PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Outcomes of a telemedicine smoking cessation programme for heated tobacco product users in Japan: a retrospective cohort study
AUTHORS	Nomura, Akihiro; Ikeda, Takaaki; Fujimoto, Toshiki; Morita, Yusaku; Taniguchi, Chie; Ishizawa, Tetsuro; Tabuchi, Takahiro

VERSION 1 – REVIEW

REVIEWER	Hedman, Linnea Umeå Universitet Medicinska fakulteten, Department of public health and clinical medicine, Section of Sustainable health, The OLIN studies
REVIEW RETURNED	14-Jun-2022

GENERAL COMMENTS	Heated tobacco products and a telemedicine smoking cessation programme: a retrospective study, by Akihiro Nomura, et al. In this study, the effectiveness of a telemedicine smoking cessation programme for continuous abstinence rates among individuals that were exclusive tobacco cigarette smokers, exclusive heated tobacco product users (HTP), and dual users was evaluated. The dual users had the lowest cessation rate while the exclusive HTP users had the highest. The authors conclude that the telemedicine smoking cessation programme may be a reasonable option also for HTP users. The research question is interesting and relevant to study, particularly in Japan, where HTPs were introduced earlier than in other countries. Thus, the study contribute important and novel knowledge as we can learn from their experiences. However there are some issues that need to be addressed: 1. The aim could be more precise, both in the abstract and the introduction. For instance, in the introduction the wording “tested the effectiveness” could be specified, i.e. by clarifying the outcome (quitting smoking and/or quitting HTP). Or whether there were any differences in smoking cessation/quitting HTP between the three groups. In the abstract, the wording “is helpful” needs clarification, i.e. helpful for what? Moreover, with a clear aim, the connection with the conclusion also improves. 2. In the Method section, there is no reference to any previous validation studies or evaluations whether this telemedicine programme is effective for smoking cessation. If they exist, please add reference. But if no such evaluation has been performed, please add information about elements included in the programme that have scientific evidence to be effective for smoking cessation support. This is particularly relevant because there is no control group and that one of the co-authors is the chief medical officer and shareholder of the company that provide the programme, and

	thus have a conflict of interest with regard to the results in terms of success or failure of the programme. 3. The primary outcome is described on page 6, under the subheading Outcomes. Please clarify in the description whether the continuous abstinence rates included both tobacco cigarettes and HTP for all three smoking categories. 4. In Results, first paragraph, line 9-12, the authors state that the exclusive HTP users were younger, had smoked for fewer years, and so on. However, in table 1 where this data is presented, there is no statistical test to back up this statement. Please provide a statistical test to confirm whether there are statistically significant differences between the groups or tone down the statement. I am not familiar with the maximum standardized difference, but it seems to evaluate the imbalance among rather than between the groups. 5. In table 2, please specify the co-variates that were included in the adjusted logistic regression analyses, for instance in a footnote. 6. Also in table 2, please use the same number of decimals for the p-values. 7. In figure 4, there are asterisks next to three data points in the figure, please include a definition of the asterisks in the figure legend. 8. In the discussion, first paragraph, line 3, the authors state that the "overall success rate…was favourable". Because there is no control group, this statement needs to be toned down. Since 90% of the participants were prescribed Varenicline, perhaps that intervention and not the telemedicine programme was the success factor for the participants. The most relevant comparison in the current study is the quitting rates depending on tobacco product and not the efficacy of the telemedicine programme in itself.

REVIEWER	Das, Payal ICMR, Epidemiology and Communicable Diseases
REVIEW RETURNED	18-Oct-2022

GENERAL COMMENTS	Heated Tobacco Products use remained prevalent in Japan. One in three current cigarette smokers used HTPs regardless of whether they were interested in quitting smoking. A smoking cessation support program is widely available in Japan for patients with nicotine dependence. However, continued surveillance is important to inform national and global tobacco control strategies. Telemedicine efforts have greatly expanded to provide a "safety-net" of medical and preventive care for vulnerable populations worldwide. This article has clearly defined the problem in Japan and through Telemedicine has used the right approach in analyzing effectiveness of a telemedicine smoking cessation programme for nicotine-dependent tobacco product users.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer #1:
1. The aim could be more precise, both in the abstract and the introduction. For instance, in the introduction the wording "tested the effectiveness" could be specified, i.e. by clarifying the outcome (quitting smoking and/or quitting HTP). Or whether there were any differences in smoking cessation/quitting HTP between the three groups. In the abstract, the wording "is helpful" needs

clarification, i.e. helpful for what? Moreover, with a clear aim, the connection with the conclusion also improves.

