

A novel mathematical model for predicting the benefits of physical activity on type 2 diabetes progression

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Abstract

Despite the well-acknowledged benefits of physical activity for type 2 diabetes (T2D) prevention, the literature surprisingly lacks validated models able to predict the long-term benefits of exercise on T2D progression and support personalized risk prediction and prevention. To bridge this gap, we developed a novel mathematical model that formalizes the link between exercise and short- and long-term glucose-insulin dynamics to predict the benefits of regular exercise on T2D progression. The model quantitatively captured the dose-response relationship (larger benefits with increasing intensity and/or duration of exercise), it consistently reproduced the benefits of clinical guidelines for diabetes prevention, and it accurately predicted persistent benefits following interruption of physical activity, in line with real-world evidence from the literature. These results are encouraging and can be the basis for future development of decision support tools able to assist patients and clinicians in tailoring preventive lifestyle interventions.

Introduction

Type 2 diabetes (T2D) is a high-prevalence, high-burden chronic disease, whose impact is becoming more and more concerning for public health worldwide¹, with the global prevalence projected to increase up to 592 millions by 2035² and with severe economic implications for the healthcare systems^{3,4}. However, evidence suggests that T2D can be prevented, for example through lifestyle interventions including physical activity^{4–10}. Digital decision support tools incorporating mathematical models can be helpful to quantitatively predict the benefits of lifestyle interventions on T2D progression and can provide a basis for reducing the individual risk through tailored recommendations for T2D prevention. For example, predictive models able to estimate the risk of T2D as a function of individual health status and lifestyle on a daily basis may be integrated into digital patient monitoring tools to continuously track individual biomarkers and support patients in achieving targets and reduce their risk through behavior change^{11,12}. Several mathematical models were introduced in the literature to describe the slow dynamics of T2D progression in the long term as a function of, e.g., individual blood glucose levels, insulin concentration, or mass of pancreatic beta-cells^{13–16}. These models are well-established and show promise for predicting the risk of developing T2D along a time span of several years. However, they do not include mechanistic descriptions of the beneficial effects of exogenous interventions, for example physical activity, on T2D risk. Regarding the effects of physical activity,

most of the models introduced so far are focused on the short-term effects of a single exercise session, on a timescale of minutes to hours^{17–20}. Hence, the available models of the short-term effects of physical activity are suitable to be employed in short-range closed-loop glucose control techniques, whose effectiveness has been shown in several works^{21,22}. However, these short-term models are not able to quantitatively describe the cumulative beneficial effects of repeated exercise sessions on the slow dynamics of T2D progression - effects that are known to occur on a timescale of weeks, months, or even years^{9,23,24}. The aim of this study is to develop a novel *two-timescale* model incorporating both the short-term and the long-term cumulative effects of physical activity on T2D progression and to assess the ability of the proposed model to describe real-world evidence on the benefits of different programs of physical activity, as available from the literature and from preventive recommendations^{7,25–27}. In our previous work²⁸, we developed a preliminary version of a two-timescale model by combining a well-established model of long-term T2D progression¹⁴ with (i) a model of the short-term effects of individual sessions of physical activity¹⁹ and (ii) a newly developed model of the long-term, cumulative effects of repeated sessions of physical activity mediated by Interleukin-6 (IL-6), a protein with anti-inflammatory action released by muscle tissue under exercise²⁹ that contributes in preserving beta-cell mass and function^{23,24,29}. Specifically, we modeled the release of IL-6 induced by physical exercise as suggested by Morettini et al.²⁹ and we described the integral, cumulative effect of IL-6 released during repeated exercise sessions by introducing an additional state variable that represents the total volume of IL-6 and acts on the balance between beta-cell proliferation and apoptosis, therefore regulating insulin release and glucose metabolism. Notably, the preliminary model proposed in our previous work²⁸ is the first one accounting for the different time scales that involve physical activity (minutes) and T2D progression (years) by combining a short-term and a long-term dynamics, and was able to consistently predict an increase in beta-cell mass (and, therefore, an increase in insulin concentration) following regular physical activity, leading to a decrease in basal glucose levels and therefore T2D prevention. However, the model did not account for the effects of varying intensity and duration of physical activity on beta-cell proliferation and apoptosis and did not include the benefits of physical activity on individual insulin sensitivity. In pursuit of the ultimate goal of developing and validating a digital support tool capable of accurately predicting the benefits of physical activity for T2D risk monitoring and prevention, this study has a dual objective: (i) to model the influence of varying physical activity on T2D progression, we modify and finely tune our preliminary model²⁸ by improving its capability to capture the long-term effects of IL-6 on beta-cells dynamics and on insulin sensitivity; (ii) to investigate if, and to what extent, the model predictions are aligned with real-world evidence, we assess the predictions of the model by considering different time courses of T2D progression (i.e., different time constants of the simulated decay in insulin sensitivity) in a range of simulated conditions, specifically: different exercise programs at varying intensity and weekly duration, different World Health Organization (WHO) recommendations for chronic disease prevention, and de-training in different diabetes prevention programs.

