Beyond intention-to-treat: secondary analyses of the FRITT study, a cluster randomized controlled trial of tobacco cessation in dentistry

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Sinziana Oncioiu

Authors: Sinziana Oncioiu, Livia Franchetti-Pardo, Suvi Virtanen, Fabrizio Faggiano and Maria Rosaria Galanti

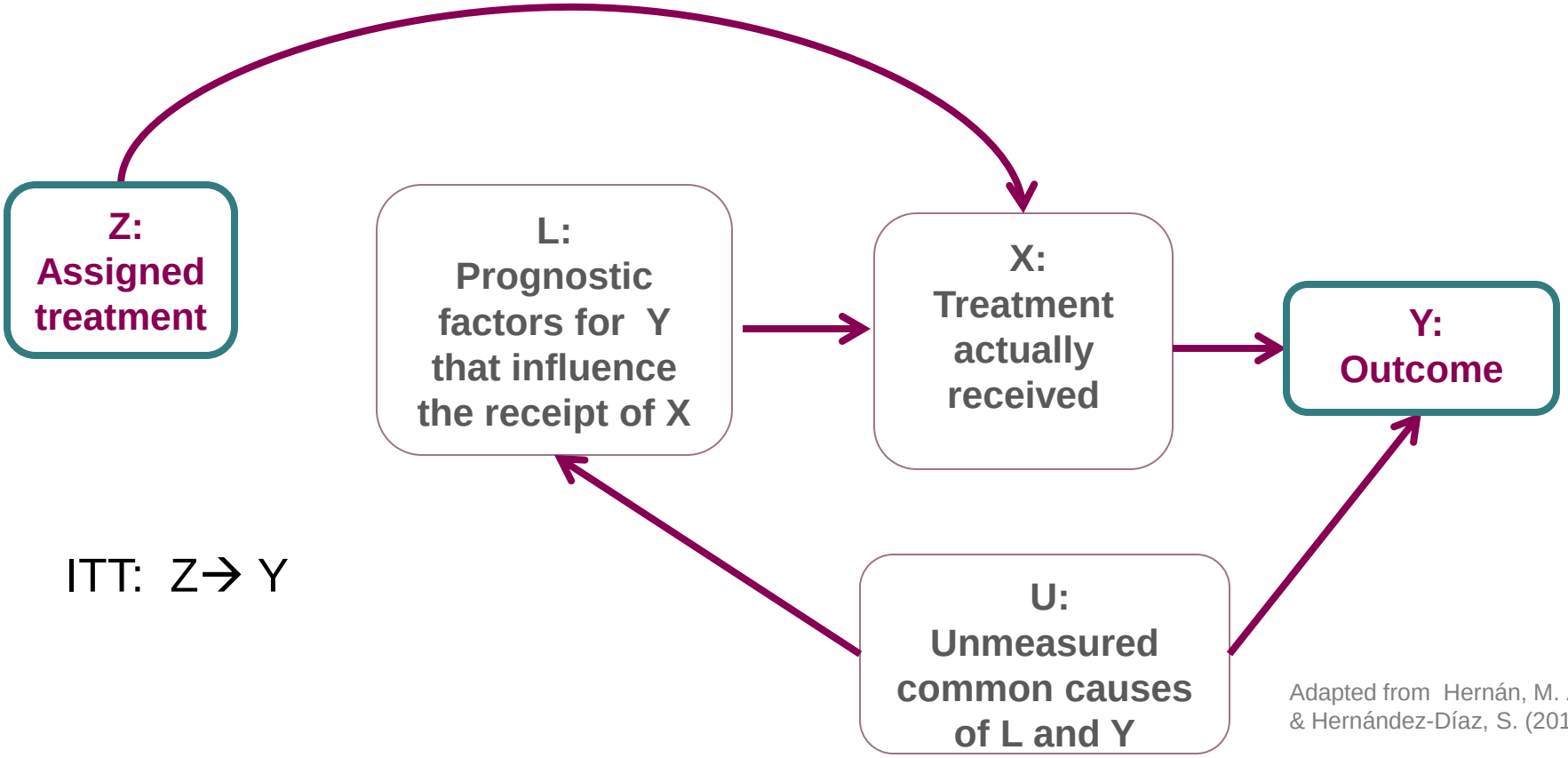
Tobacco use cessation interventions

- Effectiveness of brief advice for tobacco use cessation integrated in routine services offered in primary care (Stead et al., 2013, Carr & Ebbert, 2012)

