

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Correction of the Framingham Risk Score Data Reported in SPRINT

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021685
Article Type:	Research
Date Submitted by the Author:	12-Jan-2018
Complete List of Authors:	Warner, Frederick; Yale School of Medicine Dhruva, Sanket; Yale School of Medicine Ross, Joseph; Yale University School of Medicine, Internal Medicine Dey, Pranammya; Yale School of Medicine Karthik Murugiah, Karthik Murugiah; Yale University School of Medicine Krumholz, Harlan
Keywords:	Clinical trials < THERAPEUTICS, Hypertension < CARDIOLOGY, cardiovascular risk, open data

SCHOLARONE™
Manuscripts

View Only

Correction of the Framingham Risk Score Data Reported in SPRINT

Frederick Warner, PhD; Sanket S. Dhruva, MD; Joseph S. Ross, MD, MHS;

Pranamya Dey; Karthik Murugiah, MD; Harlan M. Krumholz, MD, SM

Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, CT (FW, JSR, KM, HMK); National Clinician Scholars Program (SSD, JSR) and Section of Cardiovascular Medicine (FW, SSD, KM, HMK), Department of Internal Medicine, Yale School of Medicine, New Haven, CT; Department of Health Policy and Management (JSR, HMK), Yale School of Public Health, New Haven, CT; Veterans Affairs Connecticut Healthcare System, West Haven, CT (SSD); Yale School of Medicine (PD), New Haven, CT

Corresponding Author: Harlan M. Krumholz MD, SM; 1 Church Street, Suite 200, New Haven, CT, USA 06510; Tel: 203-764-5885; Fax: 203-764-5653;

harlan.krumholz@yale.edu

Word Count: 1702

Key Words: clinical trials, hypertension, cardiovascular risk, open data

Funding Statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests Statement: Drs. Krumholz and Ross are recipients of research agreements from Medtronic and Johnson & Johnson (Janssen), through Yale, to develop methods of clinical trial data sharing and of a grant from Medtronic and the Food and Drug Administration, through Yale, to develop methods for post-market surveillance of medical

1
2
3 devices; and work under contract with the Centers for Medicare & Medicaid Services to
4 develop and maintain performance measures that are publicly reported. Dr. Krumholz chairs
5 a cardiac scientific advisory board for UnitedHealth; is a participant/participant
6 representative of the IBM Watson Health Life Sciences Board; is a member of the Advisory
7 Board for Element Science and the Physician Advisory Board for Aetna; and is the founder of
8 Hugo, a personal health information platform. Dr. Ross has received research support from
9 the Blue Cross Blue Shield Association to better understand medical technology evidence
10 generation. The other co-authors report no potential competing interests.
11
12
13
14
15
16
17
18
19
20

21 **Data Sharing:** The SPRINT data we used are available via the Biologic Specimen and Data
22 Repository Information Coordinating Center (BioLINCC).
23
24
25
26

27 **Authors' Contributions:** Drs. Warner and Krumholz conceived and designed the work. Dr.
28 Warner wrote the first draft of the manuscript. Drs. Warner, Dhruva, Ross, Murugiah, and
29 Krumholz, and Mr. Dey, analyzed and interpreted the data, revised the work critically for
30 important intellectual content, and approved the submitted version. Drs. Warner and
31 Krumholz are accountable for all aspects of the work in ensuring that questions related to
32 the accuracy or integrity of any part of the work are appropriately investigated and
33 resolved.
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

Objectives: To understand the discrepancy between the published 10-year cardiovascular risk and 10-year cardiovascular risk generated from raw data using the Framingham Risk Score for participants in the Systolic Blood Pressure Intervention Trial (SPRINT)

Design: Secondary analysis of SPRINT data published in *The New England Journal of Medicine* (NEJM) and made available to researchers in late 2016

Setting: SPRINT clinical trial sites

Participants: Study participants enrolled into SPRINT

Results: The number of SPRINT study participants identified as having $\geq 15\%$ 10-year cardiovascular risk was not consistent with what was reported in the original publication. Using the data from the trial, the Framingham Risk Score indicated $\geq 15\%$ 10-year cardiovascular risk for 7089 participants compared with 5737 reported in the paper, a change from 61% to 76% of the total study population. The reason for the divergence from the published paper was not clear.

Conclusions: The analysis of the clinical trial data by independent investigators identified an error in the reporting of the risk of the study population. The SPRINT trial enrolled a higher risk population than was reported in the initial publication, which was brought to light by data sharing.

Strengths and Limitations of this Study:

- We analyzed data made available to researchers to generate a 10-year Framingham Risk Score and shared our results with the National Institutes of Health.
- We explain the reason that SPRINT study participants were at higher cardiovascular risk than initially understood, which helps to inform the generalizability of the trial's results.
- We did not have access to full SPRINT data; there may be additional data that are not available to researchers at this time which could help to explain the findings.
- We were unable to explain the cardiovascular risk of 575 SPRINT study participants.