Results

Simulated effects of varying exercise intensity

The predictions of the proposed model obtained by simulating different exercise programs with varying intensity are shown in Fig. 1 and Table 1. Fig. 1 shows the basal glucose concentration (G) and the insulin concentration (I) as a function of the exercise intensity (u) (from 0 to 70%) obtained by simulating a training program of 3 sessions/week, 60 minutes/session in a time window of 5 years, with time constant of insulin sensitivity decay (τ_{SI}) equal to 150 days (thus assuming a fast diabetes course). Fig. 1 shows that the benefit produced by exercise, as determined by lower values of G and higher values of I , increases with increasing u , in line with the well-known dose-response relationship between physical activity and benefit²⁶. In particular, simulations show that for $u \geq 50\%$ (i.e., moderate-to-vigorous intensity), G does not show the steep inflection that is observed for $u < 50\%$ and for no physical activity ($u = 0\%$). Moreover, for $u = 60\%$ and $u = 70\%$, after five years G remains below the diabetic threshold of 126 mg/dl. Table 1 shows the values of G and I observed over a longer time horizon (at $t = 10, 15$, and 20 years) for $u = 50\%$, 60%, and 70%

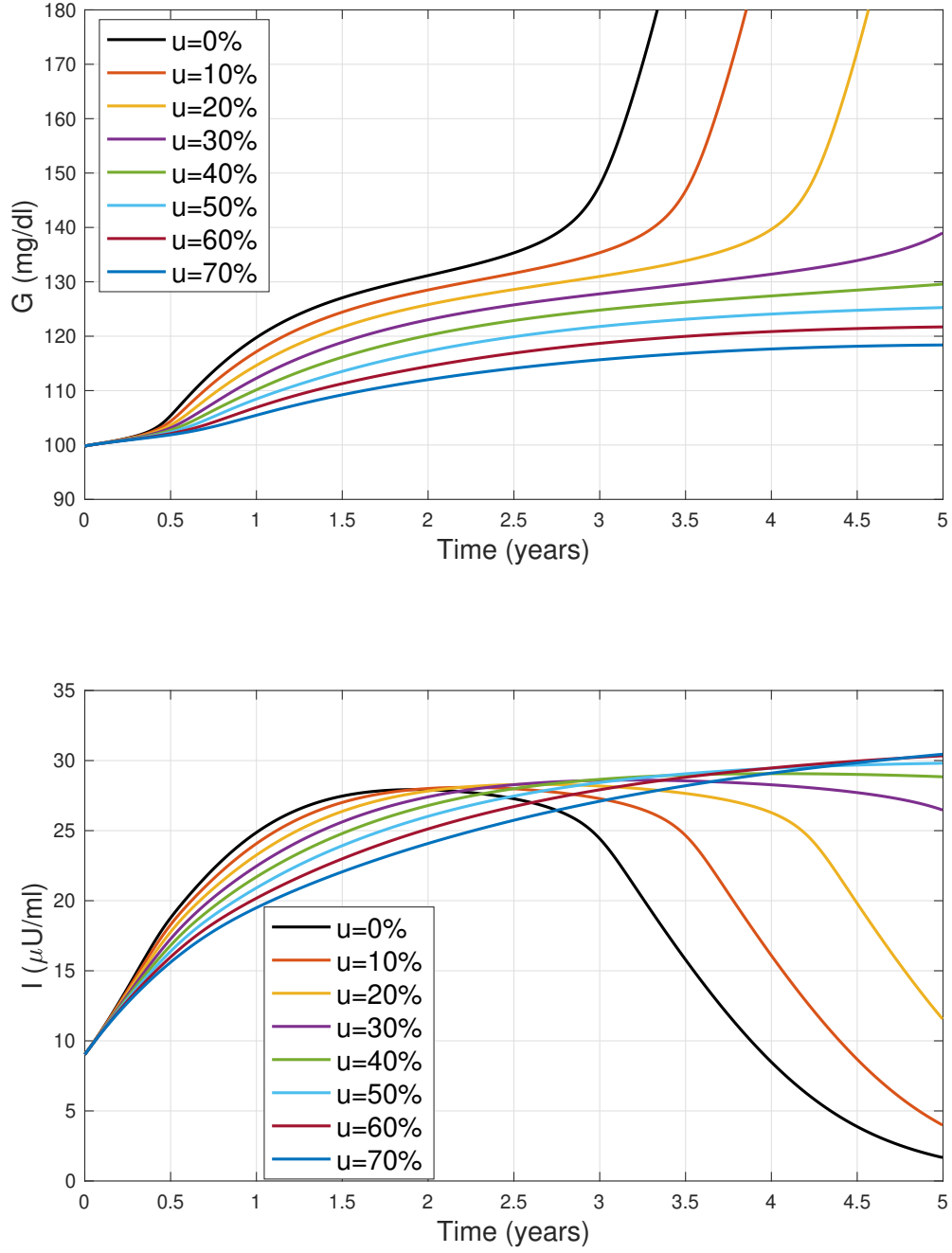


Figure 1: Basal glucose concentration (top panel) and insulin concentration (bottom panel) as a function of u over a five-year simulation horizon (simulations: 60 minutes/session, 3 sessions/week, $\tau_{SI} = 150$ days).

