons for variability between countries, we included technical parameters in multivariable models, the inclusion of which attenuated or eliminated these intercountry differences. These technical factors reflect an intermediate step in which clinical staff make changes that alter dose levels and hence can increase dose variation. Thus, CT dose differences

among countries were not attributable to patient or institutional characteristics or machine manufacturer or model, but were almost entirely associated with how institutions used the machines, presumably reflecting different decisions about technical parameters to yield optimal CT images.

Comparison with other studies

International efforts to improve radiation safety for medical imaging vary considerably across the included countries, so it is not surprising that we found CT dose differences.[3 24 29 30-36] For example, the EU adopted legislation with mandatory directives about medical radiation exposure from CT where member states are required to establish and promote diagnostic reference levels for CT.[31-34] The US has educational efforts by professional societies, such as the American College of Radiology,[29] and recommendations from government agencies ask institutions to assess their CT doses.[37] However, no US organization is tasked with collecting, monitoring, or reporting CT radiation doses, and no national US legislation sets CT dose standards.[38] Only two US states (California and Texas) have legislation related to CT scanning. In Japan, a consortium group has proposed national diagnostic reference levels, but these have not been widely adopted.[24] In Israel, a few institutions have established diagnostic reference levels, but adoption is not uniform, although currently the ministry of health is considering establishment of a national dose registry.

One approach to optimizing CT doses has been setting benchmarks for optimum target doses. Challenges in setting benchmarks include difficulty in deciding how they should be established—for example, by anatomical area, clinical indication, or protocol[3 24 25 29]—and difficulty in collecting sufficient data to reflect actual practice. The ideal approach to creating benchmarks would likely reflect a compromise, with target dose levels based on broad anatomical areas, supplemented by additional target dose levels for specific clinical indications that have unique contrast and spatial resolution needs not captured by these broad anatomic areas.[39]

Our analysis used broad anatomical areas and considered the entire CT examination for several reasons. Firstly, having fewer categories simplified comparisons across institutions. Secondly, institutional decisions to use particular approaches (eg, single or multiple CT scan examinations) affects the doses delivered, and to stratify results within these narrow categories would mask the primary contributor to dose variation. For example, if an institution routinely uses multiple CT scan examinations to assess pulmonary embolism, this will result in higher radiation doses to their patients compared with facilities that routinely use just one CT scan examination. Assessment of doses within narrowly defined categories of single or multiple phase would mask differences and would not enable identification of institutions whose doses are outside practice norms because they use multiple scan examinations. Furthermore, there are few evidence

Table 2 | Computed tomography (CT) effective radiation doses and proportion of high dose examinations by institution and machine characteristics, adjusted for patient age, sex, and size