INTRODUCTION

In April 2017, the *New England Journal of Medicine* (NEJM) hosted a summit on "Aligning Incentives for Sharing Clinical Trial Data," with the aim of providing a demonstration of the benefits of clinical trial data sharing.¹ In the months leading up to the summit, NEJM launched the Systolic Blood Pressure Intervention Trial (SPRINT) Data Analysis Challenge, which offered researchers access to the SPRINT clinical trial database in order to provide a real-world demonstration of the benefits of clinical trial data sharing. Investigators from around the world used the SPRINT data to produce novel research abstracts that were shared publicly. The SPRINT data are now available via the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).²

SPRINT, a randomized clinical trial sponsored by the National Institutes of Health (NIH), compared a more intensive systolic blood pressure (BP) target (<120 mm Hg) with a standard target (<140 mm Hg) among non-diabetic patients aged 50 or older with hypertension, and with known cardiovascular disease or known elevated risk for cardiovascular disease.¹ After observing significantly fewer cardiovascular events among patients allocated to the more intense treatment regimen, the Data Safety and Monitoring Board stopped the trial early, and the primary results were published in NEJM on November 26, 2015.

Our research group planned to use the SPRINT data as part of the SPRINT Data Analysis Challenge. We first sought to determine if we could replicate the information in the main publication. As part of this effort, we calculated the 10-year Framingham Risk Scores (FRS). The published SPRINT paper reported that 61% of the participants were identified as having $\geq 15\%$ 10-year cardiovascular risk based on the FRS.³ We found that this number did not match what we calculated from the raw data made available from BioLINCC. We emailed our findings to the coordinator of the NEJM Challenge from whom we received a response quoting a BioLINCC official, "The equation appears to have originally been calculated with the coefficients for treated systolic blood pressure and untreated systolic blood pressure

reversed" (personal communication). In this report, we describe our mathematical analysis of this discrepancy and its implications.

METHODS

Data Source

BioLINCC provided the data underlying the primary publication of the SPRINT results. These data were organized into 5 datasets: patient baseline information, blood pressure readings over time, primary and other outcomes, patient status at the end of intervention, and adverse events.

Data Variables

The variable of interest was the reported FRS, denoted by a variable labeled *'risk10yrs'* in the baseline information data set. We also used the 7 variables included in the FRS score: age, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, antihypertensive medication use, current smoking status, and sex. As a result of the exclusion criterion, no SPRINT participants had diabetes, another FRS variable, at baseline.

Risk Score Calculation

We calculated the FRS using the sex-specific formulas derived originally from Cox proportional-hazards models in a 2008 paper by D'Agostino *et al.* using the 7 variables above.⁴ The NEJM Challenge coordinators confirmed that the D'Agostino *et al.* regression model (hereafter referred to as the "true" model) was appropriate for calculating the 10-year risk used in SPRINT (personal communication).

The continuous variables were (natural) log-transformed. Regression coefficients for each variable (Table 1) were calculated via the Cox model in the D'Agostino paper. If we represent the variables as X_i (X_1 is log(age), X_2 is log(total cholesterol), etc.) and their

1
2
3 corresponding coefficients as β_i , then for each patient we can form the linear combination of
4 the above variables and coefficients, given by $\sum \beta_i X_i$. With this calculated, the final risk score
5 for women is given by
6
7
8
9

$$1 - 0.95012^{\exp(\sum \beta_i X_i - 26.1931)}$$

10
11
12
13
14 and for men by
15

$$1 - 0.88936^{\exp(\sum \beta_i X_i - 23.9802)}$$

16 17 18 19 20 21 22 23 **Statistical Analysis**

24 We compared our calculated FRS values with those in the *risk10yrs* variable. We
25 then also calculated the percentage of participants with $\geq 15\%$ 10-year risk by the
26 calculated score and compared it with the $\geq 15\%$ 10-year risk by the *risk10yrs* variable and
27 the published result in the original SPRINT paper.³ We created a scatter plot of the provided
28 *risk10yrs* variable against our calculated FRS, stratified by patients previously treated for
29 hypertension and those previously untreated for hypertension (Figure 1).
30
31
32
33
34
35

36 We tested the effect of interchanging the coefficients for the treated systolic blood
37 pressure and untreated systolic blood pressure formula in our calculated FRS in order to
38 verify the validity of the explanation provided to us for the discrepancy. The Yale University
39 Human Investigation Committee approved our analysis of SPRINT data.
40
41
42
43
44
45
46

47 **RESULTS**

48 We used the data from all 9361 study participants in SPRINT.
49
50
51
52

53 **Comparison of *risk10yrs* with Published Result**

54
55
56
57
58
59
60

1
2
3 Table 1 of the original SPRINT manuscript indicates that the number of participants whose
4 FRS is $\geq 15\%$ was 2870 and 2867 for intensive and standard treatment, respectively. The
5 mean \pm standard deviation (SD) of the FRS values were $20.1 \pm 10.9\%$ and $20.1 \pm 10.8\%$ for
6 intensive and standard treatment, respectively. All of these data agree with the numbers
7 calculated using the *risk10yrs* variable provided to SPRINT Challenge participants.
8
9
10
11
12
13
14