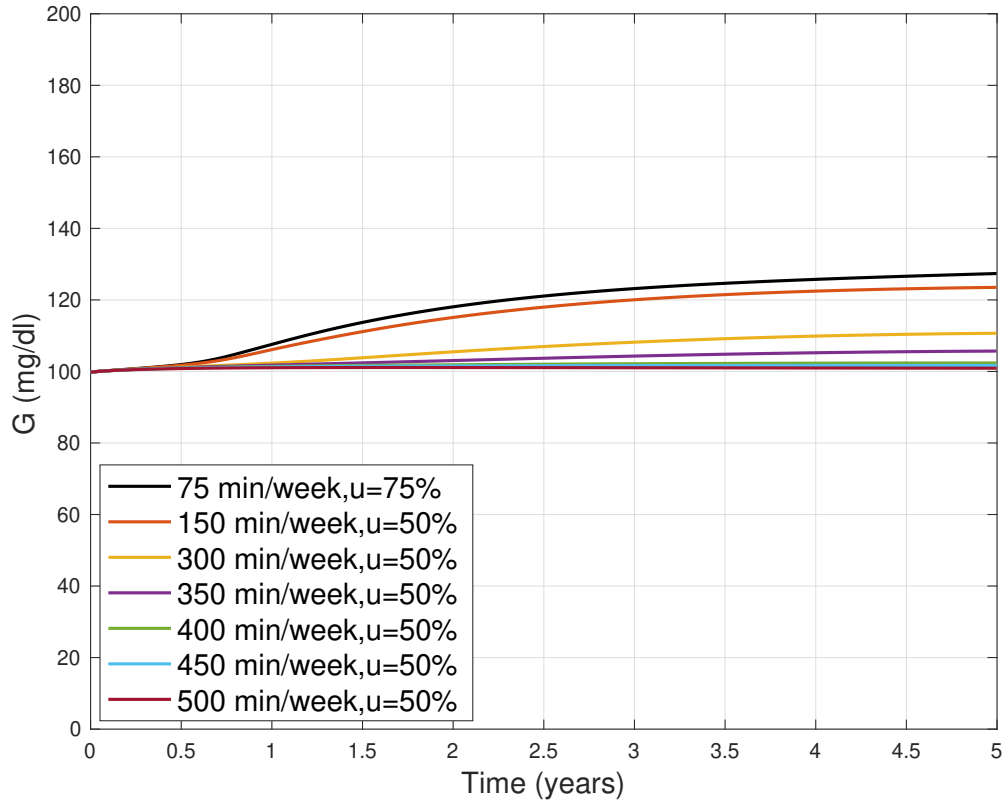


Figure 2: Basal glucose concentration of vigorous exercise ($u = 75\%$) for 75 minutes/week and moderate exercise ($u = 50\%$) as a function of exercise duration, from 150 to 500 minutes/week, using $\tau_{SI} = 180$.

(i.e., moderate-to-vigorous intensity) and for $\tau_{SI} = 150$ and 180 days (i.e., faster and slower disease course, respectively). For $\tau_{SI} = 150$ days and $u = 50\%$, G reaches the diabetic threshold after ten years, and then it steeply increases. For higher values of u , no inflection is observed and G remains below the diabetic threshold in the whole simulation window and reaches values close to the healthy range (i.e., down to about 100 mg/dl). When a slower course of T2D is assumed (i.e., $\tau_{SI} = 180$), no inflection in G is observed with $u \geq 50\%$, G remains below the diabetic threshold and gets close to the healthy range after 20 years. Overall, these results suggest that T2D onset could be delayed with a regular physical activity program of three sessions/week, 60 minutes/session at moderate or vigorous intensity, and that increased benefit is observed with increasing intensity, in line with the well-known dose-response relationships reported in the literature^{25,26}. For what concerns basal insulin concentration (I), Fig. 1 shows that it reaches progressively higher values at $t = 5$ years as u increases, due to the increased beta-cell mass promoted by exercise. Over the 20-year horizon, when exercise is not sufficient to prevent T2D ($\tau_{SI} = 150$ days, $u = 50\%$), I progressively drops due to decreased beta-cell mass. Instead, when vigorous intensity exercise is simulated ($u = 60\%$, $u = 70\%$), I increases and, thus, G decreases down to values close to the healthy range. Specifically, I reaches a steady state condition around 40 $\mu\text{U/ml}$, whenever a basal glycemia of 100 mg/dl is restored.

Simulated effects of WHO recommendations

Fig. 2 shows the results observed by simulating the WHO preventive recommendations for cardiovascular and chronic disease prevention²⁵ on a five-year horizon. Specifically, Fig. 2 shows the trend in G observed by simulating vigorous-intensity physical activity for 75 minutes/week and moderate-intensity physical activity for 150 to 500 minutes/week. The curves of the two minimum recommended exercise programs (i.e., vigorous-intensity physical activity for 75 minutes/week and moderate-intensity physical activity for 150 minutes/week) remain very close to each other for the whole duration of the simulation, being the difference between the curves at the fifth year around only 4 mg/dl, in line with the equivalence of the two training programs reported by the WHO²⁵. It should be noted that the small difference between the two curves is negligible and may be further reduced if slightly different values of u are used (i.e., higher values of u for moderate physical activity, lower values of u for vigorous physical activity). If the weekly duration of moderate-intensity exercise is increased up to 500 minutes/week, G further decreases and the observed benefit almost saturates at weekly duration of 400 minutes or higher, fully in line with the findings by Boonpor et al.²⁶.

