Propensity score analysis of lung cancer risk in a population with high prevalence of non-smoking related lung cancer

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OSIA PRESENTATION

PQHS 500

April 15, 2020

Sofija Conic

Background

- Lung cancer has been the leading cause of cancer-related mortality worldwide among both men and women.
- The National Lung Screening Trial (NLST) found that annual screening with low dose computed tomography (LDCT) in heavy smokers yielded a reduction of lung cancer mortality by 20% compared to chest x-ray.
- There is an increase in the incidence of nonsmoking-related lung cancer in recent years, namely in China, Taiwan, Korea, and Japan.

Objective

- To investigate multiple potential risk factors for non-smoking related lung cancer among Asian Ethnic groups.

Methods

- **Study population:** 1975 asymptomatic healthy subjects who voluntarily underwent self-paid LDCT at the health check-up center of Kaohsiun Veterans General Hospital (40 ~ 80 years old).
- **Time period:** August 2013 to October 2014.
- **Exposure:** Family history of lung cancer.
- **Outcome:** Non-smoking related lung cancer (lung adenocarcinoma spectrum).

Methods (cont.)

- Retrospectively reviewed clinical records
  - *Recorded age, sex, BMI, nodule number, family history of lung cancer, and family history of other cancers.*
  - *Recorded nodular characteristics according to ACR Lung-RADS classification.*
- Among 1975 subjects, 72.8% were never smokers, 16.5% were current smokers, and 10.7 were former smokers.
  - *Only 7.5% of the study subjects would have been eligible for screening based on the NLST enrollment criteria.*

Methods (cont.)

- Of the 1975 screened subjects, 27 were diagnosed with non-smoking related lung cancer.
  - *Non-smoking related lung cancer was defined as the lung adenocarcinoma spectrum (adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive adenocarcinoma)*
  - *Atypical adenomatous hyperplasia diagnosed by biopsy was excluded from the study.*
- Excluded 87 subjects with missing data for BMI
  - *Two lung cancer subjects with smoking were excluded (?)*