15 **Comparison of Calculated and Reported Risk Score**

16
17 Our calculated FRS using the true model were not consistent with the reported
18 scores in the *risk10yrs* variable. Specifically, 7089 (76%) of patients had $\geq 15\%$ 10-year
19 cardiovascular risk according to the calculated score, versus 5737 (61%) using the score
20 determined from the provided *risk10yrs* variable. The mean \pm SD 10-year cardiovascular
21 risk was $24.8 \pm 12.5\%$ for the calculated score versus $20.1 \pm 10.9\%$ for the score based on
22 the *risk10yrs* variable.
23
24
25
26
27
28

29 The SPRINT Challenge variable *InclusionFRS*, derived from *risk10yrs* variable,
30 indicated that 5737 patients were included based on $\geq 15\%$ 10-year risk. This number was
31 consistent with the data presented in Table 1 of the original SPRINT manuscript, indicating a
32 discrepancy between results calculated from the SPRINT data and the SPRINT publication.^{3 4}
33
34
35
36
37

38 As illustrated in Figure 1, our calculated FRS was lower than the *risk10yrs* variable
39 for previously untreated patients and higher for previously treated patients. The overall
40 effect, since 91% were previously treated and treatment is associated with higher risk, was
41 to represent the SPRINT study population as having lower 10-year cardiovascular risk than
42 it truly had.
43
44
45
46
47

48 Interchanging the coefficients produced a risk score matching the *risk10yrs* variable
49 for 8711 (93%) SPRINT participants, but failed to reproduce the published FRS results for
50 585 (6.3%) SPRINT participants. For 10 of these participants, the risk reported in *risk10yrs*
51 agrees exactly with the correct formula, and not the formula with the reversed coefficients.
52
53
54
55
56
57
58
59
60

1
2
3 For the remaining 575 participants, we are unable to either replicate or explain the
4 published FRS results.
5
6
7

8 9 **DISCUSSION**

10 After receiving access to the data underlying SPRINT through the SPRINT Data
11 Analysis Challenge, we found an error in the FRS calculations in the SPRINT publication.³
12 SPRINT's primary publication erroneously stated that 61% of patients had $\geq 15\%$ 10-year
13 cardiovascular risk, instead of the true value of 76%. The FRS was one of the 4 eligibility
14 criteria for SPRINT, and the most common (accounting for eligibility of 61.3% of all study
15 participants). Therefore, understanding the subset of study participants at $\geq 15\%$ risk at
16 enrollment is critical to understanding the SPRINT study population and considering the
17 real-world population to whom the study results could be generalized.
18
19
20
21
22
23
24
25
26

27 Of note, this information does not change the results of the trial, but rather shows
28 the study's particular relevance for high-risk individuals, as more participants fit into the
29 high-risk category than initially thought. The new American College of Cardiology/American
30 Heart Association Blood Pressure Guideline relied heavily on SPRINT in making
31 recommendations to lower the treatment target for which pharmacologic therapy should be
32 initiated for high-risk individuals.⁵ The finding also supports the decision by the National
33 Institutes of Health and the SPRINT investigators to share their data by showing a benefit of
34 data sharing. The error in the main paper has now been corrected.⁶ We note that this
35 correction gives 7103 participants at $\geq 15\%$ risk instead of the 7089 we cite here. This is
36 due to the fact that our analysis was restricted to participants who were assigned an FRS in
37 the SPRINT Challenge data.
38
39
40
41
42
43
44
45
46
47
48

49 Some questions persist. BioLINCC has stated that the population at $\geq 15\%$ risk was
50 determined at a pre-baseline screening visit (not reported in the main paper), but these
51 data were not available to SPRINT Challenge participants.⁷ Therefore, it is not possible to
52 determine the effect of the incorrect calculation on the inclusion criteria and whether the
53
54
55
56
57

1
2
3 calculation was used to make these determinations. Additionally, the reversing of the
4 coefficients for treatment, which was suggested as the coding error responsible for the
5 error, does not fully explain the discrepancy.
6
7
8

9 This correction highlights an often-overlooked benefit of data sharing in medicine:
10 error identification and correction by reproducing research to verify previously published
11 research findings. Many researchers report having failed to reproduce their own scientific
12 experiments, or an experiment of a colleague, and are just now beginning to establish
13 procedures to foster scientific reproducibility.⁸ Clinical trial data sharing is likely the best
14 method to facilitate reproducibility in the clinical sciences. The sharing of data can enable
15 the wisdom of crowds to emerge, proper questioning and clarification of methods, and
16 ultimately a greater understanding of particular studies. Moreover, sharing empowers other
17 researchers to ensure that the contributions of the patient participants and scientists who
18 create a study are honored by generating as much clinically - and scientifically - relevant
19 knowledge from the study as possible.
20
21
22
23
24
25
26
27
28
29
30