	Effective dose in CT scan (mSv), by anatomical area									
	Abdomen		Chest		Combined chest and abdomen		Head		Suspected pulmonary embolism	
	Mean (SD)	High dose (%)	Mean (SD)	High dose (%)	Mean (SD)	High dose (%)	Mean (SD)	High dose (%)	Mean (SD)	High dose (%)
Institutional characteristics										
Trauma center, yes	12.1 (8.6)	22	6.9 (7.2)	30	16.6 (10.8)	22	2.0 (1.0)	27	6.6 (6.1)	25
Trauma center, no	12.5 (8.7)	25	5.4 (6.1)	20	15.3 (8.6)	18	1.8 (0.9)	22	6.4 (4.4)	25
Scans 24/7, yes	11.8 (8.3)	20	6.3 (6.6)	26	15.0 (10.1)	19	1.9 (0.9)	25	6.3 (5.2)	24
Scans 24/7, no	14.5 (9.7)	36	5.3 (6.3)	17	16.7 (8.1)	21	1.5 (1.1)	17	8.4 (6.1)	40
Academic, yes	12.2 (8.3)	23	6.4 (7.0)	26	16.4 (9.1)	21	1.9 (1.0)	24	6.3 (4.2)	23
Academic, no	12.4 (8.9)	24	5.6 (6.1)	21	14.5 (9.7)	17	1.8 (0.9)	24	6.8 (6.4)	27
Private, yes	16.2 (10.2)	42	4.6 (5.3)	31	23.2 (14.6)	39	1.9 (1.0)	21	6.5 (5.4)	25
Private, no	11.9 (8.3)	21	6.2 (6.7)	23	15.4 (9.0)	19	1.9 (1.0)	25	7.0 (3.8)	26
Machine daily volume										
1-6	12.2 (8.8)	25	5.3 (6.8)	17	14.0 (7.4)	9	1.5 (1.3)	17	6.7 (5.3)	27
>6-9	11.4 (7.4)	22	5.2 (4.8)	21	13.6 (9.3)	13	1.9 (1.0)	27	7.1 (4.7)	37
>9-12	11.3 (7.9)	21	6.7 (8.5)	23	14.6 (8.3)	17	1.8 (0.8)	17	6.3 (4.6)	20
>12-20	13.0 (9.0)	28	5.9 (7.1)	24	15.0 (9.4)	16	1.9 (0.9)	23	7.3 (7.1)	30
>20-60	12.2 (8.7)	22	6.1 (5.7)	25	16.5 (9.5)	23	1.9 (1.0)	26	6.1 (4.4)	22
Facility daily volume										
1-6	12.3 (8.9)	23	6.3 (6.7)	26	15.9 (9.3)	21	1.9 (1.0)	27	6.3 (5.6)	23
>6-9	12.0 (8.6)	25	5.2 (6.6)	17	14.1 (9.2)	13	1.4 (1.0)	14	7.4 (5.8)	30
>9-20	11.7 (8.6)	24	4.9 (4.9)	20	15.8 (10.1)	19	1.8 (1.0)	23	6.2 (3.9)	27
>20-50	10.5 (8.1)	17	6.2 (8.6)	19	10.3 (5.9)	6	1.7 (1.1)	22	5.0 (3.7)	12
>50-600	12.7 (8.2)	26	5.6 (5.9)	21	16.0 (10.0)	17	1.8 (0.9)	19	7.3 (4.8)	32
Manufacturer										
GE	12.7 (8.7)	26	5.4 (5.5)	19	17.0 (8.6)	23	1.8 (1.0)	19	7.3 (5.1)	31
Philips	12.1 (8.9)	24	5.7 (5.3)	22	14.3 (10.3)	16	1.9 (0.9)	29	6.2 (4.6)	23
Siemens	12.1 (8.3)	22	6.4 (7.7)	26	12.0 (8.3)	11	1.7 (0.8)	17	5.4 (4.5)	16
Toshiba	11.8 (9.1)	17	8.3 (9.0)	42	18.5 (14.2)	26	2.3 (1.0)	49	7.4 (7.4)	33
Country										
Switzerland	8.3 (4.4)	7	1.7 (1.7)	1	13.3 (7.3)	11	1.5 (0.5)	8	2.2 (1.1)	0
Germany	8.0 (7.1)	9	3.4 (5.3)	11	10.0 (8.0)	9	1.4 (0.7)	8	2.4 (2.6)	3
Netherlands	7.0 (4.1)	4	4.7 (5.4)	14	11.8 (4.1)	2	1.4 (0.6)	15	2.2 (1.8)	1
UK	7.9 (6.0)	9	4.1 (3.3)	10	12.5 (5.2)	6	1.5 (0.6)	11	5.5 (4.1)	19
US	12.0 (7.9)	22	6.4 (6.6)	26	16.7 (8.9)	23	1.9 (1.0)	27	6.7 (4.7)	27
Israel	18.4 (11.3)	54	5.8 (5.4)	17	23.7 (15.1)	39	1.8 (1.1)	17	6.2 (5.3)	11
Japan	25.7 (16.1)	69	5.0 (9.3)	20	37.9 (20.6)	78	1.7 (0.7)	11	33.2 (25.0)	89

24/7=24 h/day, 7 days/week; mSv=millisievert; SD=standard deviation.

based guidelines for choosing different approaches to scanning most clinical indications (that is, little data are available to link dose requirements to specific indications or diagnostic accuracy), and thus the use of broad anatomical areas seems most useful. The primary disadvantage of our approach was that grouping of exams by anatomical area precluded accounting for variation in case mix for the few clinical indications that might have unique spacial resolution needs. Inclusion of institutional characteristics in our analyses probably minimized differences by institutions.