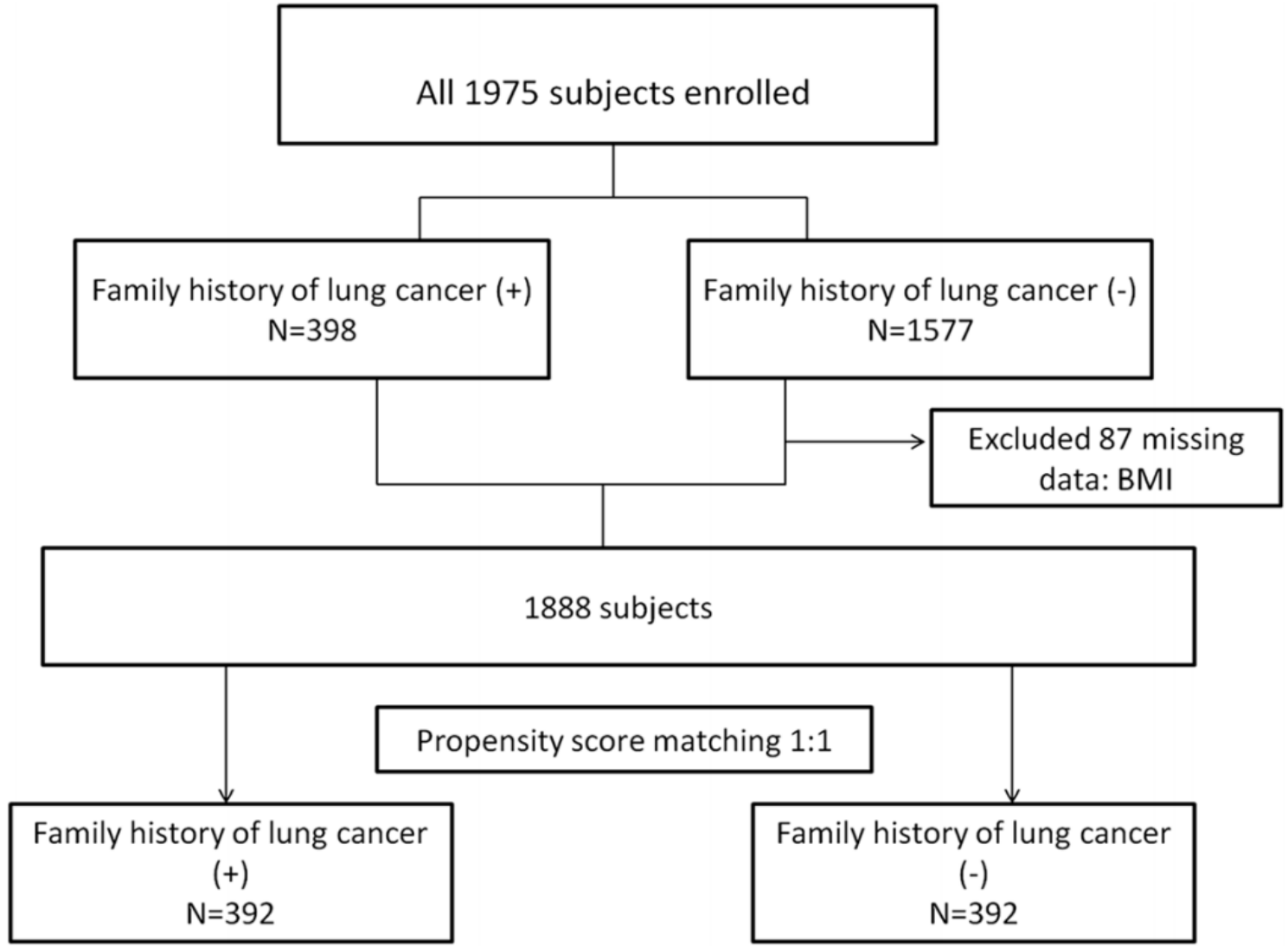

Fig. 1 Flowchart with a summary of patient enrollment and propensity score matching

Propensity Score Matching

- 1:1 propensity score matching (using SAS and SPSS)
- The covariates entered into the propensity score were age, sex, and BMI
- 392 pairs of subjects with family history of lung cancer and subjects without history
  - *Total 784 subjects*
- No differences in age, sex, BMI, and family history of other cancer after matching
- 8 out of 27 subjects (29.62%) with non-smoking related lung cancer had a diagnosis of synchronous multiple primary lung cancers (MPLCs) before PSM.
- 7 out of 20 (35%) subjects with non-smoking related lung cancer had a diagnosis of MPLCs after PSM.

Propensity Score Matching

Table 2 Patient characteristics before and after propensity score matching

	Before PSM (*N* = 1975)					After PSM (*N* = 784)				
Characterics	All		Family history (+)	Family history (–)	*P*	All		Family history (+)	Family history (–)	*P*
Age, years	56.56 ± 9.01		56.1 ± 9.39	58.39 ± 7.05	<0.0001[a]	58.61 ± 7.15		58.57 ± 6.855	58.66 ± 7.556	0.865[a]
Sex (%)					<0.0001[b]					0.94[b]
Male	1083	54.90%	136 (34.1%)	947 (60.05%)		517	65.90%	258 (65.8%)	259 (66.1%)	
Female	892	45.10%	262 (65.9%)	630 (39.95%)		267	34.10%	134 (34.2%)	133 (33.9%)	
BMI	24.32 ± 3.49		23.76 ± 3.36	24.46 ± 3.50	<0.0001[a]			23.76 ± 3.36	23.88 ± 3.56	0.644[a]
Nodule number	0.63 ± 1.16		1.09 ± 1.53	0.51 ± 1.027	<0.0001[a]	0.84 ± 1.392		1.1 ± 1.53	0.59 ± 1.17	<0.0001[a]
History of other cancers					0.023[b]					0.601[b]
Present	621	31.40%	144 (36.1%)	477 (30.2%)		275	35.10%	141 (36%)	131(34.2%)	
Absent	1354	68.50%	254 (63.9%)	1100 (69.8%)		509	64.90%	258 (64%)	251(65.8%)	
Category 4 lesion					<0.0001[b]					0.186[b]
Present	53	2.68%	21 (5.27%)	32 (2.02%)		36	4.59%	21 (5.3%)	15 (3.82%)	
Absent	1922	97.32%	377 (94.73%)	1545 (97.98%)		748	95.41%	371 (94.7%)	377 (96.18%)	
Lung cancer					<0.0001[b]					0.019[c]
Present	27	1.40%	15 (3.76%)	12 (0.76%)		20	2.60%	15 (3.8%)	5 (1.3%)	
Absent	1948	98.60%	383 (96.24%)	1565 (99.24%)		764	97.40%	377 (96.2)	387 (98.7)	