Simulated effects of de-training in diabetes prevention studies

Table 2 presents the values of G obtained by simulating the Finnish Diabetes Prevention Study (FDPS) and the China Da Qing Diabetes Prevention Study (CDQDPS) programs, which include regular physical activity programs followed by a discontinuation of exercise after four and six years, respectively. As for FDPS, following the interruption of the intervention at the fourth year, the simulated progression of T2D is significantly delayed at the seventh year in three out of the six simulated cases, specifically in those cases where G was already below the diabetic threshold at the end of the intervention (i.e., $u = 40\%$, $\tau_{SI} = 180$ days; $u = 50\%$, $\tau_{SI} = 150$ and 180 days). In the other three cases, the values of G were in the diabetic range at the end of the training at the fourth year, and simulations suggest an irreversible disease progression at the seventh year. Similar results are observed with the simulated CDQDPS. Specifically, an irreversible increase in G is observed after discontinuation of exercise at $u = 30\%$, i.e., in those cases where G is already close to or in the diabetic range at the sixth year. In three cases ($u = 40\%$, $\tau_{SI} = 180$ days; $u = 50\%$, $\tau_{SI} = 150$ and 180 days), a complete reversal is observed, with G restoring to a normoglycemic condition at about 100 mg/dl at the end of the simulation window, whereas for $u = 40\%$ and $\tau_{SI} = 150$ days a significant delay is observed after 20 years, with G remaining almost stable and slightly below the diabetic threshold. In general, for what concerns the effects of de-training following a regular exercise program, Table 2 shows that (i) the higher the intensity u and the slower the decay of insulin sensitivity, the lower the values of G at the end of the intervention and at the end of the follow-up period, and (ii) when G is lower than the

diabetic threshold at the end of the intervention, benefits can be maintained in the follow-up period, up to 14 years after the discontinuation.

Discussion

The role played by physical activity in delaying or preventing of T2D makes exercise a great ally in the battle against this serious disease, which is forecast to represent a huge challenge worldwide¹. What makes exercise *crucial* in T2D prevention is its beneficial effect that contributes to preserve beta-cell function, which is actually one of the key factors for diabetes prevention^{23,24}. Digital tools incorporating mathematical models can be of great help to support patients in reaching their healthy lifestyle targets and prevent T2D^{30,31}. Nevertheless, the literature shows a lack of mathematical models able to suggest targeted recommendations for physical activity intervention to individuals at risk of developing T2D. The model presented in this study is the first in the literature able to describe the short- and long-term effects of physical activity on T2D progression, particularly the cumulative benefits on beta-cell function and on insulin sensitivity mediated by IL-6 released during exercise. The proposed model predicts the trends of glucose and insulin concentration in individuals in the early phases of T2D progression undergoing regular physical exercise. The model is simulated under a range of conditions, and predictions are validated in relation to findings reported in the literature. For example, the modeled increase (or the slowdown in the decrease) of insulin sensitivity due to physical activity (as shown in the Methods section, Fig. 3) is aligned with findings reported in the work by Damaso et al.³² and Uusitupa et al.³³ for moderate physical activity, specifically an improvement of about 29% at the first year and about 20% at the fourth year, respectively. Moreover, the observed vanishing of the improvement in the long-term is consistent with what discussed in Balducci et al.³⁴. Moreover, the proposed model is sensitive to changes in exercise intensity, as shown in Fig. 1 and Fig. 4 (Methods section). Specifically, the model accurately captures the dose-response relationship^{26,34,35} between physical activity and long-term benefit on disease progression. For example, the model predictions show that the risk of developing T2D decreases as the exercise intensity increases, all the other parameters (weekly duration, τ_{SI} , initial conditions) being equal (Fig. 1, Tables 1-2). Similarly, the same benefit is predicted with moderate intensity exercise for 150 minutes/week and with vigorous-intensity exercise for 75 minutes/week (Fig. 2), in line with the WHO²⁵, the American Diabetes Association³⁶ and the American College of Sports Medicine³⁷ recommendations. In addition, Boonpor et al.²⁶ state that usual recommendations on physical activity (e.g., around 150 minutes/week, moderate exercise) can delay diabetes up to about 13 years (as shown in Table 1) and that increasing the dose (e.g., the weekly duration) beyond usual recommendations could lead to greater benefits (as shown in Fig. 2), up to a maximum observable benefit around 400 minutes/week for moderate-intensity physical activity, where the risk reduction levels off. Our results are fully aligned with this evidence. Moreover, the proposed model was also able to predict a maintained benefit following discontinuation of the intervention, as outlined in Table 2, where the findings from the FDPS and CDQDPS are precisely replicated. It is worth noting that in the FDPS³³ the average glycemia observed in the group of participants who developed T2D was 126 mg/dl at the fourth year. This value is accurately approximated by our model as the average value of G predicted after four years in the conditions in which T2D eventually occurs is equal to 127 mg/dl (Table 2). Similar consistence was observed for the simulated CDQDPS training and de-training experiment. The results reported in Table 2 seem to capture the different T2D incidence scenarios and glycemia levels reported in the work by Li et al.²⁷. In some cases, T2D develops at the sixth year or along the 20-year simulation, and in some other cases T2D is substantially slowed down or even reversed. Interestingly, Table 2 shows that (i) the higher the intensity u and the slower the drop in S_I , the lower the predicted values of G at the end of the intervention and at the end of the follow-up period; and (ii) when G is lower than the diabetic threshold at the end of the intervention, benefits are maintained in the follow-up period, up to 14 years after the discontinuation if a moderate-intensity exercise program has been performed for six years. The present work provides promising results as the model developed proved suitable to accurately describe the effects of physical activity and provide predictions consistent with a range of clinical findings. However, the study has some limitations that should be overcome in the future developments of the study. In particular, some of the referred works involve a combined program of diet and exercise^{7,9,27,34} and