31 In conclusion, the SPRINT Data Analysis Challenge demonstrated how clinical trial
32 data sharing enables increased knowledge generation to improve clinical practice and
33 scientific understanding. Our analysis and the NEJM correction illustrate a secondary benefit
34 to data sharing, namely that data sharing allows for outside researchers to reproduce
35 existing analyses, and in that process, discover any errors. Even in this highly curated,
36 limited dataset, known to be shared with the public and constructed by experts in the field,
37 we found an error that was likely the result of a simple miscode for most patients. Of note,
38 any study is vulnerable to such errors, and the SPRINT investigators should be credited with
39 a willingness to have their data examined by others. Greater availability of clinical trial
40 protocols and underlying datasets would allow for novel investigations as well as greater
41 verification and reproducibility of existing investigations, strengthening confidence in trial
42 results and conclusions.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

1. Riley WT, Riddle M, Lauer MS. NIH policies on experimental studies with humans. *Nat Hum Behav* 2017. Available at <https://www.nature.com/articles/s41562-017-0265-4.pdf?origin=ppub>.
2. Systolic Blood Pressure Intervention Trial Primary Outcome Paper (SPRINT-POP) Data. BioLINCC 2016. Available at https://biolincc.nhlbi.nih.gov/studies/sprint_pop/.
3. Wright JT, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**(22):2103-16.
4. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. *Circulation* 2008;**118**(4):E86-E86.
5. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2017. pii: HYP.0000000000000065. doi: 10.1161/HYP.0000000000000065.
6. Correction. *N Engl J Med* 2017;**377**(25):2506.
7. README_FRS Calculation Error. BioLINCC. Available at https://biolincc.nhlbi.nih.gov/static/studies/sprint_pop/README_FRS%20Calculation_Error.docx.
8. Baker M. 1,500 scientists lift the lid on reproducibility. *Nature* 2016;**533**(7604):452-4.

FIGURE LEGEND

Figure 1. Scatter plot of the *risk10years* variable vs. the calculated variable using the true model.⁴

Color is used to indicate the correct blood pressure treatment status of study participants. This figure illustrates the effect of interchanging the prior antihypertensive medication use variable – the Framingham Risk Score is under-estimated for those being treated and over-estimated for the untreated population.

Table 1 – Regression coefficients for Cox regression model used to predict cardiovascular disease risk.⁴

Variable	Women	Men
Log of age	2.32888	3.06117
Log of total cholesterol	1.20904	1.12370
Log of HDL cholesterol	-0.70833	-0.93263
Log of SBP if not treated	2.76157	1.93303
Log of SBP if treated	2.82263	1.99881
Smoking	0.52873	0.65451
Diabetes	0.69154	0.57367
HDL, high-density lipoprotein; SBP, systolic blood pressure		

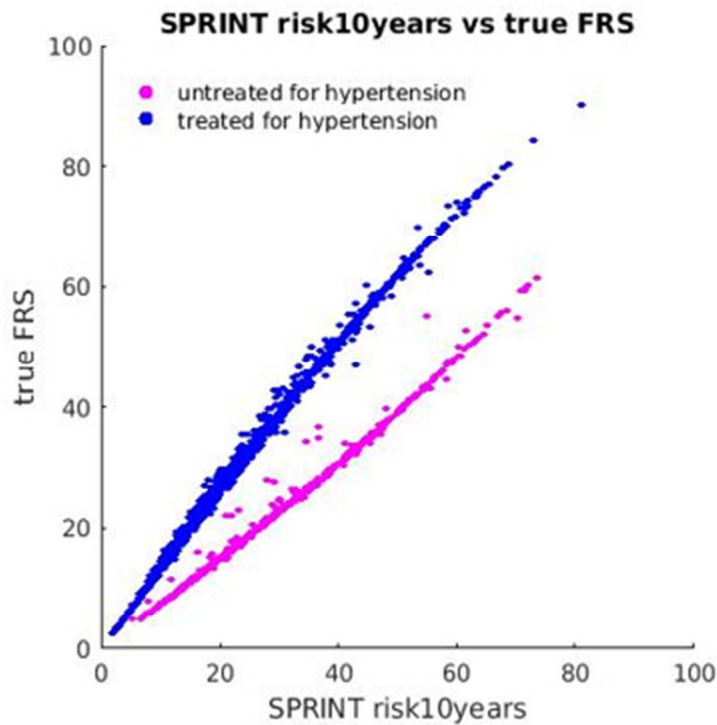


Figure 1. Scatter plot of the risk10years variable vs. the calculated variable using the true model.⁴

Color is used to indicate the correct blood pressure treatment status of study participants. This figure illustrates the effect of interchanging the prior antihypertensive medication use variable – the Framingham Risk Score is under-estimated for those being treated and over-estimated for the untreated population.

only

BMJ Open

Accurate Estimation of Cardiovascular Risk in a Non-Diabetic Adult: Detecting and Correcting the Error in the Reported Framingham Risk Score for the Systolic Blood Pressure Intervention Trial Population