Author reply: We appreciate your thoughtful suggestions. We corrected the unclear words to specify what we did in this study as follows.

Manuscript changes (bold) (*Objectives* in Abstract):

> *"Objectives: Japan is one of the largest markets for heated tobacco products (HTP), and the number of HTP users, including dual users, is burgeoning. However, it is not yet clear whether a telemedicine smoking cessation programme is* ***effective for nicotine dependent HTP users to quit smoking. Here, we tested the effectiveness of a telemedicine smoking cessation programme in terms of continuous smoking cessation among smokers who had used HTPs compared with those used exclusively cigarettes.****"*

Manuscript changes (bold) (*Second and third paragraphs* in Introduction):

> *"…Moreover, it has not yet been assessed whether these smoking cessation programmes are* ***effective to quit smoking for*** *smokers who use HTPs since they were initially made for cigarette smokers.*
>
> *Here, we tested the effectiveness of a telemedicine smoking cessation programme* ***in terms of continuous smoking cessation among smokers who had used HTPs compared with those used exclusively cigarettes."***

2. In the Methods section, there is no reference to any previous validation studies or evaluations whether this telemedicine programme is effective for smoking cessation. If they exist, please add reference. But if no such evaluation has been performed, please add information about elements included in the programme that have scientific evidence to be effective for smoking cessation support. This is particularly relevant because there is no control group and that one of the co-authors is the chief medical officer and shareholder of the company that provide the programme, and thus have a conflict of interest with regard to the results in terms of success or failure of the programme.

Author reply: We agree with your comments. As you pointed out, this was the first study to evaluate the effectiveness of the Linkage telemedicine smoking cessation program. Therefore, we added evidence of contents provided in the telemedicine smoking cessation program in the Methods section.

Manuscript change (bold) (*The Linkage telemedicine smoking cessation programme* in Methods):

> *"…the smoking cessation encouragement and facilitation advice messages.* ***All contents of the telemedicine smoking cessation programme referred to the standard procedure for smoking cessation treatment*** ***(reference #10)*** ***and the guideline for appropriate implementation of telemedicine in Japan.*** ***(reference #14)"***
>
> *Reference #10: The Standard Procedure Book for Smoking Cessation, 8th edition. (Japanese) 2021 [Available from: http://j-circ.or.jp/kinen/anti_smoke_std/pdf/anti_smoke_std_rev8_.pdf.*

Reference #14: Ministry of Health Labour and Welfare. Guideline for appropriate implementation of telemedicine 2022 [Available from: https://www.mhlw.go.jp/content/000889114.pdf accessed Oct, 23 2022.

3. The primary outcome is described on page 6, under the subheading Outcomes. Please clarify in the description whether the continuous abstinence rates included both tobacco cigarettes and HTP for all three smoking categories.

Author reply: Thank you for addressing an important point. As you pointed out, the smoking success and continuous abstinence rates (consecutive smoking successes) included quitting both tobacco cigarettes and HTPs for all three smoking categories. We added the sentence clarifying the definition of smoking cessation success at Outcomes in Methods section.

Manuscript change (bold) (*Outcomes* in Methods section):

*"…Smoking cessation success was **defined as quitting both cigarette and HTPs and** was confirmed with the structural interview performed by the telemedicine doctors at week 8 session and participant's self-reports to the follow-up survey at weeks 12, 24, 36, and 52. CAR was defined as one or more consecutive weeks of **smoking cessation successes** since the telemedicine session finished at week 8. For example, …"*

4. In Results, first paragraph, line 9-12, the authors state that the exclusive HTP users were younger, had smoked for fewer years, and so on. However, in table 1 where this data is presented, there is no statistical test to back up this statement. Please provide a statistical test to confirm whether there are statistically significant differences between the groups or tone down the statement. I am not familiar with the maximum standardized difference, but it seems to evaluate the imbalance among rather than between the groups.

Author reply: We appreciate your suggestions. We have calculated the baseline differences between exclusively cigarette group and each HTP user group (exclusively HTP or dual use) to support the significant difference written in the Results section among the groups. We added some sentences in our manuscript.