do not specifically report the separate contribution of physical activity. It is to note that research about the separate benefits of diet and exercise in lifestyle interventions for T2D prevention has not reached a consensus. However, it will be important to investigate the separate effects of exercise and diet to develop tailored recommendations for each component of the intervention. Further developments of the model should also include incorporation of diet and the balance between caloric intake and expenditure into the model. Moreover, it will be important to investigate the benefits of physical activity in healthy individuals at low risk of T2D (for example, by introducing different modeling approaches for the decay of insulin sensitivity and by modeling different individual fitness levels) to address the *key* role of exercise in early T2D prevention^{13,38,39}. These developments could pave the way to a more comprehensive personalization of model predictions in a range of scenarios to support the development of targeted recommendations for effective prevention of T2D. Future digital tools could incorporate these personalized models to simulate virtual subjects and precisely predict the benefits of exercise in order to identify personalized recommendations for reducing the risk of T2D according to the individual characteristics and the monitored progression of the disease.

Methods

Model formulation

The model proposed in this study is derived from, and improves upon, the preliminary one presented in detail in our previous work²⁸. The main equations of the proposed model are reported in the following:

$$\bar{P}(ISR) = P(ISR) \cdot \left(1 + \zeta_1 \frac{Vl^2}{k_n^2 + Vl^2}\right), \quad (1a)$$

$$\bar{A}(M) = A(M) \cdot \left(1 - \zeta_2 \frac{Vl^2}{k_n^2 + Vl^2}\right), \quad (1b)$$

$$\dot{\beta} = \frac{\bar{P}(ISR) - \bar{A}(M)}{\tau_\beta} \beta, \quad (1c)$$

$$\dot{S}_I = \frac{-(S_I - S_{I,target})}{\tau_{SI}} \cdot \left(1 - \zeta_3 \frac{Vl}{k_{n,si} + Vl}\right), \quad (1d)$$

$$P\dot{V}O_2^{\max} = -0.8PVO_2^{\max} + 0.8u, \quad (1e)$$

$$I\dot{L}_6 = SR \cdot PVO_2^{\max} - K_{IL6} \cdot IL_6, \quad (1f)$$

$$\dot{V}l = IL_6 - k_s Vl, \quad (1g)$$

$$\dot{G} = R_0 + \frac{W}{V_g} (G_{prod} - G_{up}) - (E_{g0} + S_I I) G, \quad (1h)$$

$$\dot{I} = \frac{\beta}{V} ISR - kI - I_e, \quad (1i)$$

$$\dot{\gamma} = \frac{\gamma_\infty(G) - \gamma}{\tau_\gamma}, \quad (1j)$$

$$\dot{\sigma} = \frac{\sigma_\infty(ISR, M) - \sigma}{\tau_\sigma}, \quad (1k)$$

$$(1l)$$

where $\zeta_1 = 10^{-4}$, $\zeta_2 = 10^{-4}$, $k_n = 10^6$ ((pg/ml) min), $\zeta_3 = 1.4$, $k_{n,si} = 5 \cdot 10^6$ ((pg/ml) min). For a complete description of variables and parameters reference is made to our previous work²⁸ and to the work by Ha et al.¹⁴. Specifically, to improve the long-term dynamics of the model, in this study we reformulate the equations that describe the integral effect of the released IL-6 (IL_6) on the dynamics of beta-cells by introducing a multiplicative contribution in place of the additive contribution originally used in our preliminary work²⁸ to scale the effect of the exercise with respect to natural beta-cell proliferation ($\bar{P}(ISR)$)

and apoptosis ($\bar{A}(M)$) (equations (1a)-(1b)), where ISR (insulin secretion rate) and M (metabolic rate) are defined in the work by Ha et al.¹⁴. In addition, here we model for the first time the effect of physical activity on insulin sensitivity (equation (1d)). Physical activity is captured through the state variable $PVO_2^{\max}$, representing the *sovrabasal* oxygen consumption during exercise as a function of the exercise intensity u (equation (1e)). The variable $PVO_2^{\max}$, in turn, promotes the dynamics of G_{prod} , G_{up} and I_e (describing the short-term impairment of blood glucose regulation induced by the exercise as described in our previous work²⁸), and the dynamics of IL_6 , that is released by muscle tissues under exercise (short-term) and exerts its integral anti-inflammatory action (long-term), as expressed by the state variable Vl representing the cumulative effect of IL_6 (equations (1f)-(1g)). Specifically, Vl leads to an improvement of insulin sensitivity (S_I) and an increase of beta-cell mass (β) due to increased proliferation ($\bar{P}(ISR)$) and reduced apoptosis ($\bar{A}(M)$). As a result, the basal insulin concentration (I) increases (equation (1j)) and, thus, lower values of basal glucose concentration (G) can be obtained. In equation (1d), a Michaelis-Menten function of Vl is used to account for a larger effect of physical activity in the first year of the intervention, as suggested by Damaso et al.³² and Bird et al.⁴⁰, and the parameters ζ_3 and $k_{n,si}$ were set to replicate the average improvement in S_I following one-year and four-year physical activity reported in by Damaso et al.³² and Uusitupa et al.³³, respectively. An exemplary representation of the behavior of equation (1d) with a simulated exercise program of 60 minutes/session, 3 sessions/week at $u = 50\%$ (as in Damaso et al.³²) is shown in Fig. 3, where $S_{I,target} = 0.18$ and $\tau_{SI} = 150$ days (i.e., simulating a rapid T2D progression). The example in Fig. 3 shows that an improvement in S_I of about 30% is observed at the end of the first year, in line with findings shown by Damaso et al.³², whereas after four years the distance between the two curves falls below 8%. Similarly, when the same exercise program is simulated by setting $\tau_{SI} = 180$ days, (i.e., a slower trend for T2D progression), a higher benefit on S_I is observed, specifically about 35% after one year and about 20% after four years, paralleling results shown by Uusitupa et al.³³.