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021685.R1
Article Type:	Research
Date Submitted by the Author:	04-Apr-2018
Complete List of Authors:	Warner, Frederick; Yale School of Medicine Dhruva, Sanket; Yale School of Medicine Ross, Joseph; Yale University School of Medicine, Internal Medicine Dey, Pranamma; Yale School of Medicine Murugiah, Karthik; Yale University School of Medicine Krumholz, Harlan
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Medical publishing and peer review
Keywords:	Clinical trials < THERAPEUTICS, Hypertension < CARDIOLOGY, cardiovascular risk, open data

SCHOLARONE™
Manuscripts

Only

1
2
3 **Accurate Estimation of Cardiovascular Risk in a Non-Diabetic Adult: Detecting and**
4
5 **Correcting the Error in the Reported Framingham Risk Score for the**
6
7 **Systolic Blood Pressure Intervention Trial Population**
8

9 Frederick Warner, PhD; Sanket S. Dhruva, MD; Joseph S. Ross, MD, MHS;
10
11 Pranammya Dey; Karthik Murugiah, MD; Harlan M. Krumholz, MD, SM
12
13

14
15 Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, CT
16
17 (FW, JSR, KM, HMK); National Clinician Scholars Program (SSD, JSR) and Section of
18
19 Cardiovascular Medicine (FW, SSD, KM, HMK), Department of Internal Medicine, Yale School
20
21 of Medicine, New Haven, CT; Department of Health Policy and Management (JSR, HMK),
22
23 Yale School of Public Health, New Haven, CT; Veterans Affairs Connecticut Healthcare
24
25 System, West Haven, CT (SSD); Yale School of Medicine (PD), New Haven, CT
26
27

28
29 **Corresponding Author:** Harlan M. Krumholz MD, SM; 1 Church Street, Suite 200, New
30
31 Haven, CT, USA 06510; Tel: 203-764-5885; Fax: 203-764-5653;
32
33 harlan.krumholz@yale.edu
34
35

36
37 **Word Count:** 1721
38
39

40
41 **Key Words:** clinical trials, hypertension, cardiovascular risk, open data
42
43

44
45 **Funding Statement:** This research received no specific grant from any funding agency in
46
47 the public, commercial or not-for-profit sectors.
48
49

50
51 **Competing Interests Statement:** Drs. Krumholz and Ross are recipients of research
52
53 agreements from Medtronic and Johnson & Johnson (Janssen), through Yale, to develop
54
55 methods of clinical trial data sharing and of a grant from Medtronic and the Food and Drug
56
57

1
2
3 Administration, through Yale, to develop methods for post-market surveillance of medical
4 devices; and work under contract with the Centers for Medicare & Medicaid Services to
5 develop and maintain performance measures that are publicly reported. Dr. Krumholz chairs
6 a cardiac scientific advisory board for UnitedHealth; is a participant/participant
7 representative of the IBM Watson Health Life Sciences Board; is a member of the Advisory
8 Board for Element Science and the Physician Advisory Board for Aetna; and is the founder of
9 Hugo, a personal health information platform. Dr. Ross has received research support from
10 the Blue Cross Blue Shield Association to better understand medical technology evidence
11 generation. The other co-authors report no potential competing interests.
12
13
14
15
16
17
18
19
20
21
22

23 **Data Sharing:** The SPRINT data we used are available via the Biologic Specimen and Data
24 Repository Information Coordinating Center (BioLINCC).
25
26
27
28

29 **Authors' Contributions:** Drs. Warner and Krumholz conceived and designed the work. Dr.
30 Warner wrote the first draft of the manuscript. Drs. Warner, Dhruva, Ross, Murugiah, and
31 Krumholz, and Mr. Dey, analyzed and interpreted the data, revised the work critically for
32 important intellectual content, and approved the submitted version. Drs. Warner and
33 Krumholz are accountable for all aspects of the work in ensuring that questions related to
34 the accuracy or integrity of any part of the work are appropriately investigated and
35 resolved.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

Objectives: To understand the discrepancy between the published 10-year cardiovascular risk and 10-year cardiovascular risk generated from raw data using the Framingham Risk Score for participants in the Systolic Blood Pressure Intervention Trial (SPRINT)

Design: Secondary analysis of SPRINT data published in *The New England Journal of Medicine* (NEJM) and made available to researchers in late 2016

Setting: SPRINT clinical trial sites

Participants: Study participants enrolled into SPRINT

Results: The number of SPRINT study participants identified as having $\geq 15\%$ 10-year cardiovascular risk was not consistent with what was reported in the original publication. Using the data from the trial, the Framingham Risk Score indicated $\geq 15\%$ 10-year cardiovascular risk for 7089 participants compared with 5737 reported in the paper, a change from 61% to 76% of the total study population. The reason for the divergence from the published paper was not clear.

Conclusions: The analysis of the clinical trial data by independent investigators identified an error in the reporting of the risk of the study population. The SPRINT trial enrolled a higher risk population than was reported in the initial publication, which was brought to light by data sharing.