A widely held belief is that CT dose standards and benchmarks must be created individually by each hospital,[30] region, or country,[3 40] a tailored approach necessitated by variation in achievable targets that are largely determined by the specific types and models of CT machines used and characteristics of the local patient populations.[20 21] In the EU, large differences in doses across included nations have been reported, which has contributed to the widely held belief that country specific benchmarks must be created.[3 40]

We did not find that dose variation is largely attributable to variation in patient requirements, clinical circumstances, or machine factors. We found that variations persist even when we limited analysis to patients assessed for a specific clinical condition, adjusted for patient factors, and restricted analysis to patients scanned on a single instrument model. Machine make and model are only modest predictors of dose and that substantial variance for each device type. The largest driver of dose variation was how providers or clinical staff chose to set the machine technical parameters, not the machine. Our results suggest that dose variation and outlier doses could be diminished without new equipment, which would require the creation of consistent standards, and to create those standards, the collection of standardized data across all countries similar to the data we include.

Our findings suggest that work is needed to understand why doses vary among users. The variation in radiation dose across countries will reflect the variation in image quality, and user's willingness to accept noisier images. We need to determine

Table 3 | Multivariable regression results for change in mean computed tomography (CT) effective dose per standard deviation for continuous variables and relative dose for categorical variables. SD=standard deviation; asterisks=P<0.05

	Effect size (95% CI), by anatomical area of CT scan				
	Abdomen	Chest	Combined chest and abdomen	Head	Suspected pulmonary embolism
Patient characteristics					
Age, years (per SD)	1.01 (1.00 to 1.01)*	0.98 (0.97 to 0.98)*	0.95 (0.95 to 0.96)*	1.04 (1.03 to 1.04)*	0.99 (0.99 to 0.99)*
Sex (male v female)	1.04 (1.04 to 1.05)*	1.13 (1.12 to 1.13)*	1.06 (1.06 to 1.07)*	0.96 (0.96 to 0.97)*	1.09 (1.09 to 1.10)*
Size (per SD)	1.47 (1.46 to 1.47)*	1.36 (1.35 to 1.36)*	1.43 (1.42 to 1.43)*	1.19 (1.18 to 1.19)*	1.41 (1.41 to 1.42)*
Night time scan	0.98 (0.97 to 0.98)*	1.06 (1.06 to 1.07)*	1.06 (1.04 to 1.07)*	1.04 (1.03 to 1.04)*	1.02 (1.01 to 1.03)*
Institutional characteristics					
Trauma center	0.99 (0.90 to 1.09)	1.23 (1.07 to 1.42)*	1.08 (0.93 to 1.25)	1.13 (1.03 to 1.25)*	1.10 (0.96 to 1.26)
Institution scans 24/7	0.87 (0.79 to 0.96)*	1.13 (0.97 to 1.32)	0.97 (0.82 to 1.15)	1.25 (1.13 to 1.39)*	0.93 (0.80 to 1.08)
Academic	0.98 (0.90 to 1.07)	1.10 (0.96 to 1.26)	1.15 (0.98 to 1.35)	1.09 (0.99 to 1.2)	0.99 (0.87 to 1.13)
Private	0.99 (0.81 to 1.21)	0.77 (0.57 to 1.03)	1.13 (0.84 to 1.54)	1.27 (1.01 to 1.59)*	1.11 (0.79 to 1.54)
Volume					
Machine	0.92 (0.87 to 0.98)*	1.03 (0.95 to 1.12)	1.00 (0.93 to 1.09)	1.04 (0.98 to 1.11)	0.97 (0.90 to 1.05)
Facility	1.08 (1.03 to 1.13)*	1.36 (0.92 to 1.06)	0.98 (0.91 to 1.05)	1.01 (0.97 to 1.06)	1.05 (0.99 to 1.12)
Manufacturer					
GE	Reference	Reference	Reference	Reference	Reference
Philips	0.87 (0.74 to 1.01)	0.79 (0.61 to 1.03)	0.85 (0.68 to 1.06)	1.02 (0.86 to 1.21)*	0.89 (0.71 to 1.13)*
Siemens	1.05 (0.92 to 1.20)	0.99 (0.79 to 1.23)	0.90 (0.72 to 1.12)	1.08 (0.94 to 1.25)*	0.75 (0.62 to 0.91)*
Toshiba	1.13 (0.92 to 1.37)	1.21 (0.88 to 1.67)	1.15 (0.87 to 1.53)	1.51 (1.22 to 1.87)*	1.08 (0.82 to 1.41)*
Country					
Germany	Reference	Reference	Reference	Reference	Reference
Netherlands	0.99 (0.71 to 1.39)*	0.71 (0.43 to 1.19)*	1.15 (0.68 to 1.95)*	0.96 (0.66 to 1.39)	1.18 (0.69 to 2.02)*
Switzerland	1.11 (0.77 to 1.61)*	0.38 (0.22 to 0.67)*	1.11 (0.65 to 1.91)*	1.06 (0.71 to 1.58)	1.07 (0.62 to 1.84)*
UK	0.98 (0.72 to 1.33)*	0.82 (0.52 to 1.32)*	1.02 (0.62 to 1.67)*	1.05 (0.74 to 1.48)	1.54 (0.96 to 2.45)*
USA	1.48 (1.17 to 1.86)*	1.07 (0.75 to 1.52)*	1.25 (0.81 to 1.92)*	1.22 (0.93 to 1.58)	2.31 (1.6 to 3.33)*
Israel	2.69 (1.76 to 4.11)*	1.77 (0.93 to 3.37)*	2.28 (1.18 to 4.41)*	1.1 (0.68 to 1.75)	1.86 (0.97 to 3.55)*
Japan	2.73 (1.95 to 3.83)*	0.92 (0.56 to 1.52)*	2.83 (1.61 to 5.00)*	1.18 (0.80 to 1.74)	6.49 (3.72 to 11.35)*