- Effectiveness of a brief structured counselling for tobacco use cessation delivered in dental clinics in Sweden- FRITT cluster randomized controlled trial (Virtanen, Zeebari, Rohyo, & Galanti, 2015).

- FRITT intention-to-treat analysis results
  - reduction by half of tobacco consumption from baseline to follow-up (secondary outcome) OR 95% CI 2.07 (1.28–3.35)
  - complete abstinence (primary outcome) OR 95% CI 1.40 (0.68–2.89)

Intention-to-treat (ITT) in RCTs



ITT: Z→ Y

Adapted from Hernán, M. A., & Hernández-Díaz, S. (2012)

Non-adherence

- Non-adherence in reviews:
  - Surgical intervention RCTs: 55% of included studies report non-adherence with treatment allocation (Adewuyi, MacLennan, & Cook, 2015)
  - Randomly selected RCTs: 98% of included studies reported non-adherence, but only 51% reported methods to address it (Dodd, White, & Williamson, 2012)

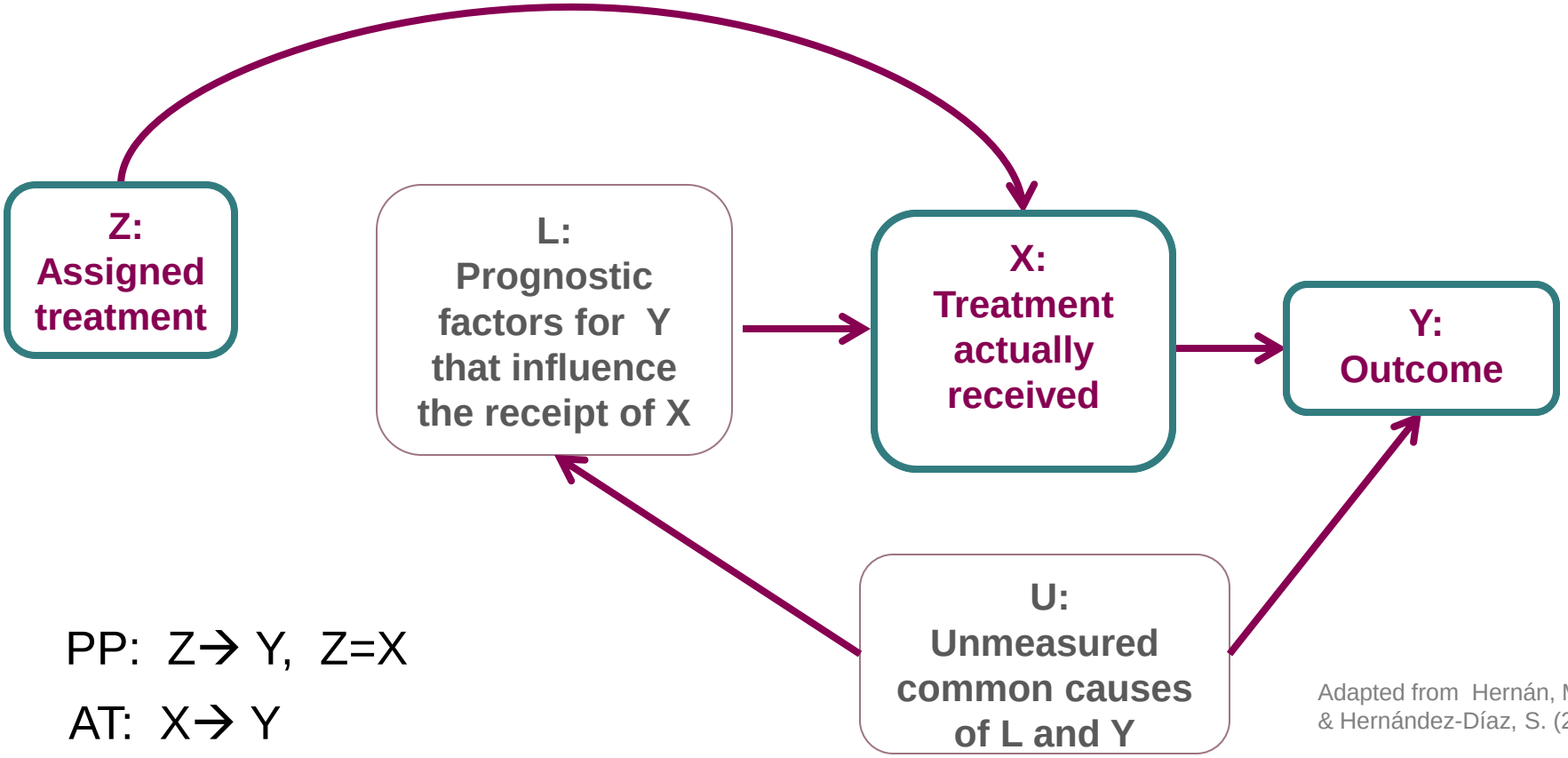
- ITT in RCTs with non-adherence
  - assigned intervention misclassified measure of received intervention
  - post-randomization confounding
  - generalizability of ITT results