In equations (1a)-(1b), the gains of the Hill functions ζ_1 , ζ_2 and k_n are set with the aim of targeting a glycemia value around 126 mg/dl after five years of the same exercise program simulated in Fig. 3 and given equation (1d) described above, consistently with the results described in the Diabetes Prevention Program study⁹. Fig. 4 shows a comparison between the preliminary version of the model²⁸ and the model proposed in this study, at two different exercise intensities. Specifically, Fig. 4 shows that the preliminary version of the model led to early saturation of the effects of physical activity on beta-cell dynamics. As such, the model was not able to capture the effects due to changes in duration or intensity of the exercise, leading to unrealistic reversal of diabetes for any exercise program. Conversely, the model here developed shows different benefits for varying intensities, in line with the dose-response relationship investigated by the simulations described in the following section.

Model simulations

The behavior of the model was characterized by simulating a range of physical activity programs, as reported in the literature and in well-known T2D preventive guidelines. Specifically, the predicted benefits of physical activity were characterized by addressing three key aspects, i.e.: (i) the effect of varying exercise intensity; (ii) the effect of applying the World Health Organization (WHO) recommendations for chronic disease prevention; (iii) the effect of a discontinued exercise program, as presented in more detail in the following. All the simulations were carried out by supposing a drop in insulin sensitivity S_I from 0.8 (at $t = 0$) to 0.18 (at $t = 5$ years) described by an exponential decay to simulate the onset of the conditions predisposing to T2D, following a typical approach in mathematical models of T2D progression^{13,14}. The time constant of the exponential decay (τ_{SI}) was set to two different values, i.e.: $\tau_{SI} = 150$ days and $\tau_{SI} = 180$ days, to simulate different time courses of T2D progression^{13,14}. Initial conditions for the variables G (mg/dl), I (μ U/ml), β (mg), γ , and σ (μ U/ μ g/day) were [99.7604, 9.025, 1000.423, -0.00666, 536.67] respectively, whereas $PVO_2^{\max}$, G_{prod} (mg/kg/min), G_{up} (mg/kg/min), I_e (μ U/ml/min), IL_6 (pg/ml), and Vl ((pg/ml)min) were initialized to 0, as in our previous work²⁸.

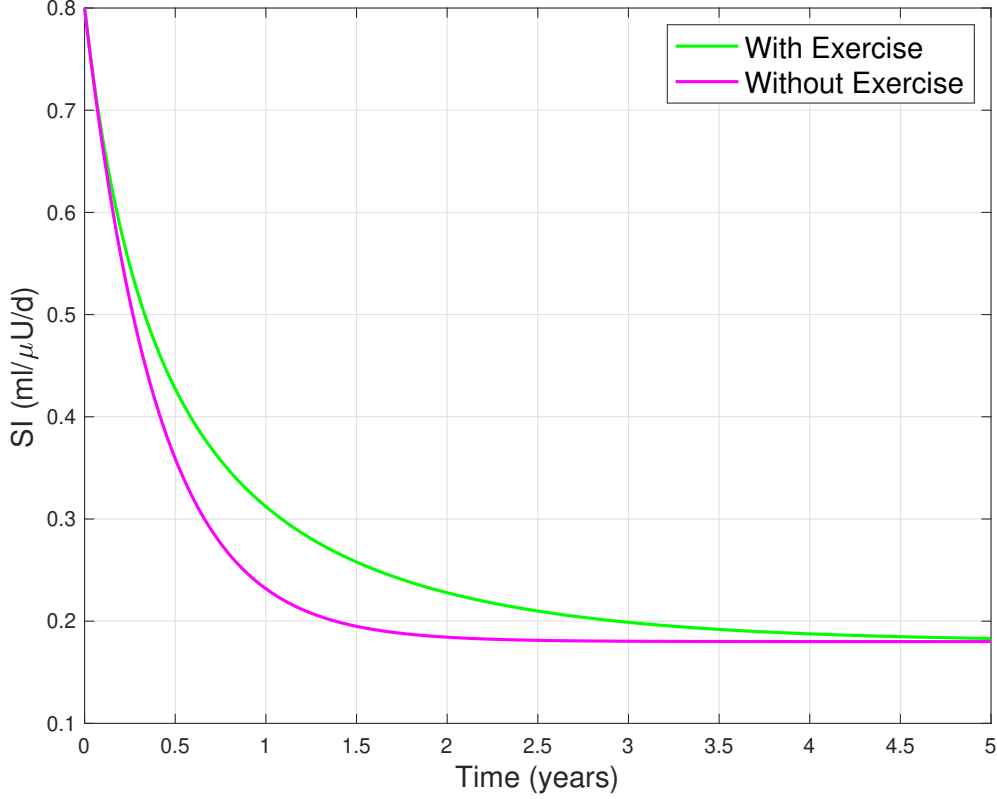


Figure 3: Time trend of insulin sensitivity over a five-year horizon (simulation: 60 minutes/session, 3 sessions/week, $u = 50\%$, $S_{I,target} = 0.18$, $\tau_{SI} = 150$ days). The green curve shows the increase produced by the exercise with respect to the trend observed when no intervention is considered (magenta curve).