[a]Using independent t-test for continuous variables; [b] Using Chi-square test for categorical variables; [c] Using Fisher's exact test for categorical variables
Abbreviations: *PSM* propensity score matching, *BMI* body mass index

Distribution of Propensity Scores

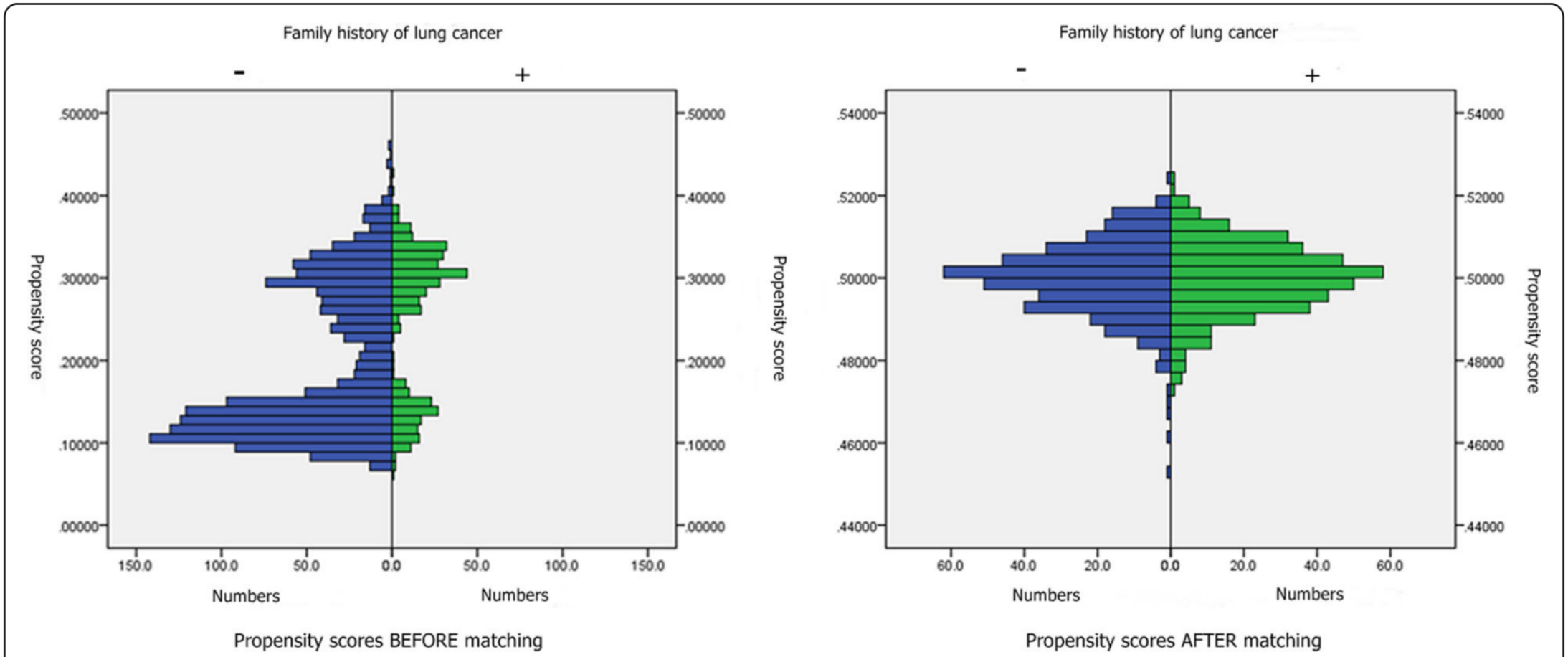

Fig. 2 a-b Histograms of propensity score distribution before and after propensity score matching. Distribution of the propensity scores before and after matching for group of family history of lung cancer (+) and group of family history of lung cancer (–). **a** presents histograms of unbalanced propensity score distribution in both groups before propensity matching. **b** presents histograms of balanced propensity score distribution in both groups after propensity matching

Logistic Regression Results

Table 3 Univariate and multivariate logistic regression analyses for predictors of lung cancer in 784 subjects after propensity score matching

	Univariate analysis			Multivariate analysis		
Characterics	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age, years	1.015	0.953–1.082	0.641	0.994	0.923–1.070	0.871
Sex (female gender)	10.149	1.351–76.227	0.024	11.199	1.444–86.862	0.021
BMI, kg/m^2	1.015	0.895–1.151	0.815	1.079	0.953–1.221	0.23
Nodule number	1.353	1.114–1.642	0.02	1.309	1.066–1.607	0.01
Family history of lung cancer	3.08	1.108–8.557	0.031	2.831	1.000136–8.015	0.05
Family history of other cancer	1.241	0.501–3.073	0.641	1.078	0.425–2.732	0.875

Abbreviations: *BMI* body mass index, *CI* confidence interval

Discussion

- Female gender and family history of lung cancer were identified as predictors of non-smoking related lung cancer
  - *In line with findings from previous case-control and retrospective cohort studies*
- There were more nodules in the group with a positive history of lung cancer compared to those with a negative history (1.09 ± 1.53 versus 0.51 ± 1.027).