how institutions set up their CT scanning protocols and how to develop consensus about balancing image quality with diagnostic accuracy. Education and collaboration in setting standards could offer the largest effect on optimizing dose.[41 42] Choosing appropriate CT protocol parameters might be less complex than widely believed. Institutions with lower doses shared scanning approaches. These institutions tended to limit the number of protocols, with each relying on the minimum dose required to answer the clinical question. They used multiple CT scanning infrequently, had lower settings for tube current and tube potential, and used higher pitch for most, if not all, imaging indications. The key to protocol optimization is updating physician awareness and

recalibrating expectations about what constitutes a diagnostic CT scan based on better alignment of CT protocol parameter choices with diagnostic image quality requirements.

Strengths and limitations

The main advantages of our study are its large size and detailed and standardized collection of data that allowed us to determine potential contributors to radiation dose. This study also had several limitations. The number of participating institutions for each country outside the US was limited so our data cannot be considered representative of any country as a whole. However, country specific doses in our registry are similar to those reported elsewhere,[3 24 25 40] suggesting our estimates are

Table 4 | Multivariable linear regression results for relative computed tomography (CT) effective dose by country, accounting for all patient, institute, and machine characteristics with and without technical factors. Asterisks=P<0.05

	Effect size (95% CI), by anatomical area of CT scan (with and without technical factors)									
	Abdomen		Chest		Combined chest and abdomen		Head		Suspected pulmonary embolism	
	Without	**With**	**Without**	**With**	**Without**	**With**	**Without**	**With**	**Without**	**With**
Germany	Reference		Reference		Reference		Reference		Reference	
Netherlands	0.99 (0.71 to 1.39)*	0.88 (0.74 to 1.04)*	0.71 (0.43 to 1.19)*	0.91 (0.72 to 1.15)*	1.15 (0.68 to 1.95)*	1.09 (0.87 to 1.36)	0.96 (0.66 to 1.39)	1.10 (0.92 to 1.30)*	1.18 (0.69 to 2.02)*	1.35 (1.01 to 1.81)*
Switzerland	1.11 (0.77 to 1.61)*	0.64 (0.53 to 0.78)*	0.38 (0.22 to 0.67)*	0.73 (0.56 to 0.94)*	1.11 (0.65 to 1.91)*	0.86 (0.68 to 1.09)	1.06 (0.71 to 1.58)	1.03 (0.85 to 1.25)*	1.07 (0.62 to 1.84)*	1.15 (0.85 to 1.56)*
UK	0.98 (0.72 to 1.33)*	0.84 (0.71 to 0.99)*	0.82 (0.52 to 1.32)*	0.91 (0.73 to 1.14)*	1.02 (0.62 to 1.67)*	1.02 (0.83 to 1.27)	1.05 (0.74 to 1.48)	1.26 (1.06 to 1.49)*	1.54 (0.96 to 2.45)*	1.49 (1.14 to 1.93)*
US	1.48 (1.17 to 1.86)*	0.92 (0.81 to 1.04)*	1.07 (0.75 to 1.52)*	0.92 (0.78 to 1.09)*	1.25 (0.81 to 1.92)*	1.02 (0.85 to 1.23)	1.22 (0.93 to 1.58)	1.08 (0.96 to 1.23)*	2.31 (1.60 to 3.33)*	1.44 (1.18 to 1.76)*
Israel	2.69 (1.76 to 4.11)*	0.95 (0.75 to 1.19)*	1.77 (0.93 to 3.37)*	1.00 (0.73 to 1.36)*	2.28 (1.18 to 4.41)*	1.15 (0.87 to 1.54)	1.10 (0.68 to 1.75)	1.17 (0.93 to 1.48)*	1.86 (0.97 to 3.55)*	1.47 (1.02 to 2.11)*
Japan	2.73 (1.95 to 3.83)*	0.98 (0.83 to 1.17)*	0.92 (0.56 to 1.52)*	0.88 (0.70 to 1.11)*	2.83 (1.61 to 5.00)*	1.27 (1.00 to 1.63)	1.18 (0.8 to 1.74)	0.94 (0.78 to 1.13)*	6.49 (3.72 to 11.35)*	1.70 (1.25 to 2.31)*