Aim

- To conduct secondary analyses in the FRITT study through which the effect of the intervention taking into account non-adherence is estimated.

- Secondary analyses performed:
  - Per-protocol (PP)
  - As-treated (AT)
  - Instrumental variable (IV)

Secondary analytical methods in RCTs



PP: Z→ Y, Z=X

AT: X→ Y

IV: X→ Y, if Z is a valid instrument

Adapted from Hernán, M. A., & Hernández-Díaz, S. (2012)

Methods

- Study design
  - 27 dental clinics randomized to deliver alternative intervention or usual care (control group)
  - Follow-up time: 6 months

- Outcomes – self-reported:
  - Primary: 7-days abstinence
  - Secondary: 3-months abstinence, half-reduction, 24-hour quit attempts

- Potential confounders
  - age, sex, occupation, education, disease status
  - tobacco-related characteristics: readiness to quit, length of tobacco use, time to tobacco use from waking-up, amount of tobacco used daily, previous quit attempts

Sample

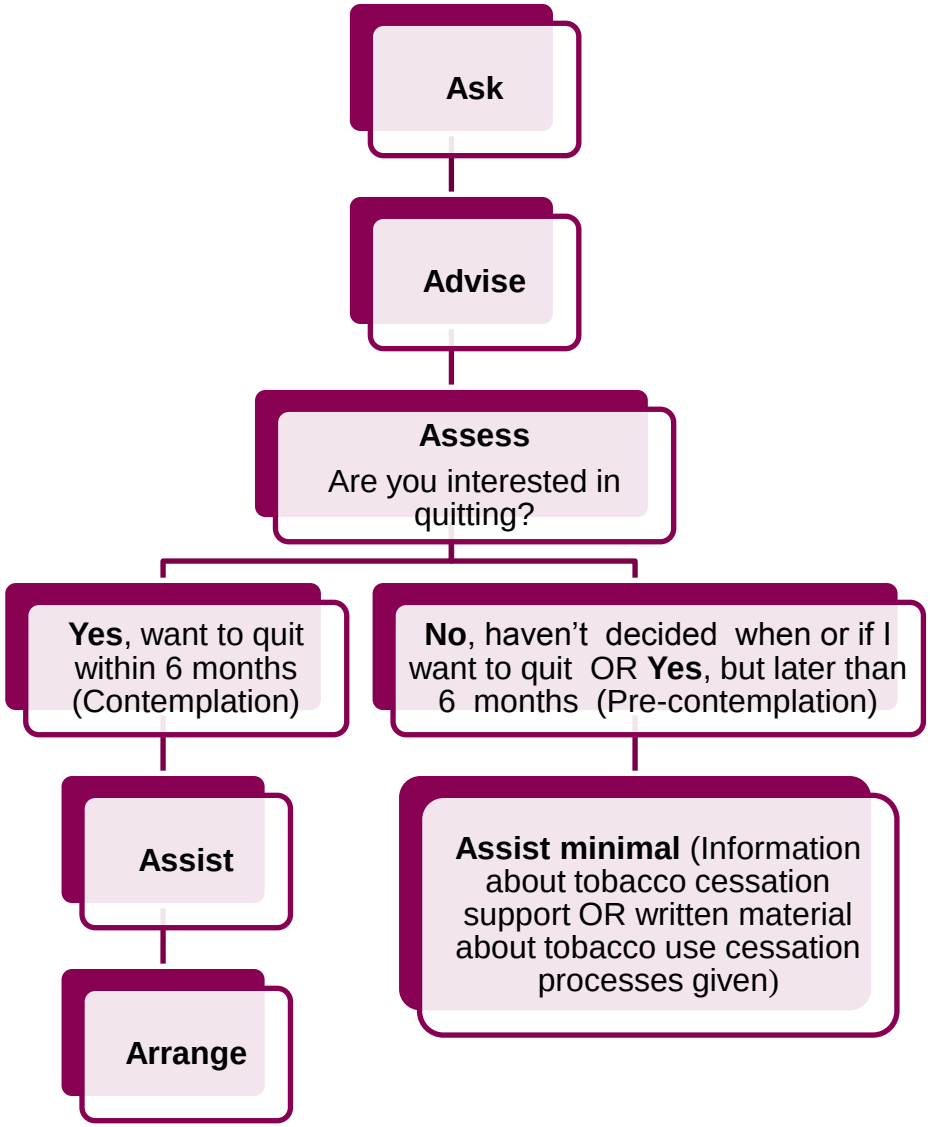
- 467 patients participated in the study:
  - mean age was 45.5 years (SD 14.9),
  - 63.4 % were males,
  - 78.9% had at least secondary school degree,
  - 62.5% full-time employed

Concerning tobacco use:

- 43.6% used snus, 47.5% smoked cigarettes, 8.9% dual users.
- 81.1% were not considering quitting tobacco at all or in the next 6 months
- 51.2% light or moderate tobacco users (used less than 10 cigarettes/snuff pouches daily)

- 452 patients (97%) who participated in the 6-month follow-up (analytical sample)

Intervention “as-intended”