- The group with a positive family history of lung cancer had several characteristics higher at baseline, including female sex (65.9% vs 39.95%), percentage of category 4 lesions (5.27% vs 2.02%), the percentage of family history of other cancers (36.1% vs 30.2%) and the percentage of lung cancer (3.76% vs 0.76%).
- Risk-based prediction model based on family history of lung cancer and female sex can potentially improve efficiency of lung cancer screening in Taiwan
  - *Is this generalizable?*

Limitations

- Propensity score matching can only adjust for observed covariates
- Study population voluntarily paid for LDCT
- Reduced sample size after propensity score matching
  - *Only analyzed 784 out of 1888 eligible subjects*

OSIA 2nd Reader - Propensity score analysis of lung cancer risk in a population with high prevalence of non-smoking related lung cancer

Lin *et al.* (2017)

Joseph Hnath

16 April 2020

Propensity Score Overview

- Their PS model: age, gender, BMI
  - Relationship with family history of lung cancer?
  - Unclear if gender or sex
  - Why not use the nodule and other cancer history variables too?
- Did not seem very knowledgeable about PS
  - Nearest neighbor, calipers?
  - Didn't check other PS models
    - 2:1 matching
    - Other variables
- Family history of lung cancer
  - Unclear if general or smoking / non-smoking specific
- Background:
  - No mention of other PS studies looking at lung cancer

What To Include in the Propensity Score Model

- **All** covariates that subject matter experts (and subjects) judge to be important when selecting treatments.
- **All** covariates that relate to treatment and outcome, certainly including any covariate that improves the prediction of treatment group.
- Sop up as much "signal" as possible.

Results

- Over 11x the odds of non-smoking lung cancer for female vs. male??
  - Huge confidence interval
- Some evidence in literature about genetic mutations more common in women leading to NS-lung cancer
  - Did not mention specifics about family history
- Why not stratified analysis, matching fixed on sex?