Strengths and Limitations of this Study:

- We analyzed data made available to researchers to generate a 10-year Framingham Risk Score and shared our results with the National Institutes of Health.
- We explain the reason that SPRINT study participants were at higher cardiovascular risk than initially understood, which helps to inform the generalizability of the trial's results.
- We did not have access to full SPRINT data; there may be additional data that are not available to researchers at this time which could help to explain the findings.
- We were unable to explain the cardiovascular risk of 575 SPRINT study participants.

INTRODUCTION

In April 2017, the *New England Journal of Medicine* (NEJM) hosted a summit on "Aligning Incentives for Sharing Clinical Trial Data," with the aim of providing a demonstration of the benefits of clinical trial data sharing.¹ In the months leading up to the summit, NEJM launched the Systolic Blood Pressure Intervention Trial (SPRINT) Data Analysis Challenge, which offered researchers access to the SPRINT clinical trial database in order to provide a real-world demonstration of the benefits of clinical trial data sharing. Investigators from around the world used the SPRINT data to produce novel research abstracts that were shared publicly. The SPRINT data are now available via the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).²

SPRINT, a randomized clinical trial sponsored by the National Institutes of Health, compared a more intensive systolic blood pressure target (<120 mm Hg) with a standard target (<140 mm Hg) among non-diabetic patients aged 50 or older with hypertension, and with known cardiovascular disease or known elevated risk for cardiovascular disease.¹ After observing significantly fewer cardiovascular events among patients allocated to the more intense treatment regimen, the Data Safety and Monitoring Board stopped the trial early, and the primary results were published in NEJM on November 26, 2015.

Our research group planned to use the SPRINT data as part of the SPRINT Data Analysis Challenge. We first sought to determine if we could replicate the information in the main publication. As part of this effort, we calculated the 10-year Framingham Risk Scores (FRS). The published SPRINT paper reported that 61% of the participants were identified as having $\geq 15\%$ 10-year cardiovascular risk based on the FRS.³ We found that this number did not match what we calculated from the raw data made available from BioLINCC. We emailed our findings to the coordinator of the NEJM Challenge from whom we received a response quoting a BioLINCC official, "The equation appears to have originally been calculated with the coefficients for treated systolic blood pressure and untreated systolic blood pressure

reversed" (personal communication). In this report, we describe our mathematical analysis of this discrepancy and its implications.

METHODS

Data Source

BioLINCC provided the data underlying the primary publication of the SPRINT results. These data were organized into 5 datasets: patient baseline information, blood pressure readings over time, primary and other outcomes, patient status at the end of intervention, and adverse events.

Data Variables

The variable of interest was the reported FRS, denoted by a variable labeled *'risk10yrs'* in the baseline information data set. We also used the 7 variables included in the FRS score: age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, antihypertensive medication use, current smoking status, and sex. As a result of the exclusion criterion, no SPRINT participants had diabetes, another FRS variable, at baseline.

Risk Score Calculation

We calculated the FRS using the sex-specific formulas derived originally from Cox proportional-hazards models in a 2008 paper by D'Agostino *et al.* using the 7 variables above.⁴ The NEJM Challenge coordinators confirmed that the D'Agostino *et al.* regression model (hereafter referred to as the "true" model) was appropriate for calculating the 10-year risk used in SPRINT (personal communication).

The continuous variables were (natural) log-transformed. Regression coefficients for each variable (Table 1) were calculated via the Cox model in the D'Agostino paper. If we represent the variables as X_i (X_1 is log(age), X_2 is log(total cholesterol), etc.) and their

1
2
3 corresponding coefficients as β_i , then for each patient we can form the linear combination of
4 the above variables and coefficients, given by $\sum \beta_i X_i$. With this calculated, the final risk score
5 for women is given by
6
7
8
9

$$1 - 0.95012^{\exp(\sum \beta_i X_i - 26.1931)}$$

10
11
12
13
14 and for men by
15

$$1 - 0.88936^{\exp(\sum \beta_i X_i - 23.9802)}$$

16 17 18 19 20 21 22 23 **Statistical Analysis**

24 We compared our calculated FRS values with those in the *risk10yrs* variable. We
25 then also calculated the percentage of participants with $\geq 15\%$ 10-year risk by the
26 calculated score and compared it with the $\geq 15\%$ 10-year risk by the *risk10yrs* variable and
27 the published result in the original SPRINT paper.³ We created a scatter plot of the provided
28 *risk10yrs* variable against our calculated FRS, stratified by patients previously treated for
29 hypertension and those previously untreated for hypertension (Figure 1).
30
31
32
33
34
35

36 We tested the effect of interchanging the coefficients for the treated systolic blood
37 pressure and untreated systolic blood pressure formula in our calculated FRS in order to
38 verify the validity of the explanation provided to us for the discrepancy. The Yale University
39 Human Investigation Committee approved our analysis of SPRINT data.
40
41
42
43
44
45
46

47 **Patient and Public Involvement**

48 Neither patients nor the public were involved, as the research is a secondary analysis
49 of data from the SPRINT trial.
50
51
52
53
54
55
56
57
58
59
60

RESULTS

We used the data from all 9361 study participants in SPRINT.