Table 5 | Technical details of computed tomography (CT) protocols included in the registry for suspected pulmonary embolism CT examinations at institutions with Siemens Somatom Definition AS machines. Data are mean (with or without standard deviation), adjusted for patient age, sex, and size; table rows ordered by mean effective dose

Country	Effective dose (mSv)	Adjusted effective dose (mSv)	$CTDI_{vol}$ (mGy)	Adjusted $CTDI_{vol}$ (mGy)	X ray tube potential (kVP)	X ray tube current (mAs)	Collimation	Pitch	Scan length (cm)	Slice thickness (mm)	No of CT scans per examination
Switzerland	1.9 (1.0)	1.7 (0.6)	4.4 (2.3)	4.0 (1.7)	103	137	38	1.5	32	1.8	1.0
Germany	2.0 (1.3)	1.6 (0.8)	4.0 (2.2)	3.4 (1.4)	103	109	19	1.4	33	1.9	1.1
US	2.2 (1.1)	1.6 (0.6)	5.0 (2.5)	4.1 (1.6)	101	92	19	0.9	30	2.1	1.0
Switzerland	2.4 (1.3)	2.2 (1.1)	4.9 (2.4)	4.6 (1.9)	109	125	38	1.5	34	1.4	1.0
Germany	2.5 (2.2)	2.3 (2.0)	4.8 (1.9)	4.4 (1.5)	98	146	38	1.2	33	2.3	1.1
US	3.9 (2.2)	3.4 (1.1)	8.5 (4.3)	7.5 (2.5)	105	81	14	1.0	16	5.8	2.2
US	4.2 (2.0)	3.3 (1.2)	8.4 (3.7)	7.1 (2.3)	113	159	38	1.2	34	2.0	1.0
US	4.5 (2.4)	3.8 (1.3)	8.8 (3.3)	7.7 (2.2)	116	261	18	1.1	35	4.2	1.0
US	4.6 (2.9)	3.4 (2.6)	9.1 (1.7)	7.3 (1.4)	120	172	19	1.5	32	1.0	1.0
US	4.6 (2.4)	3.9 (1.4)	9.8 (4.2)	8.8 (2.7)	116	114	19	0.8	32	1.1	1.0
US	4.7 (2.5)	3.8 (1.5)	10.4 (5.1)	9.0 (3.1)	103	175	19	0.9	31	1.5	1.0
US	4.8 (1.7)	3.7 (1.0)	11.2 (3.9)	9.4 (2.1)	118	165	19	1.1	30	2.0	1.0
US	4.8 (3.0)	4.6 (2.4)	8.9 (3.0)	8.8 (2.6)	112	123	19	0.9	33	3.2	1.1
US	4.9 (2.4)	4.0 (1.3)	10.7 (5.0)	9.3 (2.9)	104	179	19	0.9	31	1.5	1.0
US	4.9 (2.5)	5.2 (3.0)	11.6 (6.0)	11.9 (6.4)	107	193	19	1.0	31	1.5	1.0
US	5.5 (3.3)	4.4 (1.7)	12.2 (5.7)	10.5 (3.9)	114	157	19	0.9	31	1.4	1.0
US	5.8 (2.8)	4.7 (1.7)	12.6 (4.6)	10.8 (2.9)	114	163	38	0.8	32	2.0	1.0
US	6.0 (1.9)	5.4 (1.3)	13.8 (5.1)	12.8 (3.8)	112	201	19	0.9	29	2.2	1.1
US	6.9 (3.6)	6.7 (3.5)	14.3 (2.7)	14.2 (2.6)	120	187	19	1.0	32	3.9	1.0
US	6.9 (4.5)	6.8 (3.7)	13.3 (4.2)	13.3 (3.8)	118	152	18	0.9	29	3.7	1.3
US	7.1 (2.9)	7.5 (3.7)	15.2 (5.4)	15.7 (5.4)	120	175	19	0.9	31	3.1	1.1
US	8.0 (6.5)	7.8 (5.6)	16.2 (9.4)	15.8 (6.0)	121	174	38	0.8	30	1.1	1.1
US	8.2 (6.0)	8.2 (6.2)	10.0 (5.4)	10.0 (5.7)	105	172	12	1.0	23	4.0	2.7
US	9.1 (5.5)	7.3 (4.4)	9.3 (4.3)	8.0 (3.4)	109	132	19	0.8	37	2.8	1.1
US	10.5 (1.6)	7.1 (1.9)	22.7 (2.8)	17.1 (3.2)	120	278	14	1.0	16	5.1	2.1
US	11.4 (8.2)	9.9 (6.3)	18.3 (6.5)	16.8 (4.4)	112	265	27	1.0	21	2.9	2.2
US	11.5 (4.7)	9.1 (4.0)	9.5 (3.8)	7.9 (3.2)	111	277	17	1.0	42	4.4	1.9
US	13.4 (4.0)	18.3 (8.0)	51.5 (11.1)	65.9 (25.4)	120	180	19	0.2	19	2.0	1.0
US	15.4 (7.3)	12.4 (2.7)	13.2 (5.8)	10.9 (2.2)	109	200	19	1.0	39	5.0	2.0
US	16.5 (7.5)	12.6 (3.1)	13.4 (5.4)	11.1 (2.8)	115	199	38	1.0	43	2.8	2.0
US	26.2 (17.6)	20.0 (11.3)	16.9 (8.7)	13.8 (6.0)	116	190	38	0.8	41	3.1	1.2
US	29.3 (13.1)	29.7 (7.3)	14.1 (4.7)	14.4 (2.7)	120	161	19	0.9	35	4.0	4.1
US	37.4 (15.4)	32.7 (11.6)	21.3 (6.2)	19.4 (3.6)	120	211	19	0.8	41	4.6	2.8
Lowest tenth in protocols	2.0 (1.1)	1.6 (0.7)	4.5 (2.3)	3.8 (1.6)	102	113	25	1.2	32	1.9	1.0
Highest tenth in protocols	31.0 (15.4	27.5 (10.1)	17.4 (6.6)	15.9 (4.1)	119	188	26	0.8	39	3.9	2.7