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Limitations

- “PS can only control for observed covariates (age, gender, BMI)”
  - Only guaranteed to balance observed, but can balance unobserved covariates correlated with observed
    - Reason to include as many as possible?
- “PS reduced power by throwing out a lot of subjects”
  - Okay, but could have tried 2:1 matching
- “Large number of subjects eliminated after PS matching because of limited numbers within exposure group despite the algorithm for full matching”
  - 2:1 matching
- Selection bias in sample, “voluntarily underwent self-paid LDCT exam at health check up”
  - Who is able / going to pay for LDCT exam?
- Other risk factors for non-smoking lung cancer not included
  - American Cancer Society: Radon, secondhand smoke, occupational carcinogen exposure, air pollution, diet
- What is the purpose of the study?
  - “Investigate multiple risk factors”
  - PS usually for a clearer treatment?

December 20, 2016

Research

JAMA | Original Investigation

Association Between Early Participation in Physical Activity Following Acute Concussion and Persistent Postconcussive Symptoms in Children and Adolescents

Anne M. Grool, MD, PhD; Mary Aglipay, MSc; Franco Momoli, PhD; William P. Meehan III, MD; Stephen B. Freedman, MDCM, MSc; Keith Owen Yeates, PhD; Jocelyn Gravel, MD; Isabelle Gagnon, PhD; Kathy Boutis, MD; Willem Meeuwisse, MD, PhD; Nick Barrowman, PhD; Andrée-Anne Ledoux, PhD; Martin H. Osmond, MDCM; Roger Zemek, MD; for the Pediatric Emergency Research Canada (PERC) Concussion Team

OBSERVATIONAL STUDIES IN ACTION

Morgan McGrath
April 16, 2020

Grool, et al. (2016)

BACKGROUND

- Traditional concussion management = cognitive and physical rest
- These guidelines are primarily based on expert consensus and caution, not research
- Concern that protracted rest can actually lead to secondary symptoms, especially in youth (e.g. depression, anxiety)
- Some evidence that early return to physical activity may improve outcomes

Grool, et al. (2016)

STUDY DESIGN

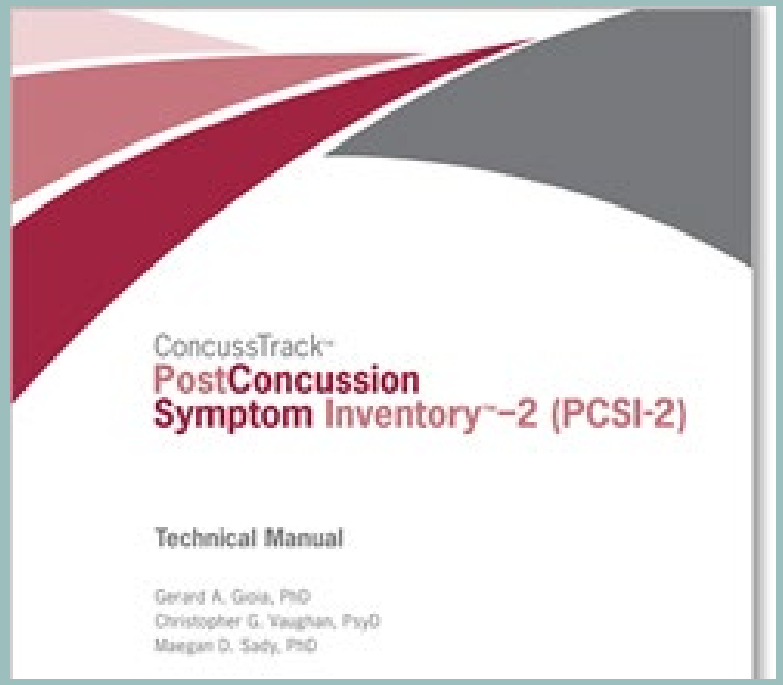
- **Objective:** Examine the association between participation in physical activity within 7 days post-injury and occurrence of persistent postconcussive symptoms (PPCS) in children and adolescents