Comparison of *risk10yrs* with Published Result

Table 1 of the original SPRINT manuscript indicates that the number of participants whose FRS is $\geq 15\%$ was 2870 and 2867 for intensive and standard treatment, respectively. The mean \pm standard deviation (SD) of the FRS values were $20.1 \pm 10.9\%$ and $20.1 \pm 10.8\%$ for intensive and standard treatment, respectively. All of these data agree with the numbers calculated using the *risk10yrs* variable provided to SPRINT Challenge participants.

Comparison of Calculated and Reported Risk Score

Our calculated FRS using the true model were not consistent with the reported scores in the *risk10yrs* variable. Specifically, 7089 (76%) patients had $\geq 15\%$ 10-year cardiovascular risk according to the calculated score, versus 5737 (61%) using the score determined from the provided *risk10yrs* variable. The mean \pm SD 10-year cardiovascular risk was $24.8 \pm 12.5\%$ for the calculated score versus $20.1 \pm 10.9\%$ for the score based on the *risk10yrs* variable.

The SPRINT Challenge variable *InclusionFRS*, derived from *risk10yrs* variable, indicated that 5737 patients were included based on $\geq 15\%$ 10-year risk. This number was consistent with the data presented in Table 1 of the original SPRINT manuscript, indicating a discrepancy between results calculated from the SPRINT data and the SPRINT publication.^{3 4}

As illustrated in Figure 1, our calculated FRS was lower than the *risk10yrs* variable for previously untreated patients and higher for previously treated patients. The overall effect, since 91% were previously treated and treatment is associated with higher risk, was to represent the SPRINT study population as having lower 10-year cardiovascular risk than it truly had.

1
2
3 Interchanging the coefficients produced a risk score matching the *risk10yrs* variable
4 for 8711 (93%) SPRINT participants, but failed to reproduce the published FRS results for
5 585 (6.3%) SPRINT participants. For 10 of these participants, the risk reported in *risk10yrs*
6 agrees exactly with the correct formula, and not the formula with the reversed coefficients.
7
8 For the remaining 575 participants, we are unable to either replicate or explain the
9 published FRS results.
10
11
12
13
14
15
16

17 **DISCUSSION**

18
19 After receiving access to the data underlying SPRINT through the SPRINT Data
20 Analysis Challenge, we found an error in the FRS calculations in the SPRINT publication.³
21 SPRINT's primary publication erroneously stated that 61% of patients had $\geq 15\%$ 10-year
22 cardiovascular risk, instead of the true value of 76%. The FRS was one of the 4 eligibility
23 criteria for SPRINT, and the most common (accounting for eligibility of 61.3% of all study
24 participants). Therefore, understanding the subset of study participants at $\geq 15\%$ risk at
25 enrollment is critical to understanding the SPRINT study population and considering the
26 real-world population to whom the study results could be generalized.
27
28
29
30
31
32
33
34

35 Of note, this information does not change the results of the trial, but rather shows
36 the study's particular relevance for high-risk individuals, as more participants fit into the
37 high-risk category than initially thought. The new American College of Cardiology/American
38 Heart Association Blood Pressure Guideline relied heavily on SPRINT in making
39 recommendations to lower the treatment target for which pharmacologic therapy should be
40 initiated for high-risk individuals.⁵ The finding also supports the decision by the National
41 Institutes of Health and the SPRINT investigators to share their data by showing a benefit of
42 data sharing. The error in the main paper has now been corrected.⁶ We note that this
43 correction gives 7103 participants at $\geq 15\%$ risk instead of the 7089 we cite here. This is
44 due to the fact that our analysis was restricted to participants who were assigned an FRS in
45 the SPRINT Challenge data.
46
47
48
49
50
51
52
53
54
55
56
57

1
2
3 Some questions persist. BioLINCC has stated that the population at $\geq 15\%$ risk was
4 determined at a pre-baseline screening visit (not reported in the main paper), but these
5 data were not available to SPRINT Challenge participants.⁷ Therefore, it is not possible to
6 determine the effect of the incorrect calculation on the inclusion criteria and whether the
7 calculation was used to make these determinations. Additionally, the reversing of the
8 coefficients for treatment, which was suggested as the coding error responsible for the
9 error, does not fully explain the discrepancy.

10
11 This correction highlights an often-overlooked benefit of data sharing in medicine:
12 error identification and correction by reproducing research to verify previously published
13 research findings. Many researchers report having failed to reproduce their own scientific
14 experiments, or an experiment of a colleague, and are just now beginning to establish
15 procedures to foster scientific reproducibility.⁸ Clinical trial data sharing is likely the best
16 method to facilitate reproducibility in the clinical sciences. The sharing of data can enable
17 the wisdom of crowds to emerge, proper questioning and clarification of methods, and
18 ultimately a greater understanding of particular studies. Moreover, sharing empowers other
19 researchers to ensure that the contributions of the patient participants and scientists who
20 create a study are honored by generating as much clinically - and scientifically - relevant
21 knowledge from the study as possible.