SD standard deviation; $CTDI_{vol}$=volumetric CT dose index.

likely to reflect country norms. We report effective dose, but the results were similar when limited to volumetric CT dose index or to single CT scans. We do not have a measure of image quality and cannot be sure that institutions with the lowest doses had image quality sufficient for diagnosis; however, each institution determined that their protocols provided adequate diagnostic information for their patients.

Our analyses did not include several technical factors associated with dose (eg, use of iterative reconstruction software), but such software, when used in actual practice, has been shown to have only a modest effect on dose.[43] The inclusion of these factors would probably further reduce dose variation. The availability of alternative imaging modalities (eg, magnetic resonance imaging) could affect the case mix of patients who undergo CT, and we did not have information on availability of other imaging modalities. Our report on dose variation for a single indication on a single machine model indicates that some variability might be due to how the machines were configured.

Finally, the institutions included in this registry are a convenience sample of institutions that use Radimetrics dose monitoring software. Institutions that invest in dose monitoring software might systematically differ from institutions that do not, although our doses were similar to published accounts by country. We plan to diversify our CT registry, and invite any institution that would like to participate.

Conclusions and policy implications

CT scanning doses varied widely across included countries. Variation was chiefly driven by how machines were used, rather than by patient or machine manufacturer or model. Optimizing doses to a more consistent standard should be possible both within and between countries by modifying the decisions made by radiology teams in developing CT protocols for patients. Future research should focus on understanding factors that drive institutions, and scientifically comparing different approaches for optimizing doses.

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Web appendix: Supplementary materials