Manuscript change (bold) (*Statistical analysis* in Methods):

"…**Random forest imputation was conducted using Python version 3.8.3 with the MissForest package. **We used Mann-Whitney U test for continuous variables or Fisher's exact test for categorical variables to evaluate the baseline differences between exclusively cigarette group and each HTP user group (exclusively HTP or dual use).** In addition, …**"

Manuscript change (bold) (*First paragraph* in Results):

*"…In terms of smoking cessation medication, varenicline was prescribed to 90% of programme participants. **Compared with exclusively cigarette users, exclusively HTP users were younger, had smoked for fewer years, and more attempts for smoking cessation.** Additionally, dual users were younger and had smoked for fewer years compared to cigarette users. After …"*

Table change (Table 1):

Table 1 Baseline characteristics among exclusively cigarette smokers, exclusively heated tobacco product users, and dual product users.

	Total	Tobacco product types			Maximum standardised difference**	
		Exclusively cigarettes	Exclusively HTP	Dual use of cigarettes and HTP	Before	After
N	733	383 (52%)	230 (31%)	120 (16%)		
Age, mean ± SD	42.4 ± 9.8	43.4 ± 10	41.7 ± 8.6 *	40.5 ± 10 *	0.29	0.07
Male sex, n (%)	689 (94)	359 (94)	218 (95)	112 (93)	0.04	0.01
Body mass index, median [IQR]	23.5 [22–26]	23.4 [21–25]	23.5 [22–26] *	23.8 [22–26]	0.19	0.10
Years of smoking, median [IQR]	22 [15–30]	24 [16–30]	20 [15–28] *	20 [12–26] *	0.33	0.11
Past attempt for cessation, n (%)	453 (62)	223 (58)	157 (68) *	73 (61)	0.20	0.12
TDS score, median [IQR]	7 [5–8]	7 [6–8]	7 [5–8]	7 [6–9]	0.06	0.10
Regular alcohol intake, n (%)	121 (17)	70 (18)	32 (14)	19 (16)	0.11	0.07
Comorbidities						
Hypertension, n (%)	57 (8)	26 (7)	18 (8)	13 (11)	0.16	0.00
Diabetes mellitus, n (%)	5 (1)	1 (0.3)	2 (1)	2 (2)	0.28	0.15
Cardiovascular diseases, n (%)	14 (2)	6 (2)	5 (2)	3 (3)	0.08	0.04
Mental disorders, n (%)	21 (3)	12 (3)	7 (3)	2 (2)	0.08	0.09
Medications						
Varenicline, n (%)	660 (90)	336 (88)	213 (93)	111 (93)	0.15	0.15
Nicotine, n (%)	57 (8)	37 (10)	12 (5)	8 (7)	0.15	0.12

*: P-value <0.05. P-values were calculated compared with the exclusively cigarette group by Mann-Whitney *U* test for continuous variables and by Fisher's exact test for categorical variables.

**: Maximum absolute standardised mean difference before and after inverse probability weighting

HTP, heated tobacco product; IQR, interquartile range; SD, standard deviation; TDS, Tobacco Dependence Screener.

5. In table 2, please specify the co-variates that were included in the adjusted logistic regression analyses, for instance in a footnote.

Author reply: We added the covariates information in a footnote of Table 2.

Manuscript change (bold) (*Footnote* in Table 2):

> *"*: P-value < 0.05. Values are reported as the rates (95% CI). P-values were calculated using an inverse probability-weighted dataset* ***adjusted by all variables shown in Table 1 (age, sex, body mass index, years of smoking, past attempt of cessation, TDS score, regular alcohol intake, hypertension, diabetes mellitus, cardiovascular diseases, mental disorders, varenicline, and nicotine)*** *with logistic regression."*

6. Also in table 2, please use the same number of decimals for the p-values.

Author reply: We arranged the decimals for the p-values in Table 2.