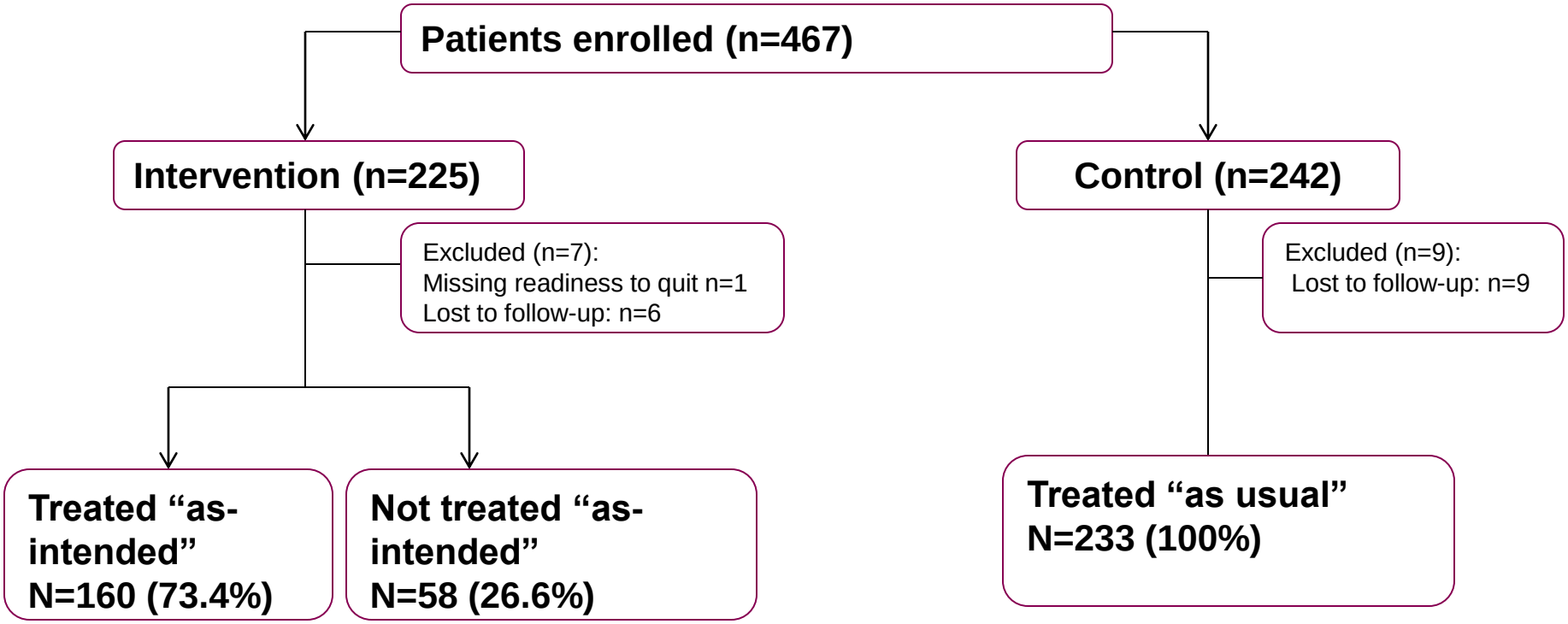


RESULTS

Delivery of different components of the intervention according to treatment group

Intervention components	Intervention (N=219) n (%)	Control (N=233) n (%)
Ask	**219 (100.0)**	**156 (67.0)**
Advise	**208 (95.0)**	**95 (40.8)**
Assess readiness to quit	**202 (92.2)**	**85 (36.5)**
Assist (At least one of the following)	**210 (95.9)**	**49 (21.0)**
Offer information about available support for quitting tobacco	170 (77.6)	16 (6.9)
Offer leaflet about tobacco use cessation process	139 (63.5)	0 (0.0)
Present motivational arguments to quit tobacco	159 (72.6)	29 (12.4)
Ask about decision regarding quitting date	35 (16.0)	5 (2.1)
Discuss abstinence problems	86 (39.3)	13 (5.6)
Offer information about pharmacological treatment	154 (70.3)	9 (3.9)
Prescribe/suggest pharmacological treatment	41 (18.7)	3 (1.3)
Arrange (At least one of the following)	**121 (55.3)**	**17 (7.3)**
Appointment for continued counselling	16 (7.3)	2 (0.9)
Refer to counselling with other care provider at the clinic	11 (5.0)	3 (1.3)
Refer to counselling with external care provider outside the clinic	60 (27.4)	5 (2.1)
Refer to the Swedish Tobacco Quit Line	76 (34.7)	8 (3.4)
Other	9 (4.1)	1 (0.4)

Intervention's delivery



Effect of “as-intended” intervention on tobacco cessation outcomes (PP)