Simulations of a regular exercise program with varying intensity

The existence of a dose-response relationship between the intensity of physical activity and the incidence of T2D is well known from the literature^{26,34}. To assess the ability of the proposed model to predict the increased benefits of physical activity as a function of exercise intensity, simulations of an exercise program of three sessions/week, 60 minutes/session in a time window of 5 years, with u varying from 0% to 70% were performed to span the full range of light, moderate and vigorous intensity. In addition, the same training program was simulated on a time window of 20 years considering moderate and vigorous intensities ($u = 50\%$, 60%, and 70%).

Simulations of a regular exercise program following the WHO preventive recommendations

The WHO addressed the problem of preventing cardiovascular and chronic diseases through exercise by developing the following, equivalent recommendations²⁵:

- at least 75 minutes/week of vigorous-intensity aerobic physical activity;
- at least 150 minutes/week of moderate-intensity aerobic physical activity.

Moreover, as suggested by Boonpor et al.²⁶, the benefit of moderate-intensity aerobic physical activity tends to saturate at about 400 minutes/week. To assess the ability of the proposed model to reflect the expected benefits of the WHO recommendations, the two suggested training programs were simulated by distributing the weekly duration in three sessions, each lasting 25 and 50 minutes, respectively. The variable u was set equal to 75% for vigorous intensity and equal to the 50% for moderate intensity¹⁹. In addition, to assess if the proposed model is able to replicate the expected saturation in benefit for weekly duration of moderate-intensity exercise equal to or higher than 400 minutes/week²⁶, simulations were performed for a total duration of 300, 350, 400, 450 and 500 minutes/week, distributed in three exercise sessions per week, by setting $u = 50\%$.

Simulations of a discontinued exercise program

The literature provides evidence that the benefits of exercise persist after the discontinuation of the intervention^{7,27}. Specifically, in the work by Lindström et al.⁷ (in the following referred to as FDPS) adults with impaired glucose tolerance were involved in a four-year lifestyle intervention program that included moderately intense physical activity for a minimum of 30 minutes per day. Participants were followed for three more years after the intervention. Results outlined that the incidence rates of T2D and the glycemia values at the end of the intervention and in the post-intervention period varied only slightly, suggesting that beneficial lifestyle effects were maintained after the discontinuation of the intervention. Similar findings are described in Li et al.^{27,41} (in the following referred to as CDQDPS), in which adults with impaired glucose tolerance were involved in a 20-year follow up, with lifestyle intervention (moderate intensity exercise, 2 sessions/day, 20 minutes/session) discontinued at the sixth year and benefits in terms of reduced T2D incidence were observed up to 14 years after the intervention. Scenarios similar to the ones described by the two studies were simulated, specifically:

- for FDPS: moderate intensity exercise was simulated at three different values of u (30%, 40%, 50%), with daily sessions of 30 minutes. The exercise was interrupted at the fourth year, with a simulation horizon of seven years.
- for CDQDPS: moderate intensity exercise was simulated at three different values of u (30%, 40%, 50%), with two exercise sessions per day, each lasting twenty minutes, as in suggested in Pan et al.⁴¹. The exercise was interrupted at the sixth year, with a simulation horizon of twenty years.

		$G_{10-year}$ (mg/dl)	$G_{15-year}$ (mg/dl)	$G_{20-year}$ (mg/dl)	$I_{10-year}$ (μ U/ml)	$I_{15-year}$ (μ U/ml)	$I_{20-year}$ (μ U/ml)
$u = 50\%$	$\tau_{SI} = 150$	128	>>150	>>150	29	< 3	< 3
	$\tau_{SI} = 180$	116	105	101	33	38	40
$u = 60\%$	$\tau_{SI} = 150$	117	108	101	33	36	39
	$\tau_{SI} = 180$	111	101	100	35	39	40
$u = 70\%$	$\tau_{SI} = 150$	112	102	100	35	39	40
	$\tau_{SI} = 180$	108	101	100	36	39	40

Table 1: Basal glucose and insulin concentration observed over a 20-year horizon for $u = 50\%$, 60% , and 70% and $\tau_{SI} = 150$ and 180 days.

Data availability

The datasets generated during the current study may be made available to qualified researchers on reasonable request to the corresponding author.

FDPS		$G_{4\text{th-year}}$ (mg/dl)	$G_{7\text{th-year}}$ (mg/dl)	CDQDPS		$G_{6\text{th-year}}$ (mg/dl)	$G_{20\text{th-year}}$ (mg/dl)
$u = 30\%$	$\tau_{SI} = 150$	131	$>> 150$	$u = 30\%$	$\tau_{SI} = 150$	133	$>> 150$
	$\tau_{SI} = 180$	126	136		$\tau_{SI} = 180$	125	$>> 150$
$u = 40\%$	$\tau_{SI} = 150$	127	$>> 150$	$u = 40\%$	$\tau_{SI} = 150$	124	123
	$\tau_{SI} = 180$	123	126		$\tau_{SI} = 180$	119	101
$u = 50\%$	$\tau_{SI} = 150$	124	128	$u = 50\%$	$\tau_{SI} = 150$	119	101
	$\tau_{SI} = 180$	120	121		$\tau_{SI} = 180$	115	100

Table 2: Basal glucose concentration (G) observed in the simulations of the FDPS and CDQDPS programs, with $\tau_{SI} = 150$ and $\tau_{SI} = 180$ days and with u in the moderate-intensity range.