Manuscript change (bold) (Table 2):

	Exclusively cigarettes	Exclusively HTP	Adjusted OR for cigarettes	P-value (HTP vs Cigarettes)	Dual use of Cigarettes and HTP	Adjusted OR for cigarettes	P-value (Dual vs Cigarettes)
Point abstinence rates							
PA at week 12	70.8% [66–75]	80.9% [76–86]	1.08 [0.99–1.17]	**0.070**	69.2% [61–77]	0.96 [0.85–1.07]	**0.462**
PA at week 24	55.4% [50–60]	67.8% [62–74]	1.11 [1.01–1.21]	**0.026***	43.3% [34–52]	0.86 [0.77–0.96]	**0.008***
PA at week 36	48.3% [43–53]	58.2% [52–65]	1.08 [0.99–1.19]	**0.092**	41.7% [33–50]	0.91 [0.81–1.02]	**0.086**
PA at week 52	52.0% [47–57]	62.2% [57–70]	1.09 [0.996–1.20]	**0.061**	45.0% [36–54]	0.91 [0.81–1.02]	**0.111**
Continuous abstinence rates							
CAR9-24	53.8% [49–59]	67.0% [61–73]	1.12 [1.02–1.23]	**0.017***	40.8% [32–50]	0.85 [0.76–0.95]	**0.004***
CAR9-52	41.0% [36–46]	50.9% [44–57]	1.09 [0.99–1.19]	**0.084**	30.8% [23–39]	0.88 [0.79–0.97]	**0.011***

7. In figure 4, there are asterisks next to three data points in the figure, please include a definition of the asterisks in the figure legend.

Author reply: We added the definition of the asterisks in the figure legends.

Manuscript change (bold) (*Figure 4* in Figure legends):

> ***"****Figure 4. Continuous abstinence rates (CARs) from 9 to 12 weeks (CAR9-12) to 24 weeks (CAR9-24) and 52 weeks (CAR9-52) among exclusively cigarette smokers (Cigarette), exclusively HTP users (HTP), and dual users (dual).* ****: P-value < 0.05 compared with exclusively cigarette group.****"*

8. In the discussion, first paragraph, line 3, the authors state that the "overall success rate…was favourable". Because there is no control group, this statement needs to be toned down. Since 90% of the participants were prescribed Varenicline, perhaps that intervention and not the telemedicine programme was the success factor for the participants. The most relevant comparison in the current study is the quitting rates depending on tobacco product and not the efficacy of the telemedicine programme in itself.

Author reply: We agree with your comment. As you mentioned, this study did not have control group, so we changed the sentence to be toned down, just describing the success rates (CARs) as below.

Manuscript change (bold) (*First and second paragraph* in Discussion):

"This study, using inverse probability weighting, assessed whether the telemedicine smoking cessation programme was effective among adult nicotine-dependent patients using HTPs. We found that: ***1) overall success rates of the telemedicine smoking cessation programme were 55.8% for CAR9-24 and 42.4% for CAR9-52;*** *2) exclusively HTP users had significantly higher smoking cessation success rates compared with the exclusively cigarette group in CAR9-24; and 3) dual users had significantly lower smoking cessation success rates compared with the exclusively cigarette group in CAR9-24 and CAR9-52. To our knowledge, this is the first study to elucidate the effectiveness of a telemedicine smoking cessation programme for adult smokers using HTP* ***compared with those using exclusively cigarettes****.*

This study provides several conclusions. First, ***overall smoking cessation success rates by the Linkage telemedicine smoking cessation programme were 55.8% for CAR9-24 (short-term) and 42.4% for CAR9-52 (long-term).*** *Kato et al. previously reported …"*

Response to Reviewer #2:

Heated Tobacco Products use remained prevalent in Japan. One in three current cigarette smokers used HTPs regardless of whether they were interested in quitting smoking. A smoking cessation support program is widely available in Japan for patients with nicotine dependence. However, continued surveillance is important to inform national and global tobacco control strategies. Telemedicine efforts have greatly expanded to provide a “safety-net” of medical and preventive care for vulnerable populations worldwide. This article has clearly defined the problem in Japan and through Telemedicine has used the right approach in analyzing effectiveness of a telemedicine smoking cessation programme for nicotine-dependent tobacco product users.

Author reply: Thank you for reviewing our manuscript. We very appreciate your comments.

VERSION 2 – REVIEW

REVIEWER	Hedman, Linnea Umeå Universitet Medicinska fakulteten, Department of public health and clinical medicine, Section of Sustainable health, The OLIN studies
REVIEW RETURNED	14-Nov-2022

GENERAL COMMENTS	I am happy with the revisions made by the authors and have no further comments or notes.