Outcome	Patients with the outcome/ patients treated “as-intended”	Patients with the outcome/ comparison group	Crude OR (95% CI)	Adjusted OR (95% CI)*
7-days abstinence	11/160 (6.9%)	14/233 (6.0%)	1.15 (0.51, 2.61)	1.09 (0.48, 2.51)
3-months abstinence	6/160 (3.8%)	8/233 (3.4%)	1.10 (0.37, 3.22)	1.03 (0.35, 3.06)
Half-reduction	36/160 (22.5%)	31/224 (13.8%)	1.81 (1.06, 3.07)	1.76 (1.03, 3.00)
Quit attempts	83/160 (51.9%)	100/233 (42.9)	1.43 (0.96, 2.15)	1.59 (1.03, 2.45)

*Adjusted for Time to tobacco use from waking-up

Effect of received intervention on tobacco cessation outcomes (AT)

Outcome	Patients with the outcome/ patients treated “as-intended”	Patients with the outcome/ comparison group	Crude OR (95% CI)	Adjusted OR (95% CI)*
7-days abstinence	11/160 (6.9%)	20/291 (6.9%)	1.00 (0.47, 2.14)	0.94 (0.43, 2.03)
3-months abstinence	6/160 (3.8%)	13/291 (4.5%)	0.83 (0.31, 2.24)	0.78 (0.29, 2.11)
Half-reduction	36/160 (22.5%)	50/282 (17.7%)	1.35 (0.83, 2.18)	1.30 (0.80, 2.11)
Quit attempts	83/160 (51.9%)	128/291 (44.0%)	1.37 (0.93, 2.02)	1.45 (0.96, 2.20)

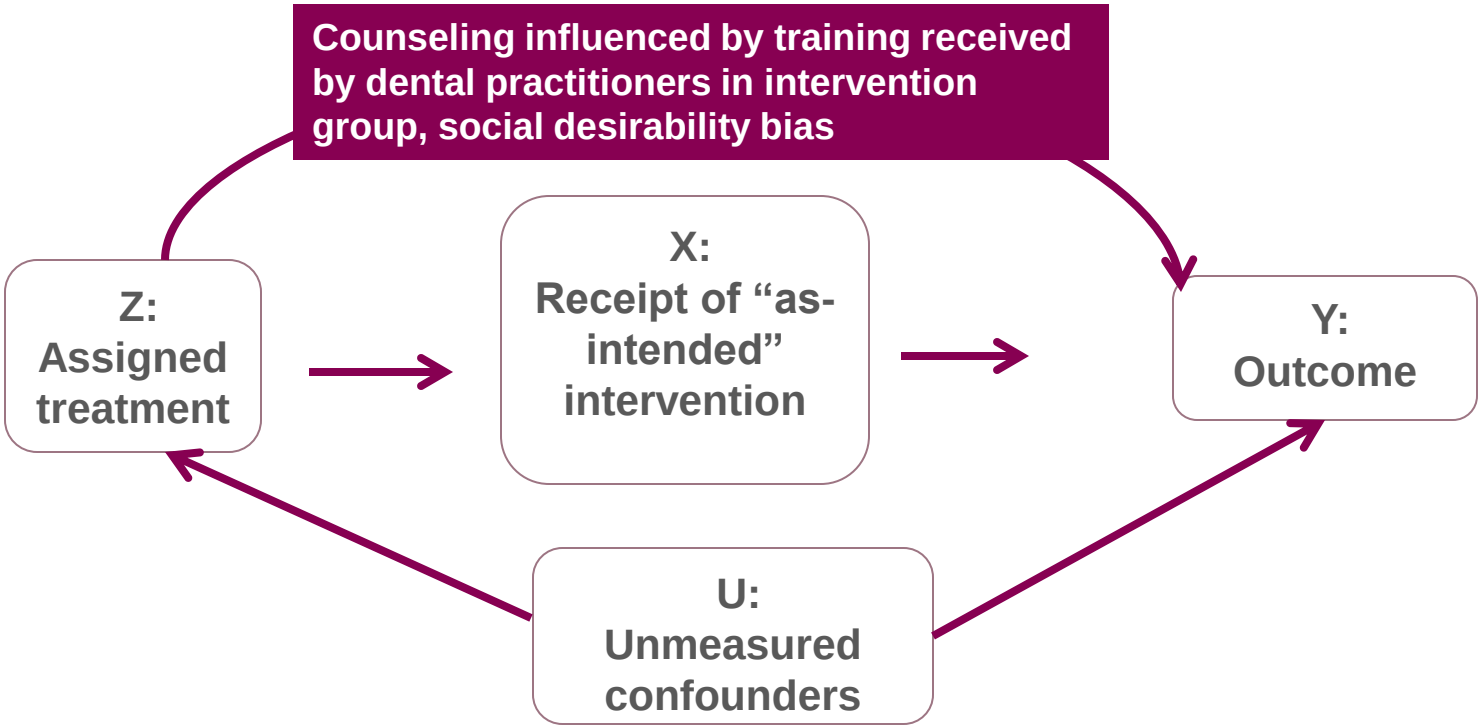
*Adjusted for Time to tobacco use from waking-up