Code availability

The underlying code for this study is not publicly available but may be made available to qualified researchers on reasonable request to the corresponding author.

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Author Contributions

PFDP designed the study, developed the code, performed the simulations, wrote and revised the manuscript. AB participated in the design of the study, contributed to the code development, revised the manuscript. FD participated in the design of the study, supervised the development of the work, revised the manuscript. KK contributed to the development of the work and to the interpretation of results. PP participated in the design of the study and revised the manuscript. AP designed the study, supervised the development of the work, contributed to the interpretation of results, wrote and revised the manuscript. All authors read and approved the final manuscript.

Competing interests

NA

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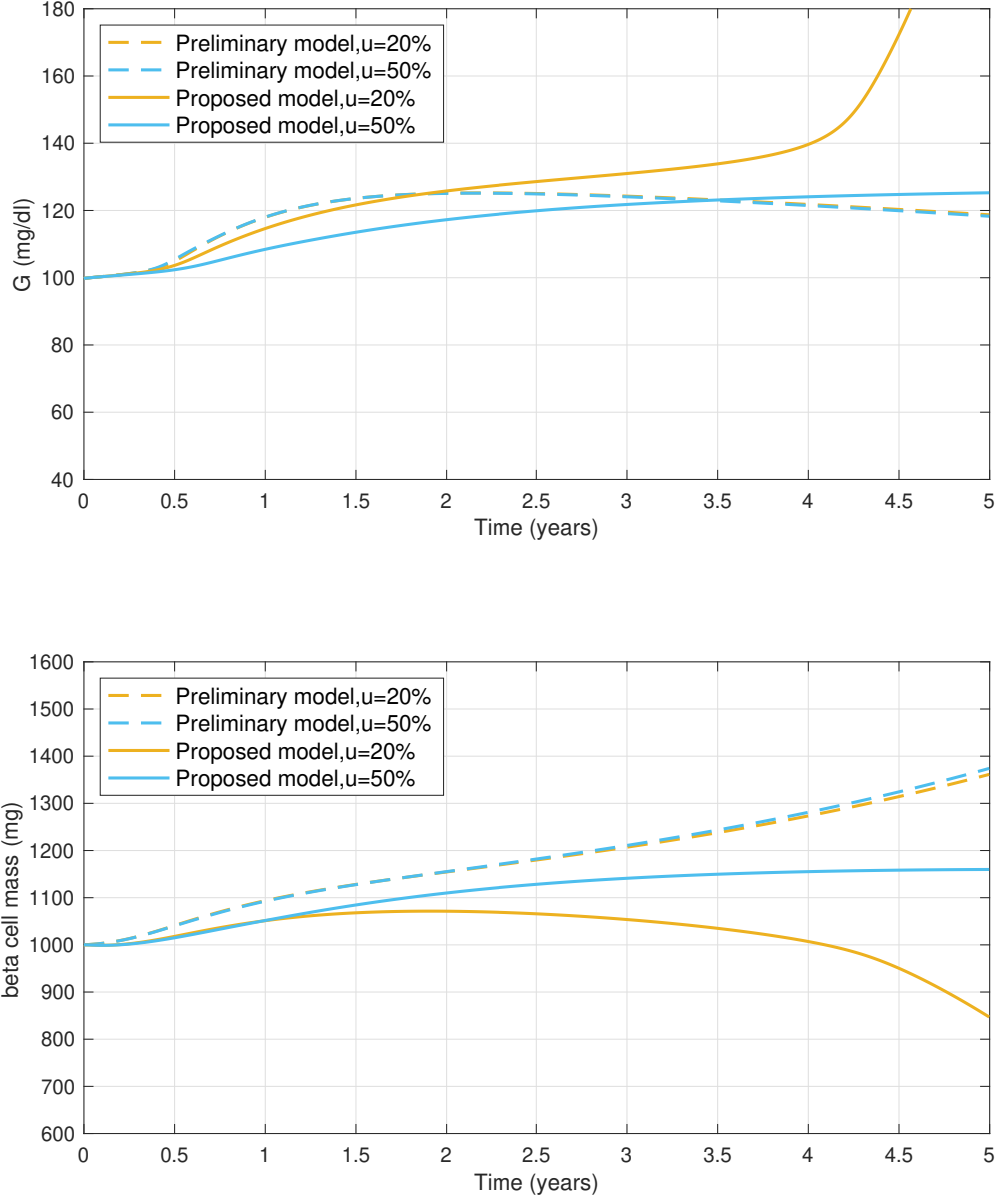


Figure 4: Glucose concentration (top panel) and beta-cell mass (bottom panel) as a function of time obtained using the preliminary version of the model²⁸ (dotted lines) and the model here proposed (Equations (1), continuous lines) (simulation: 60 minutes/session, 3 sessions/week, $u = 20\%$ and 50% , $S_{I,target} = 0.18$, $\tau_{SI} = 150$ days).