- Secondary analysis of the Predicting Persistent Postconcussive Problems in Pediatrics (5Ps) study
  - Prospective, multicenter cohort study
  - Recruited participants from 9 pediatric EDs in Canada (2013-2015)
  - Participants age 5-18, presenting to ED for acute head injury within preceding 48 hrs
    - N = 2413 for this secondary analysis

Grool, et al. (2016)

STUDY PROCEDURES

- At enrollment in ED:
  - Demographics & medical history
  - Injury characteristics (Acute Concussion Evaluation inventory)
  - Pre-injury and current symptoms (Post-Concussion Symptom Inventory)
- Follow-up procedures:
  - Web-based or telephone survey
  - At 7 days post-enrollment and 28 days post-enrollment
  - Current level of physical activity
  - Current symptoms



Grool, et al. (2016)

OPERATIONAL DEFINITIONS

Exposure: level of physical activity reported at 7 days post-injury

- No activity (physical rest) → No activity
- Light aerobic exercise (walking, swimming) → Light aerobic exercise
- Sport-specific exercise (e.g. skating drills for ice hockey)
- Non-contact training drills (e.g. passing drills) → Moderate exercise
- Full-contact practice
- Return to competition → Full exercise

Outcome: presence of PPCS

- At least 3 new or worsening symptoms measured at post-injury day 28 as compared to pre-concussion symptom status as reported at ED

STATISTICAL METHODS

1. Unadjusted association between early physical activity and PPCS
   - Relative Risk (RR) and Absolute Risk Difference (ARD)
2. Propensity score matching:
   - Propensity score "reflects the probability of a participant having engaged in early physical activity based on baseline characteristics"
   - 1:1 greedy (nearest neighbor) match with max caliper = 0.1
   - Without replacement? (554 matches)
3. Inverse probability of treatment weighting
   - All participants weighted by inverse of probability of engaging in physical activity at post-injury day 7 (1/PS)
   - Done properly?

Note: Used no covariates in outcome models other than PS

Grool, et al. (2016)

RESULTS - UNADJUSTED

	PPCS	No PPCS	
Early physical activity	413	1264	1677 (69.5%)
No physical activity	320	416	736 (30.5%)
	733 (30.4%)	1680 (69.6%)	

24.6% of participants with early physical activity developed PPCS

43.5% of participants with no physical activity developed PPCS

Absolute Risk Difference = 18.9% (95% CI 14.7 – 23.0%)

Relative Risk = 0.75 (95% CI 0.70, 0.80)

Grool, et al. (2016)

RESULTS – PROPENSITY SCORE MATCHING & WEIGHTING

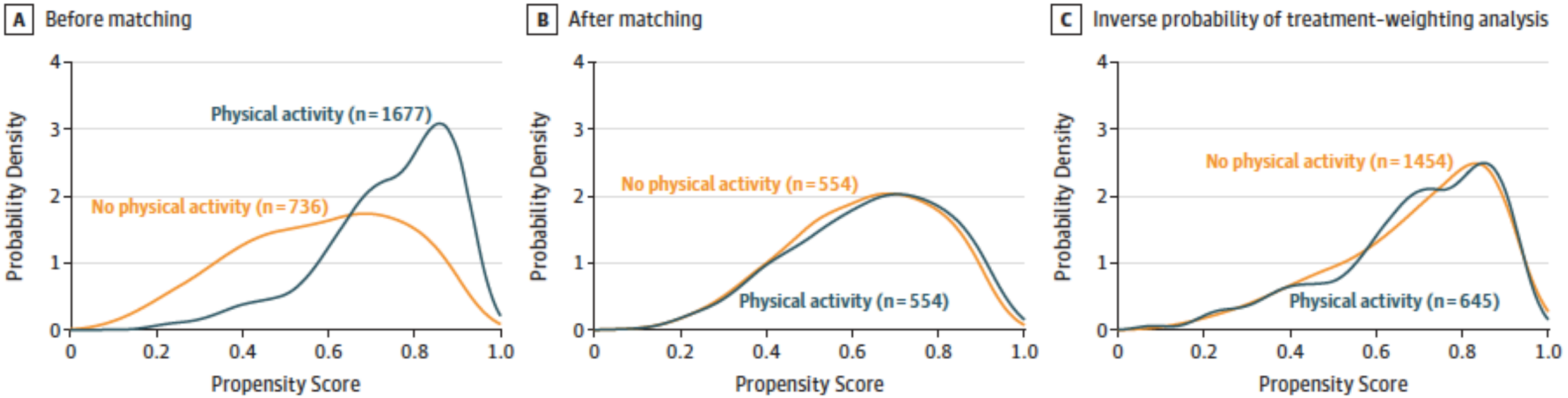
Table 1. Baseline Characteristics Total Sample, Unweighted Sample, Propensity Score-Matched Sample, and Inverse Probability of Treatment-Weighted Sample