IV estimation

	Z=1			Z=0		
	X=1 Co-operative		X=0 Non-co-operative	X=1 Non-co-operative	X=0 Co-operative	
	C=1 (complier)	N=1 (always receivers)	N=0 (never receivers)	N=1 (always receivers)	N=0 (never receivers)	C=1 (complier)
Proportion	p_c	p_0	$1-p_1$	p_0	$1-p_1$	p_c
Average success ratio Y	m_{1c}	m_{1n}	m_{0n}	m_{1n}	m_{0n}	**m_{0c}**
Overall average Y	$p_c * m_{1c} + p_0 * m_{1n} + (1-p_1) * m_{0n}$			$p_0 * m_{1n} + (1-p_1) * m_{0n} + p_c * m_{0c}$		

From Greenland, S. (2000).

Assumptions for Instrumental Variable Analysis



Assumptions underlying IV analysis

1. Z is independent of U
2. Z is associated with X
3. **Z is independent of Y given X and U**
4. Z affects X only among patients of dental practitioners who adhere to the assigned task
5. Independent observations. Other versions of the treatment do not exist

Results from instrumental variable (IV) analysis

	Z=1			Z=0			IV estimation
	X=1	X=0	Total	X=1	X=0	Total	Success Ratio
7-days abstinence	14	6	20	0	14	14	**1.56**
Total	160	58	218	0	233	233	
Success ratio (%)	6.9	10.3	9.17	-	6.0	6.0	
3-months abstinence	6	5	11	0	8	8	**2.57**
Total	160	58	218	0	233	233	
Success ratio (%)	3.8	8.6	5.04	-	3.4	3.4	
Half-reduction	36	19	55	0	31	31	**3.32**
Total	160	58	218	0	224	224	
Success ratio (%)	22.5	32.8	25.23	-	3.4	13.8	
Quit attempts	83	28	111	0	100	100	**1.27**
Total	160	58	218	0	233	233	
Success ratio (%)	51.9	48.3	50.92	-	42.9	42.9	

Discussion

- Good agreement between PP & ITT results
  - → practitioners highly adherent to the protocol
  - → prognostic factors of tobacco use cessation evenly distributed

- AT results – largest departure from ITT
  - → comparison group very heterogeneous: counseling in the intervention group differed in intensity and quality from the “usual care”, even when not delivered “as-intended”

- IV – central assumption violated

Summary

- RCT with high adherence, PP and ITT results similar
- Monitoring of the implementation process
- Adherence's definition
  → novel intervention arm– defined a posteriori
  → "usual care" – not manualized
- Secondary analysis strengthen the inference from ITT

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