22
23 In conclusion, the SPRINT Data Analysis Challenge demonstrated how clinical trial
24 data sharing enables increased knowledge generation to improve clinical practice and
25 scientific understanding. Our analysis and the NEJM correction illustrate a secondary benefit
26 to data sharing, namely that data sharing allows for outside researchers to reproduce
27 existing analyses, and in that process, discover any errors. Even in this highly curated,
28 limited dataset, known to be shared with the public and constructed by experts in the field,
29 we found an error that was likely the result of a simple miscode for most patients. Of note,
30 any study is vulnerable to such errors, and the SPRINT investigators should be credited with
31 a willingness to have their data examined by others. Greater availability of clinical trial

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

protocols and underlying datasets would allow for novel investigations as well as greater verification and reproducibility of existing investigations, strengthening confidence in trial results and conclusions.

For peer review only

REFERENCES

1. Riley WT, Riddle M, Lauer MS. NIH policies on experimental studies with humans. *Nat Hum Behav* 2017. Available at <https://www.nature.com/articles/s41562-017-0265-4.pdf?origin=ppub>.
2. Systolic Blood Pressure Intervention Trial Primary Outcome Paper (SPRINT-POP) Data. BioLINCC 2016. Available at https://biolincc.nhlbi.nih.gov/studies/sprint_pop/.
3. Wright JT, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**(22):2103-16.
4. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. *Circulation* 2008;**118**(4):E86-E86.
5. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2017. pii: HYP.0000000000000065. doi: 10.1161/HYP.0000000000000065.
6. Correction. *N Engl J Med* 2017;**377**(25):2506.
7. README_FRS Calculation Error. BioLINCC. Available at https://biolincc.nhlbi.nih.gov/static/studies/sprint_pop/README_FRS%20Calculation_Error.docx.
8. Baker M. 1,500 scientists lift the lid on reproducibility. *Nature* 2016;**533**(7604):452-4.

FIGURE LEGEND

Figure 1. Scatter plot of the *risk10years* variable vs. the calculated variable using the true model.⁴

Color is used to indicate the correct blood pressure treatment status of study participants. This figure illustrates the effect of interchanging the prior antihypertensive medication use variable – the Framingham Risk Score is under-estimated for those being treated and over-estimated for the untreated population.

Table 1 – Regression coefficients for Cox regression model used to predict cardiovascular disease risk.⁴

Variable	Women	Men
Log of age	2.32888	3.06117
Log of total cholesterol	1.20904	1.12370
Log of HDL cholesterol	-0.70833	-0.93263
Log of SBP if not treated	2.76157	1.93303
Log of SBP if treated	2.82263	1.99881
Smoking	0.52873	0.65451
Diabetes	0.69154	0.57367
HDL, high-density lipoprotein; SBP, systolic blood pressure		

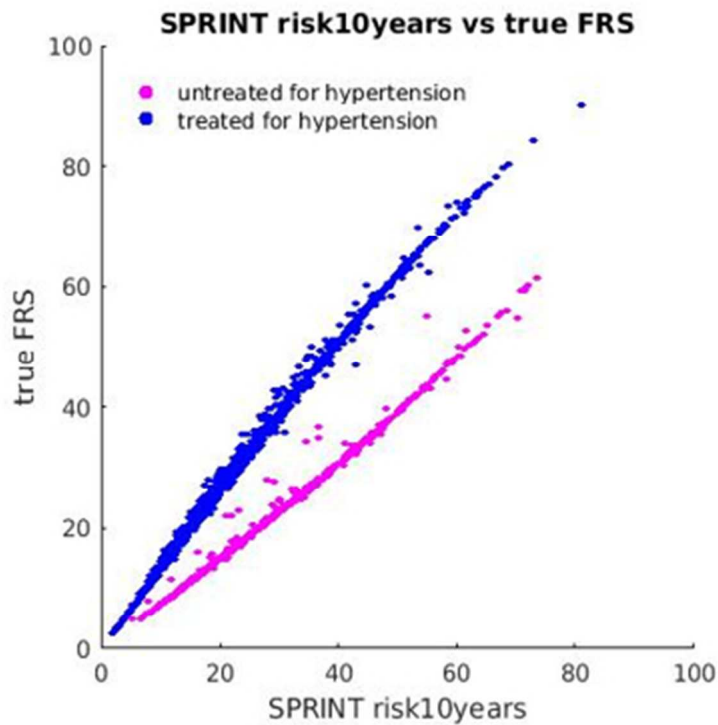


Figure 1. Scatter plot of the risk10years variable vs. the calculated variable using the true model. Color is used to indicate the correct blood pressure treatment status of study participants. This figure illustrates the effect of interchanging the prior antihypertensive medication use variable – the Framingham Risk Score is under-estimated for those being treated and over-estimated for the untreated population.

only