	Physical Activity at 7 Days, No. (%)									
		Unweighted Sample (n = 2413)			Propensity 1:1 Matching (n = 1108)			IPTW (n = 2099)[a,b]		
Characteristic	Total (N = 3063)	No (n = 736)	Yes (n = 1677)	Standardized Mean Difference	No (n = 554)	Yes (n = 554)	Standardized Mean Difference	No (n = 645)	Yes (n = 1454)	Standardized Mean Difference
Age, y[c]										
5-7	534 (17.4)	73 (9.9)	343 (20.5)		69 (12.5)	79 (14.3)		352.5 (16.9)	379.4 (18.0)	
8-12	1282 (41.9)	268 (36.4)	762 (45.4)	0.434	226 (40.8)	232 (41.9)	0.068	935.9 (44.8)	906.1 (43.1)	0.040
13-18	1247 (40.7)	395 (53.7)	572 (34.1)		259 (46.8)	243 (43.9)		798.5 (38.3)	818.5 (38.9)	
Female sex[c]	1205 (39.3)	350 (47.6)	605 (36.1)	0.234	237 (42.8)	243 (43.9)	0.022	822.4 (39.4)	822.5 (39.1)	0.007
Time between head injury and triage, median (SD), h[c]	8.7 (11.8)	10.3 (12.8)	8.0 (11.0)	0.197	9.5 (12.1)	9.6 (12.1)	0.004	9.0 (11.7)	8.8 (11.6)	0.011

Grool, et al. (2016)

RESULTS – PROPENSITY SCORE MATCHING & WEIGHTING

Figure 2. Distribution of Propensity Scores in the Physical Activity Group and the Rest Group



Grool, et al. (2016)

RESULTS – PROPENSITY SCORE MATCHING & WEIGHTING

Table 2. Summary of Results of the Primary Analysis

Type Analysis	No. (Absolute Risk, %)		Absolute Risk Difference, % (95% CI)	Relative Risk (95%CI)
	Physical Activity	No Physical Activity		
Unweighted sample	1677 (24.6)	736 (43.5)	18.9 (14.7-23.0)	0.75 (0.70-0.80)
Light activity vs none (subgroup 1)	795 (31.4)	736 (43.5)	12.0 (7.2-16.8)	0.82 (0.76-0.89)
Moderate activity vs none (subgroup 2)	357 (24.4)	736 (43.5)	19.1 (13.2-24.6)	0.75 (0.69-0.81)
Full-contact activity vs none (subgroup 3)	525 (14.5)	736 (43.5)	29.0 (24.2-33.5)	0.66 (0.61-0.71)
Matched	554 (28.7)	554 (40.1)	11.4 (5.8-16.9)	0.84 (0.77-0.92)
Inverse probability of treatment weighting	1454	645	9.7 (5.7-13.5)	0.74 (0.65-0.84)

Grool, et al. (2016)

RESULTS – "SENSITIVITY ANALYSES"

1. Recalculated outcome: PPCS is now defined as having worse symptoms at 28 day F/U than at 7 day F/U
   - Calculated outcome using (post-injury day 28 symptom score – post-injury day 7 symptom score) rather than (post-injury day 28 score – pre-injury score)

2. Excluded participants who were completely recovered (symptom score < 3) at day 7

3. Examined interaction between age group and physical activity
   - For each additional year of age, RR increased by factor of 1.01

Grool, et al. (2016)

RESULTS – "SENSITIVITY ANALYSES"

Table 3. Summary of Sensitivity Analysis 1 and 2

Type Analysis	No. (Absolute Risk, %)		Absolute Risk Difference (95% CI)	Relative Risk (95% CI)
	Physical Activity	No Physical Activity		
Sensitivity analysis 1				
Unweighted sample	1667 (30.4)	736 (69.6)	18.9 (14.7 to 23.0)	0.75 (0.70 to 0.80)
Matched	519 (39.1)	519 (38.3)	−0.77 (−6.7 to 5.1)	1.01 (0.92 to 1.11)
IPTW			−0.041 (−4.1 to 4.0)	1.00 (0.88 to 1.14)
Sensitivity analysis 2				
Unweighted sample	803 (43.0)	584 (52.9)	9.9 (4.6 to 15.2)	0.83 (0.74 to 0.92)
Subgroup 1 (light activity vs none)	494 (46.4)	584 (52.9)	6.6 (0.6 to 12.5)	0.88 (0.78 to 0.99)
Subgroup 2 (moderate activity vs none)	176 (38.6)	584 (52.9)	14.3 (5.9 to 22.2)	0.77 (0.66 to 0.89)
Subgroup 3 (full exercise vs none)	133 (36.1)	584 (52.9)	16.8 (7.5 to 25.5)	0.74 (0.63 to 0.86)
Matched	388 (47.2)	388 (51.5)	4.4 (−2.6 to 11.3)	0.92 (0.80 to 1.05)
IPTW	687	507	4.0 (−1.7 to 9.7)	0.92 (0.82 to 1.04)

Grool, et al. (2016)

OVERALL CONCLUSIONS

- Main takeaway, consistent across all analytic approaches and intensities of exercise:

> Physical activity within 7 days post-concussion was associated with a lower risk of PPCS as compared with no physical activity.

- Results did not hold up in robustness checks
- MUCH more work is needed
- Results are important because:
  - Contrary to current guidelines for concussion management
  - Potential to impact a large pediatric population due to high incidence of concussion

Grool, et al. (2016)

DISCUSSION

- Analysis approach was reasonable, but seemed to have some flaws
  - Operational definition of outcome was ambiguous – room for misinterpretation
  - RR calculation
  - Method of weighting by inverse probability of treatment
    - "Treated" individuals should be weighted by 1/PS
    - "Control" individuals should be weighted by 1/(1-PS)

} To estimate average treatment effect

  - After matching/weighting, only calculated RR and ARD, no modeling with covariates
- Conceptual and design limitations:
  - Asked to rate pre-injury symptom scores *after the injury*…will inherently be biased
  - Symptom and physical activity data are all self-report ☹
  - Does not address the role of cognitive rest in concussion recovery
  - Says nothing about ideal timing, type, and duration of physical activity

OSIA Second Reader

Joshua Froess

JAMA | Original Investigation

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Definition of Outcome

- 3 new or worsening individual symptoms
  - Individual symptoms are defined as a positive difference between current minus perceived pre-injury rating
  - Pre-injury rating was given after the concussion
- Vague measurement of outcome and could lead to misclassification

Primary Outcome Measure

Primary outcome was the presence of PPCS, defined as at least 3 new or worsening individual symptoms compared with the preconcussion status measured at day 28 according to the validated PCSI.[12,13,18] An individual symptom was defined as a positive difference between the current minus the perceived pre-injury symptom rating as completed 28 days postenrollment.[12,13]

Physical Activity

- Self-reported
- Sports related subgroups being used for activity measurement
- Children 8 to 17 answered these questions themselves
- Don’t measure cognitive rest like not doing school work

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